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## SECTIONS



## ARTICLES

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# Pregnant, uninfected, stressed, and confined in the COVID-19 period: what can we expect in the near future?

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Pregnancy can be associated with a period of distress and psychological vulnerability. The transition to parenting involves fast physical, psychological, and social changes. Stress is the perception of a discrepancy in the availability of resources to meet the demands of external events or stimuli[1]. Stress and anxiety are highly related and involve systemic responses as cortisol reactivity[2]. Anxiety is the perception of external stimuli to uncertain danger or potential threats and involves an organic response[3].

The World Health Organization declared COVID-19 as a public health emergency of international concern in January 2020. In Face of the possibility of an uncontrolled outbreak, many cities and countries have established mass quarantine, and public authorities have asked the population to self-isolate at home for weeks. Quarantine involves the loss of freedom, uncertainty over disease status, physical distance from beloved relatives, and boredom. The imposition of quarantine presents psychological costs that cannot be measured and are sometimes neglected[4].

During the COVID-19 outbreak, pregnant women are experiencing stress and anxiety from the perception of disruption in prenatal services and reduced access to health facilities and medication for themselves and for their newborns[5], fear of infecting family members and the newborn, boredom, frustration, financial loss, and the effect of the disease or its treatment on the fetus. These perceptions are contrived or enhanced by many reliable and unreliable media sources[6].

In pregnancy, little is known about the stress in infectious outbreaks and/or quarantine. However, the effects of stress and anxiety during pregnancy and delivery are very well documented and should be expected in the large population of uninfected or asymptomatic pregnant women[7]. The consequences of stress nowadays on these patients may affect the obstetrics and fetal medicine services, and the neonatal intensive care units in a very short period due to increased risks of preterm delivery and low birth weight. Additionally, the effects of anxiety extend to a risk of puerperal complications, such as poor parental bonding and postpartum depression. The long-term effects on a child extend beyond inherited genes and the quality of the pregnancy care and are known as functional teratology or Baker hypothesis. Maternal stress is also linked to interferences in the neurodevelopment of the fetus, which adds to the risk of inherited psychiatric illness[8].

Maternal–fetal medicine has developed and achieved great results in the prevention of pregnancy complications through various measures such as early fetal ultrasound, maternal psychological support, and by increasing the maternal–fetal attachment and helping parents to cope with adverse conditions through the prediction and prevention of fetal growth restrictions, preeclampsia, and spontaneous preterm delivery. During the COVID-19 outbreak, maternal–fetal specialists know they have a great task ahead: to continue supporting those suffering from known conditions and to face new, unknown challenges. However, stress and anxiety are well-known threats that silently harm women and future generations and cannot be neglected. Hence, further knowledge about the harmful effects of stress and anxiety during pregnancy is necessary in the future.

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# In the time of corona - is it safe to delay treatment for prostate cancer?

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Recently, the outbreak of a new disease denominated Coronavirus 2019 (COVID-19) occurred in Wuhan, China[1]; it rapidly spread to other regions of China and around the world[2,3]. This pandemic has implications on the continuity of treatment for patients, especially of cancer. There has been a shift in priorities. Human, medical, and paramedical resources are being directed at care for individuals infected by COVID-19. Moreover, measures to confine the population have led to the restriction of travel for appointments, exams, and clinical/surgical treatment.

Patients with prostate cancer, which is the most common form of cancer among men in Brasil, have a slow-moving condition[4], and delaying treatment due to the pandemic is not likely to affect survival in the long term. In the current scenario, delaying surgical treatment for a localized, locally advanced disease is under discussion since it is an elective procedure and, therefore, among those that health authorities are advising to be delayed.

Most patients with prostate cancer are asymptomatic at the time of diagnosis and do not require urgent care. Morini et al.[5] evaluated 908 patients submitted to radical prostatectomy and found no change in the oncological outcome when the procedure was delayed for six to 12 months after diagnosis in patients with low or intermediate risk. Likewise, O'Callaghan et at.[6] found no worsening of overall survival or specific cancer in the Australian population with a delay of up to 8.8 months.

However, patients may attempt to persuade surgeons to opt for the surgical procedure even in this time of crisis. One should bear in mind that patients may be in the incubation period at the time of surgery. In a study involving 2,007 Chinese individuals hospitalized with COVID-19, Liang et al.[7] found a significantly higher incidence of serious events such as death or admission to the ICU, requiring invasive mechanical ventilation, among individuals with a history of cancer than those without such a history (39% vs. 8%; P = 0.0003). In a study conducted by Yu et al.[8], a total of 1,524 patients with cancer in Wuhan were analyzed and the authors estimated that those with cancer had a twofold higher risk of infection by COVID-19 in comparison to the general population. Therefore, cancer and hospitalization contribute to a greater risk of infection and worse outcomes.

In conclusion, even with the uncertainties regarding the period of isolation and the delaying of elective procedures, patients with localized prostate cancer of low risk have a low probability of progression of the neoplasm, even with the delay of surgical treatment. Therefore, such patients can wait up to six months.

## Conflicts of Interest

The authors have no conflicts of interest to declare.

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# Does psychological preparation improve pretreatment anxiety in patients with prostate cancer?

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Prostate cancer (PC) is more common in developed countries, but its incidence is increasing throughout the world. Most cases are detected when the tumor is still intraprostatic, and the prognosis is good[1]. Despite the high survival rate, some common outcomes of treatment exert a negative impact on the quality of life[1], which can lead to a feeling of regret with regards to the therapeutic option[2].

Psychological stress is common among patients with PC and emerges mainly in the form of anxiety and depression[3]. Treatment options for PC are radical prostatectomy, radiotherapy, and hormone therapy, all of which have some side effects, the most common of which are urinary, sexual, and gastrointestinal disorders[1]. Surgery generally results in erectile dysfunction[1,4]. Radiotherapy is associated with gastrointestinal dysfunction and an increase in the frequency of urination[4]. Hormone therapy is associated with hot flashes and mood swings[1]. One study demonstrated that measures of stress, anxiety, and depression were more stable among patients submitted to surgery, whereas a rapid decline in these measures was found in those submitted to radiotherapy, followed by a slight improvement in the long term[3].

Regret regarding the decision to undergo treatment is common, affecting 11 to 18% of patients[2]. Miles et al.[5] found that four out of every 10 patients with PC have some negative outcomes associated with treatment and related to sexual or urinary function, with an impact on one's sex life. Moreover, the authors found that 22% of patients were dissatisfied with radical prostatectomy, and 11% were dissatisfied with radiotherapy. Moreover, 5% had the impression that they had made the decision too hastily and felt that they should have sought a second opinion or opted for conservative treatment. Although most patients are satisfied with the treatment, these figures indicate that patients should be made better aware of the possible complications inherent to surgical or radiotherapeutic procedures[5]. Thus, the prognosis, adverse

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effects of treatment, and the impact of these on the quality of life should be taken into consideration when deciding which treatment to employ[1].

Investigating the patients' perceptions regarding the risks associated with the treatment of localized PC, van Stam et al.[4] found that 68% of them did not understand the differences between surgery and radiotherapy with regards to clinical outcomes and the risk of adverse effects, which could lead to the obtainment of inadequate informed consent and experiences of unexpected or disappointing outcomes. Another study found that 71% of patients accepted the first medical opinion regarding treatment and the rest opted for alternative treatment, considering it more effective at combating cancer without being concerned with the possible complications of the therapeutic option[5].

Preoperative patient education is part of a physician's routine and is challenging when there are risks involved, such as urinary incontinence and erectile dysfunction[6]. It is important to consider the patent's preoperative anxiety related to concerns about the disease, hospitalization, anesthesia, and surgery as well as the fear of the unknown. Such anxiety could be significantly reduced through patient education[7]. Moreover, short-term psychological interventions can prevent preoperative anxiety in patients with cancer[7]. A patient-centered approach has the potential to improve the quality of the care provided, generating empathy, and a sustainable patient-physician relationship. It is possible that urologists are not adequately trained to prepare patients psychologically with regard to complications related to the treatment.

AFAQ, BRS, LCFS, FNFJ - Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; agreement to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval of the version to be published.

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# Is the use of microwave ablation more effective and/or safe that radiofrequency ablation in the treatment of hepatocellular carcinoma?

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*The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize producers to assist the reasoning and decision-making of doctors.*
*The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.*

## INTRODUCTION

Liver cancer can be of two types: primary (which begins at the organ itself) and secondary or metastatic (originating in another organ and, with the progression of the disease, also affecting the liver). The secondary type is most often due to a malignant tumor in the large intestine or rectum.

Among the types of primary liver cancer, the most common is the hepatocellular carcinoma - an extremely aggressive tumor that presents several risk factors, the main ones being cirrhosis and chronic diseases such as infections by the hepatitis B and C virus.

The ideal management of this type of tumor depends on many factors, including their size, the number of lesions, the distribution of the tumor, the relationship between the tumor and hepatic vascularization, the presence or absence of distant metastasis or lymph nodes, the Child-Pugh score[1], the functional status of the patient, and the adequacy to a liver transplant.

When the tumor is small, the treatment consists of surgically removing the tumor and part of the liver, provided that the function of the organ is preserved; if these criteria are not present, the alternative is liver transplantation.

There are, however, other treatment options, which are considered more conservative, among

them is cryosurgery (freezing of the malignant cells), tumor ablation by radiofrequency - RFA (electrical waves cause an increase of the temperature inside the tumor), microwave ablation - MWA, alcoholization (injection of alcohol into the tumor), and chemoembolization (application of microspheres containing chemotherapeutic agents).

For hepatocellular carcinomas of 4 to 5 cm or less, radiofrequency ablation presents good results and few complications. This same procedure can be performed using microwaves, with a shorter duration, higher temperature, and larger ablation zone, with the possibility of using multiple probes, and with less heat dissipation through the liver.

The goal of this assessment is to compare the efficacy and safety of microwave ablation in comparison with radiofrequency ablation in the treatment of hepatocellular carcinoma.

## METHODS

In the methodology, we present the clinical question, the structured question (PICO), the eligibility criteria, the sources of information and search strategies used, the method for critical assessment (risk of bias) and quality of evidence (GRADE[2]), the data to be extracted, the measures used to express the results, and the method of analysis.

### Clinical Question

Is the treatment of hepatocellular carcinoma more effective and/or safe with the use of microwave ablation than with radiofrequency ablation?

### Structured question

| | |
|---|---|
| **P** | (Population): Patients with hepatocellular carcinoma |
| **I** | (Intervention): Microwave ablation |
| **C** | (Comparison): Radiofrequency ablation |
| **O** | (Outcome): local recurrence, mortality, lession progression, and complications |

### Eligibility criteria

- PICO components;
- Randomized clinical trials (RCTs);
- No time restrictions;
- English, Spanish, and Portuguese languages;
- Full text or summary with the necessary data;
- Outcomes expressed as the absolute number of events or mean/median with variation

### Exclusion criteria

- Observational and non-comparative studies.
- In vitro and/or animals studies.
- Case series or case reports.
- Narrative or systematic reviews.

### Sources of information consulted and search strategies

Medline via PubMed, EMBASE, and manual search

#1: (Liver Neoplasm OR Hepatic Neoplasms OR Hepatic Neoplasm OR Hepatocellular Cancer OR Hepatocellular Cancers OR Hepatic Cancer OR Hepatic Cancers OR Liver Cancer OR Liver Cancers OR Hepatocellular Carcinomas OR Liver Cell Carcinoma OR Liver Cell Carcinomas OR Hepatocellular Carcinoma OR Hepatoma OR Hepatomas)

#2: (Radiofrequency OR Radio Frequency OR Catheter Ablation)

#3: (Microwave OR Waves OR Wave)

#4: (#1 OR #2 OR #3)

#5: #4 AND random*

### Risk of bias and quality of evidence

For RCTs, we assessed the following risks of bias: randomization, blinding, double-blinding, blinding of the evaluator, losses, analysis by intention to treat (ITT), definition of the outcomes and sample size calculation, early interruption.

### Extracted data

Author, Year of publication, study design, characteristics and number of patients, intervention, comparison, outcomes (local recurrence, mortality, lesion progression, and complications).

### Outcome measures

For the variables, we used absolute numbers, percentage, absolute risk, reduction or increase of risk, the number needed to treat (NNT) or to harm (NNH), confidence interval of 95% (95% CI).

Presentation of the results

If there is the possibility to combine the results of the studies included regarding one or more shared outcomes, a meta-analysis will be carried outcome. [RevMan 5.3 software (Cochrane)][3].

### Analysis of the quality of evidence

The quality of the evidence was assessed by using the GRADE[2] (GRADEpro software)[4].

## RESULTS

The results presented are: diagram of recovery and selection of studies (Figure 1), characteristics of the studies (Table 1), risks of bias (Table 2), results by outcomes (Table 3), quality of evidence (Table 4), and synthesis of evidence.

We retrieved 126 studies; after applying the eligibility criteria, 18 studies were selected, of which 09 were included (07 for full-text evaluation and 2 for abstract evaluation) (Figure 1). The list of studies excluded is available in Table 5.

**TABLE 1.** DESCRIPTION OF THE WORKS

| Author/year | PIMD | Type of design | Population (n) | Intervention (n) | Comparison (n) | Outcome | Follow-up time |
|---|---|---|---|---|---|---|---|
| Kamal 2019 | 31183208 | RCT | 56 | 28 | 28 | local recurrence / mortality / complications | 12 months |
| Vietti Violi 2018 | 29503247 | RCT | 152 | 76 | 76 | local recurrence / mortality / complications | 24 months |
| Yu.J 2017 | 27884919 | RCT | 403 | 203 | 200 | local recurrence / mortality / complications | 36 months |
| Shibata 2002 | 11997534 | RCT | 72 | 36 | 36 | local recurrence / complications | 24 months |
| Abdelaziz 2014 | 24935203 | RCT | 111 | 66 | 45 | local recurrence / survival / complications | 27 months |
| Di Vece F 2014 | 24196263 | RCT | 40 | 20 | 20 | Complications | ? |
| Sheta E 2016 | 27362551 | RCT | 30 | 10 | 20 | Complications / local recurrence | 6 months |
| Naïk VV 2017 | | RCT | 144 | 71 | 73 | Progression / survival (mortality) | 20 months |
| Chong C 2017 | | RCT | 81 | 40 | 41 | Local recurrence / survival (mortality) | 6 months |

RCT = RANDOMIZED CLINICAL TRIAL

**TABLE 2.** RISKS OF BIAS

| Author/year | Randomization | Blinded allocation | Double-blind | Losses | Prognosis | Outcome | Intention-treat analysis | Sample size calculation | Early termination |
|---|---|---|---|---|---|---|---|---|---|
| Kamal 2019 | | | | | | | | | |
| Vietti Violi 2018 | | | | | | | | | |
| Yu.J 2017 | | | | | | | | | |
| Shibata 2002 | | | | | | | | | |
| Abdelaziz 2014 | | | | | | | | | |
| Di Vece F 2014 | | | | | | | | | |
| Sheta E 2016 | | | | | | | | | |
| Naïk VV 2017 | | | | | | | | | |
| Chong C 2017 | | | | | | | | | |

Blue: Absence of biases; Yellow: Unknow; Orange: Presence of biases

**TABLE 3.** RESULTS OF THE OUTCOMES

| Microwave / Radiofrequency | | | local recurrence | | Mortality | | Complications | | Progression of the disease | | Follow-up time |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Microwave | Radiofrequency | Microwave | Radiofrequency | Microwave | Radiofrequency | | | |
| Kamal 2019 | 28 | 28 | 2 | 2 | 4 | 4 | 4 | 0 | - | - | 12 months |
| Vietti Violi 2018 | 76 | 76 | - | - | 15 | 15 | - | - | 6 | 12 | 24 months |
| Yu.J 2017 | 203 | 200 | - | - | 37 | 38 | 7 | 5 | 9 | 12 | 36 months |
| Shibata 2002 | 36 | 36 | 4 | 1 | - | - | 1 | 4 | - | - | 24 months |
| Abdelaziz 2014 | 66 | 45 | 3 | 7 | 5 | 9 | 5 | 2 | | | 27 months |
| Di Vece F 2014 | 20 | 20 | | | | | 1 | 1 | | | Not informed |
| Sheta E 2016 | 10 | 20 | 1 | 2 | a | | 1 | 2 | | | 6 months |
| Naïk VV 2017 | 71 | 73 | | | 8 | 9 | 2 | 0 | 6 | 7 | 20 months |
| Chong C 2017 | 40 | 41 | 23 | 21 | 15 | 22 | | | | | 6 months |

**TABLE 4.** MICROWAVE ABLATION COMPARED TO RADIOFREQUENCY ABLATION FOR HEPATOCELLULAR CARCINOMA

| Certainty assessment | | | | | | | # of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| # of studies | Design of the study | Risk of bias | Inconsistency | Indirect evidence | Imprecision | Other considerations | Microwave ablation | Radiofrequency ablation | Relative (95% CI) | Absolute (95% CI) | | |
| LOCAL RECURRENCE | | | | | | | | | | | | |
| 4 | randomized clinical trials | very severe a | not severe | not severe | very severe b | none | 30/114 (26.3%) | 26/125 (20.8%) | not estimable | 40 less per 1,000 (from 120 less to 30 more) | ⊕○○○ VERY LOW | IMPORTANT |
| COMPLICATIONS | | | | | | | | | | | | |
| 5 | randomized clinical trials | very severe a | not severe | not severe | very severe b | none | 12/297 (4.0%) | 12/304 (3.9%) | not estimable | 10 less per 1,000 (from 40 less to 20 more) | ⊕○○○ VERY LOW | IMPORTANT |
| MORTALITY | | | | | | | | | | | | |
| 5 | randomized clinical trials | severe a | not severe | not severe | very severe b | none | 79/418 (18.9%) | 88/418 (21.1%) | not estimable | 20 more per 1,000 (from minus 40 to 70 more) | ⊕○○○ VERY LOW | IMPORTANT |
| PROGRESSION OF THE DISEASE | | | | | | | | | | | | |
| 3 | randomized clinical trials | severe a | not severe | not severe | severe b | none | 21/350 (6.0%) | 31/349 (8.9%) | not estimable | 20 more per 1,000 (from minus 10 to 60 more) | ⊕⊕○○ LOW | IMPORTANT |

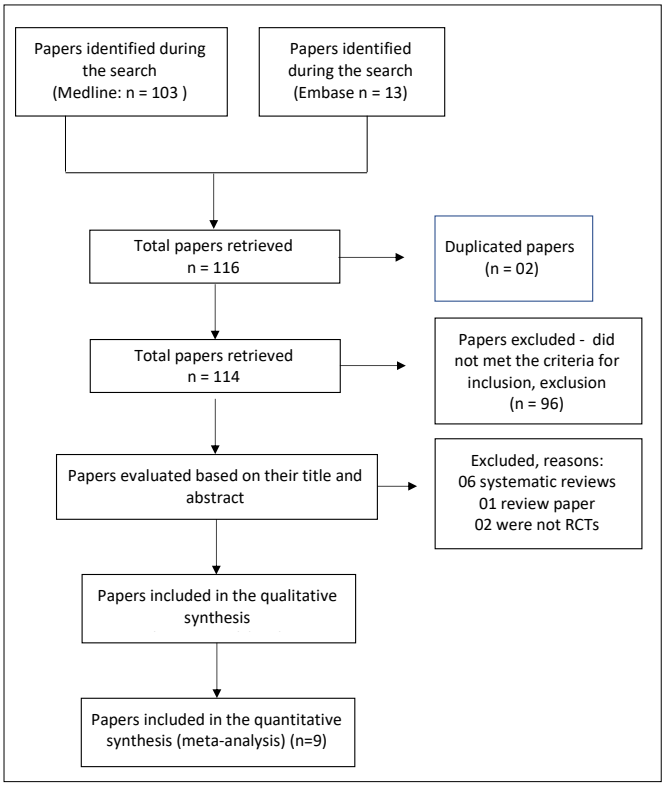
CI: Confidence interval. a. Biases in the blinded allocation, losses, blinding, prognostic characteristics, and sample size calculation b. Wide confidence interval

**TABLE 5.** PAPERS EXCLUDED

| List of papers excluded | Reason for exclusion |
|---|---|
| Tan 2019 | SR/meta-analysis |
| Mokdad 2017 | Descriptive study |
| Majumdar 2017 | SR |
| Lou 2017 | SR |
| Facciorusso 2016 | SR |
| Yi Y 2014 | RCT with combined chemoembolization |
| Galandi D 2004 | SR |
| Gaiani S 2003 | Article of treatment review |
| Glassberg 2019 | SR |

SR: Systematic review. RCT: Randomized clinical trial

**FIGURE 1.** FLOWCHART OF THE STUDIES RETRIEVED AND SELECTED ON THE USE OF MICROWAVE ABLATION VERSUS RADIOFREQUENCY ABLATION IN HEPATOCELLULAR CARCINOMA



## Characteristics of the studies included

1. A total of 56 patients were selected with hepatocellular carcinoma and lesions ≤ 3.0 cm, without lesions larger than 5.0 cm, vascular invasion, or extra-hepatic metastases. A total of 28 underwent treatment by radiofrequency ablation, and 28 by microwave ablation. The outcomes were assessed based on local recurrence, mortality, and complications. The follow-up time was 12 months[5].

2. Of the 152 patients selected with hepatocellular carcinoma, 76 underwent treatment by radiofrequency ablation, and 76 by microwave ablation. The evaluation was carried out by analysis of the protocol. Five patients were excluded from the group of microwave ablation and three from the group of radiofrequency ablation. The outcomes evaluated were: mortality and progression of the disease. The follow-up time was 26 months in the microwave ablation group and 25 months in the radiofrequency ablation group[6].

3. A total of 403 patients with hepatocellular carcinoma, with the following information: tumor size ≤5 cm in diameter, number of tumors ≤3, Child-Pugh class A or B, without evidence of extra-hepatic metastasis, tumor embolism of veins or the bile duct, lesions visible on ultrasound with an acceptable puncture path. A total of 200 patients underwent treatment by radiofrequency ablation, and 203 by microwave ablation. The outcomes evaluated were: mortality, complications, and progression of the disease. The follow-up time was 36 months[7].

4. A total of 72 patients were selected with hepatocellular carcinoma and lesions smaller than 4 cm in diameter or with two or three nodules smaller than or equal to 3 cm in diameter. A total of 36 patients underwent treatment by radiofrequency ablation, and 36 by microwave ablation. The outcomes evaluated were: local recurrence and complications. The follow-up time was 18 months[8].

5. A total of 111 patients were selected with early-stage hepatocellular carcinoma and preserved liver function (Child-Pugh A and B), performance status 0, and with 3 or less focal lesions (the larger of which not exceeding 5 cm in size). A total of 45 patients underwent treatment by radiofrequency ablation, and 66 by microwave ablation. The outcomes evaluated were: local recurrence, complications, and mortality. The follow-up time was 27 months[9].

6. A total of 40 patients were selected with a single hepatocellular carcinoma tumor > 2.0 and < 7,0cm diameter, located ≥ 3.0 cm away from the capsule of the liver, gallbladder, main left or right hepatic ducts or main vessels. A total of 20 patients underwent treatment by radiofrequency ablation, and 20 by microwave ablation. The evaluated outcome was complications. The follow-up time was not reported[10].

7. A total of 50 patients were included with Child-Pugh class A or B, serum albumin ≥ 3 g/l, serum bilirubin <2.5 mg/dl, platelet count ≥ 70,000 mm3, international normalized ratio (INR) ≤ 1.6, serum creatinine <2 mg/dl, and tumor size greater than 4 cm, and confined to one lobe of the liver. The patients were randomized as follows: 20 for arterial chemoembolization, 20 for arterial chemoembolization combined with radiofrequency ablation, and 10 for arterial chemoembolization combined with microwave ablation. The outcomes evaluated were: local recurrence and complications. The follow-up time was 6 months[11].

8. A total of 144 patients with chronic liver disease with HCC ≤4 cm, BCLC stage A, not eligible for surgery were evaluated. Of these, 73 were treated with radiofrequency ablation, and 71 with microwave ablation. The outcomes evaluated were: survival (mortality), complications, and disease progression. The follow-up time was 20 months[12].

9. A total of 81 patients were selected with hepatocellular carcinoma and averages lesions of 3.0 cm. A total of 41 patients were treated with radiofrequency ablation, and 40 with microwave ablation. The outcomes evaluated were: local recurrence and mortality. The follow-up time was 6 months[13].

## Risk of bias and quality of evidence

1. The randomization, prognostic characteristics, and outcomes were adequate; however, the allocation was not blinded, there was no double-blinding, and there is no description of losses or sample size calculation. There was no early interruption[5].

2. Demonstrated adequacy of randomization, prognostic characteristics, outcomes, sample size calculation, and description of losses; however, there was no double-blinding and no description of how patients were allocated. There was no early interruption[6].

3. The randomization was performed, prognostic characteristics and outcomes are described; the allocation was not blinded, there was no double-blinding, and there is no description of losses or sample size calculation. There was no early interruption[7].

4. The randomization and outcomes were adequate; there was no blinded allocation, no double-blinding, and there is no description of losses or of prognostic

characteristics or sample size calculation. There was no early interruption. The analysis of intention-to-treat was carried out.

5. The randomization process was inadequate (by currency) and there were losses greater than 20%; the prognostic characteristics and outcomes were adequate; there was no blinded allocation, blinding, or sample size calculation; there was no early interruption or analysis by intention to treat[9].

6. A randomized study with losses below 20%, in which the prognostic characteristics and outcomes were adequate; there was no blinded allocation, and only the evaluators were blinded; there is no sample size calculation; there was no early interruption or analysis by intention to treat[10].

7. Although the randomization and outcomes presented are adequate and there were no losses greater than 20%, the blinded allocation, blinding, and sample size calculation were not carried out, and there is no description of the prognostic characteristics. The evaluation was performed by analysis of intention to treat and there was early interruption[11].

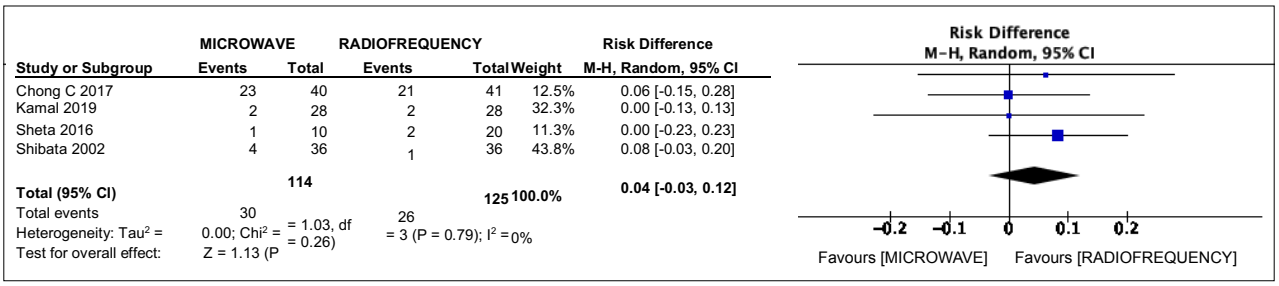
8. Randomized study; the information was obtained from the summary, which is limited only to the appropriate outcomes and does not clarify on other risks of bias[12].

9. Data obtained from the summary of this randomized study provide information on the outcomes but not on the risks of bias[13].

## Analysis of results by outcomes

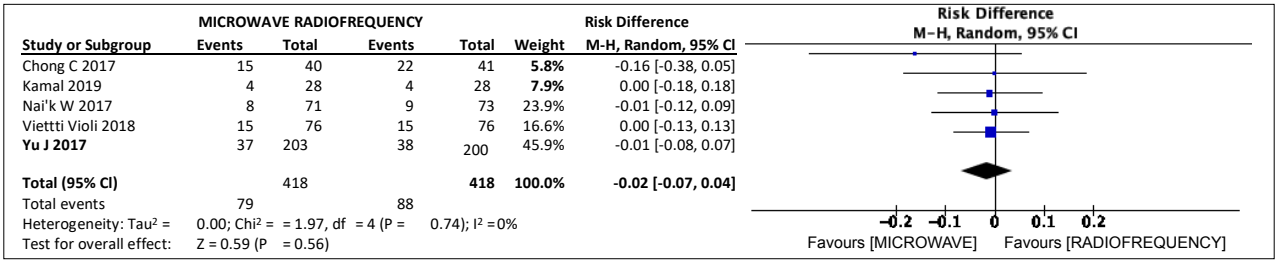
We describe the meta-analyzed results of the following outcomes: local recurrence, mortality, complications, and disease progression:

### Local recurrence



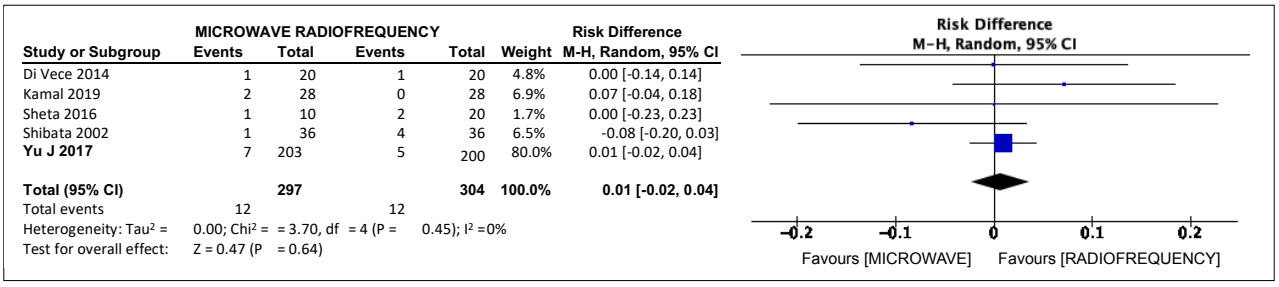

There is no difference (greater or lesser effectiveness) in relation to the outcome of local recurrence when comparing the use of microwave and radiofrequency [risk difference 0.04 (- 0.03 to 0.12)].

### Mortality



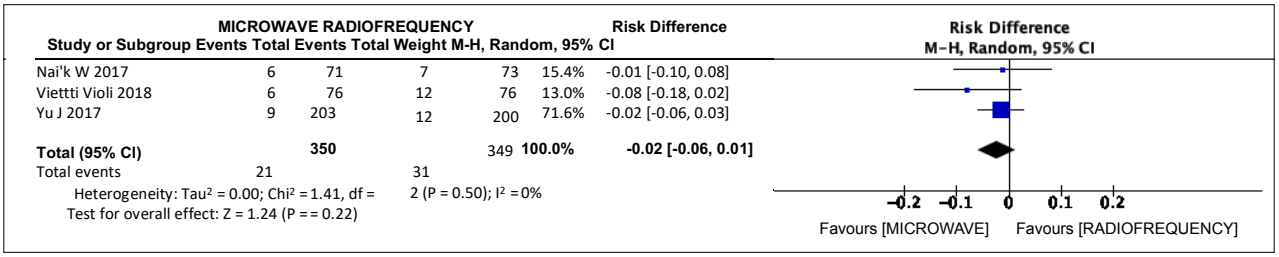

There is no difference between the two forms of treatment in relation to the outcome of mortality (risk difference -0.02 [-0.07 to 0.04])

Complications




There is no difference between the two forms of treatment in relation to the outcome of complications (risk difference 0.01 [-0.02 to 0.04])

Progression of the disease




There is no difference between the two forms of treatment in relation to the outcome of progression of the disease (risk difference -0.02 [-0.07 to 0.01]).

## QUALITY OF EVIDENCE

The quality of the evidence for all outcomes (local recurrence, mortality, disease progression, and complications) is very low (TABLE 4).

## SYNTHESIS OF EVIDENCE

There are no differences between the use of microwave ablation in comparison with radiofrequency ablation in the treatment of hepatocellular carcinoma lesions ≤ 5.0 cm regarding the outcomes: local recurrence, mortality, complications, and progression of the disease. This means that it is not known whether the efficacy or safety is greater or SMALLER than those of the treatment already in use (radiofrequency). The quality of the evidence is very low.

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# Neonatal sepsis with neutropenia: granulocytecolony stimulating factor (G-CSF)

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**Question: What is the impact on overall mortality outcomes (death from any cause) and adverse events of g-csf in the treatment of newborns with neonatal sepsis and neutropenia [absolute neutrophil count (anc)<5,000 mm³] compared to the conventional therapy?**[1]

**Answer:** In newborns with sepsis and neutropenia ≤5,000 cells/mm³, the use of g-csf reduces the risk of in-hospital death by 19% (nnt = 5). G-csf has proved to be a safe drug.

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# Misdiagnosing multicentric Castleman's disease in an HIV-positive patient

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## INTRODUCTION

The differential diagnosis of fever and lymphadenopathy in an HIV-positive patient is extensive and complex. Castleman's disease (CD) represents a heterogeneous group of lymphoproliferative disorders, which includes unicentric and multicentric CD (MCD), subdivided into HHV-8-associated MCD, generally in HIV-positive and other immunocompromised individuals, and HHV-8-negative/idiopathic MCD (iMCD), of unknown etiology. Despite significant advances in recent years, the overall understanding of CD remains limited, and formal diagnostic criteria for HHV-8-associated MCD have not been established. Furthermore, since there is significant clinical, histologic, and immunologic overlap with other malignant, autoimmune, and infectious disorders, and given the rarity of CD and the nonspecific nature of its symptoms, a high level of suspicion is required in patients with a compatible clinical picture.

We report the case of a 57-year-old man with HIV infection who presented with recurrent and unexplained fever, lymphadenopathies, and severe pancytopenia.

## CASE PRESENTATION

We describe the case of a 57-year-old male patient with a history of cocaine and heroin use in the past, heavy smoking, drinking and poorly controlled HIV infection for the past 20 years (nadir CD4+ count 500/μL), although currently suppressed. He had presented several times in the past 6 years with unexplained recurrent low-grade fever, malaise, anorexia, and night sweats. Physical examination was remarkable for mild hepatosplenomegaly and generalized, infracentimetric, non-tender lymphadenopathies. Analytical findings included sustained pancytopenia and elevated

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inflammatory markers. Blood cultures and viral serologies were repeatedly negative, and bronchoalveolar lavage showed no abnormal findings. Fine needle aspiration biopsies of one axillary and two inguinal nodes showed a reactive pattern. Beta-2-microglobulin was slightly elevated, but immunophenotyping of peripheral blood circulating B cells was normal. Serum immunofixation electrophoresis demonstrated oligoclonal bands (IgG, kappa, and lambda), and bone marrow biopsy revealed mild plasmocytosis (16%).

A month after the last hospitalization, the patient presented once again with the same complaints and was admitted for study. Physical examination and blood work remained unchanged (Table 1). Bone marrow examination was repeated, which confirmed mild plasmocytosis, with no other atypical findings. Hence, the combined findings of fever, lymphadenopathy, hepatosplenomegaly, and severe cytopenias along with plasma cell disorder led to a suspicion of MCD. HHV-8 DNA was detected in the plasma through quantitative real-time PCR, and an excisional biopsy of an axillary node was performed, revealing an increased number of follicles, of variable morphology, penetrated by hyalinized blood vessels ("lollipop appearance") and with concentric rimming of mantle zone lymphocytes, arranged in an "onion skin" fashion (Figure 1), as well as HHV-8 infection (Figure 2), compatible with a plasmablastic variant of MCD. The patient was referred to the Hematology Department and initiated on rituximab 375mg/m$^2$ and etoposide 100mg/m$^2$ for 4 weeks, with significant clinical and analytical improvement. No serious adverse events of therapy occurred. At 12-month follow-up, the patient remains asymptomatic, with a considerable decrease in the size of all adenopathies and normalized blood counts.

## DISCUSSION

HHV-8 infects B cells and plasmablasts and is present in up to 10 to 30% of mantle zone lymphoid cells of HHV-8-associated MCD[1]. Human IL-6 and viral IL-6 are important drivers of B cell proliferation by activating the human IL-6 receptor (gp130) and inducing VEGF expression in interfollicular areas and, consequently, cause the symptoms observed, particularly during lytic infection[2]. Immunohistochemistry for LANA-1 in the lymph node is the gold standard for HHV-8 detection, and excisional biopsy should be performed if initial exams fail to confirm the diagnosis and clinical suspicion remains high, as in this case.

The epidemiology of CD is difficult to characterize accurately, given its rarity and clinical heterogeneity[3]. Due to unknown reasons, among HIV-infected individuals, the incidence of CD has increased over

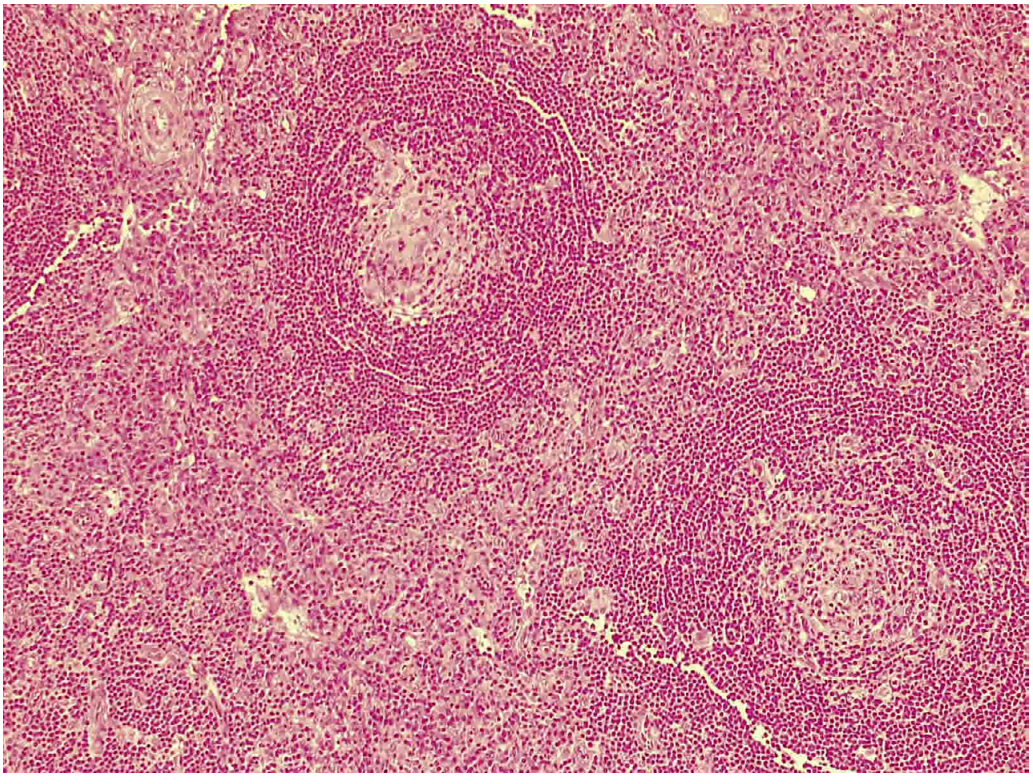

**FIGURE 1.** LYMPHOID FOLLICLES WITH EXPANDED MANTLE ZONE WITH A CONCENTRIC APPEARANCE (H&E X100)

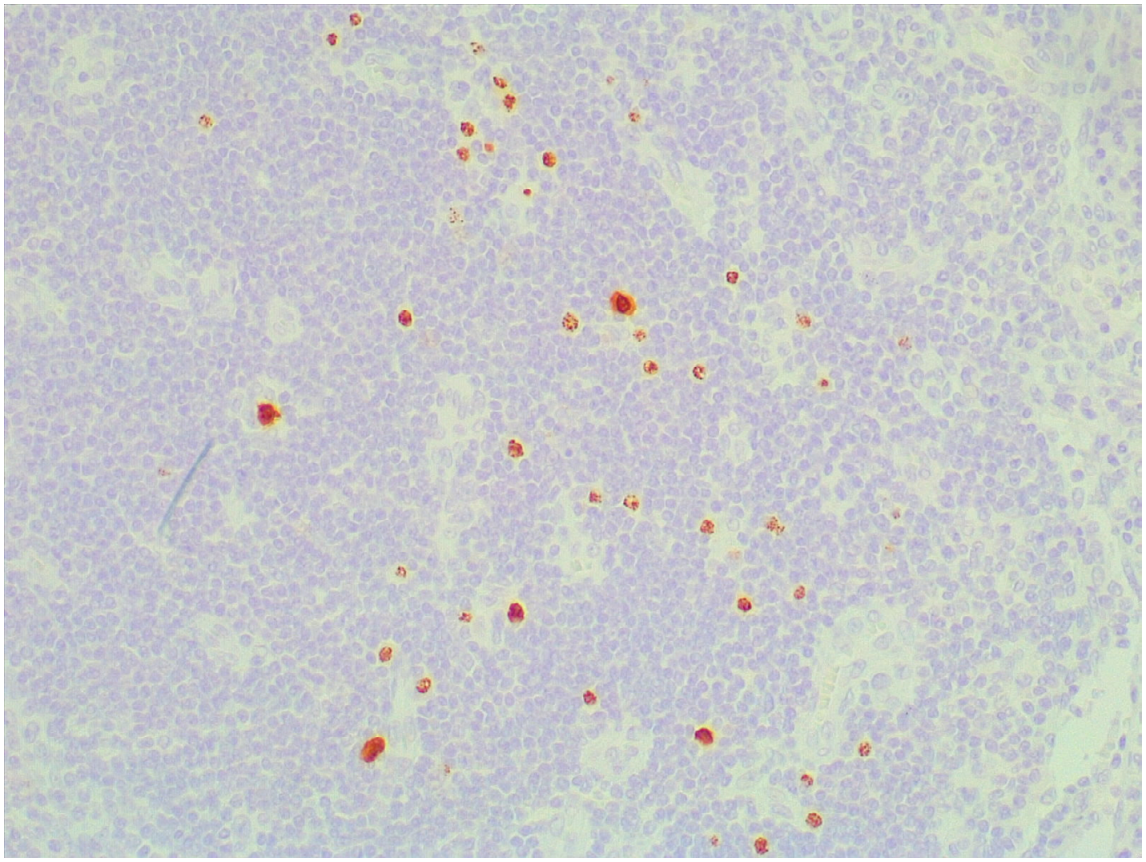

**FIGURE 2.** IMMUNOHISTOCHEMISTRY SHOWING PLASMABLASTS POSITIVE FOR HHV-8 LANA-1

**TABLE 1.** BIOCHEMICAL DATA ON ADMISSION, AT DISCHARGE, AND AT 6-MONTH FOLLOW-UP

| | On admission | At discharge | Follow-up | Reference values |
|---|---|---|---|---|
| Hemoglobin (g/dL) | 6.2 | 8.2 | 11.4 | 13-17 |
| Hematocrit (%) | 24 | 26 | 36 | 40-50 |
| Reticulocyte index | 0.9 | 1.2 | - | 1-3% |
| Platelets (103/µL) | 36 | 144 | 175 | 150-350 |
| WCC (103/µL) | 4.3 | 5.4 | 5.2 | 4.5-11.4 |
| LUC (%) | 11 | - | - | - |
| Serum iron (µg/dL) | 38 | - | 94 | 60-170 |
| Ferritin (ng/mL) | 1366 | - | 579 | 20-250 |
| Transferrin (mg/dL) | 67 | - | 75 | 170-370 |
| Folic acid (ng/mL) | 20.7 | - | - | 2.7-17 |
| Vitamin B12 (pg/mL) | 509 | - | - | 160-950 |
| Sodium (mEq/L) | 130 | 141 | 143 | 136-146 |
| Potassium (mEq/L) | 4.0 | 4.0 | 4.2 | 3.5-5.1 |
| Calcium (mg/dL)* | 8.3 | 8.5 | 8.4 | 8-10 |
| Lactate dehydrogenase (UI/L) | 82 | 97 | 90 | 105-330 |
| Urea (mg/dL) | 95 | 48 | 39 | 18-55 |
| Creatinine (mg/dL) | 1.7 | 0.8 | 0.8 | 0.7-1.25 |
| Total bilirubin (mg/dL) | 0.9 | 0.9 | 0.5 | <1.2 |
| Alkaline phosphatase (UI/L) | 52 | 52 | 46 | 20-140 |
| Albumin (g/dL) | 2.3 | 2.5 | 3.0 | 3.5-5.0 |
| ESR (mm/h) | 76 | 65 | 20 | <20 |
| PCR (mg/dL) | 14 | 2 | 1.1 | <0.5 |
| Beta-2-microglobulin | 6.8 | - | - | 1.1-2.4 |

the years since the introduction of antiretroviral therapy[4]. The course of the disease may be variable, from a slow onset over a few years to a rapidly progressive illness that can lead to death in a few weeks. However, in HIV-positive patients, HHV-8-associated MCD tends to follow an acute course, and risk factors in these individuals include increased age (>33 years), non-Caucasian ethnicity, no previous ART exposure, and nadir CD4+ count >200/μL[5]. The prognosis of untreated HHV-8-associated MCD is poor[6,7], and rituximab-based approaches, alone or in combination with chemotherapy (generally intravenous etoposide or liposomal doxorubicin), are currently the mainstay of treatment. These have dramatically improved survival and reduced the risk of associated lymphomas, including in the setting of multiply relapsed disease[8-11], which may be predicted by rising levels of plasma HHV8 DNA[12]. Antiretroviral therapy should also be started or continued in all patients since the reduction in viral load and improvement in immune function result in better tolerance of chemotherapy, fewer opportunistic infections, and improved overall outcome.

## CONCLUSION

Due to its rarity and nonspecific manifestations, HHV-8 associated multicentric Castleman's disease remains an elusive diagnosis, but one to be considered, especially when unexplained fever and adenopathies are present. Further studies and the introduction of formal diagnostic criteria would represent an important step in aiding clinicians to diagnose this disease more frequently and in earlier stages.

### Author's Contributions

Manuel Toscano: Conception and design of the work, acquisition of data, drafting and revising the work critically for important intellectual content and final approval of the version to be published. Sergio Cristina: Conception of the work, revising the work critically for important intellectual content and final approval of the version to be published. Patricia Cipriano: Conception of the work, revising the work critically for important intellectual content and final approval of the version to be published. Ana Rafaela Alves: Revising the work critically for important intellectual content and final approval of the version to be published.

PALAVRAS-CHAVE: *HIV. Hiperplasia do linfonodo gigante. Transtornos linfoproliferativos.*

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RAPID COMMUNICATION

# Clinical research protocol to evaluate the effectiveness and safety of individualized homeopathic medicine in the treatment and prevention of the COVID-19 epidemic

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Employing an integrative approach in the diagnosis and treatment of organic disorders (mental, general, and physical), homeopathy can act preventively in most acute or chronic diseases, moving forward to the process of their installation. To accomplish this intent, homeopathic medicines must stimulate a systemic and homeostatic reaction of the body against the various idiosyncrasies that predispose to illness, being indispensable to apply the principle of curative similarity according to the totality of symptoms characteristic of the diseased individuality (individualized medicine).[1]

In addition to its recognized application in chronic diseases, individualized homeopathy can also act in a resolutive or complementary way in acute cases, including is epidemics. However, to achieve this intent, a specific semiologic and therapeutic methodology cannot be disregarded.

In the case of epidemic diseases, which due to the virulence of their agents causes a common symptomatological picture in most susceptible individuals, individualized homeopathic medicine *(homeopathic medicine of the epidemic genius)* should bear similarity with the set of signs and symptoms of the patients affected by the different stages or phases of each epidemic outbreak. According to Samuel Hahnemann's approach, and per individual involvement, these individualized homeopathic medicines should be prescribed in isolation, in succession, or in alternation, but never as homeopathic complexes (mixtures of medicines in the same formula).[2-4]

After a survey of individualized homeopathic medicine(s) of the epidemic genius for the different stages of a given epidemic, the 'state of the art' of Hahnemannian homeopathic semiology, the application of therapeutic and/or large-scale prophylaxis should be accompanied by properly designed experimental and/or observational studies so that the results can be analyzed according to the premises of modern clinical epidemiology, avoiding systematic errors (biases) and chances of contaminated isolated results.[2-4]

Unfortunately, in recent years, we have observed several homeopathic proposals for the treatment and/

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or prophylaxis of dengue and influenza epidemics that contradict the homeopathic episteme, suggesting the application of complex homeopathic medicines (mixtures of homeopathic and/or allopathic medicines, which disregard previous pathogenetic experimentation and individualization according to the symptomatic totality that is characteristic of each stage of the current epidemic) for the entire population of a region, without using structured research protocols to assess the efficacy and safety of such proposal.[2-4]

The indiscriminate distribution of homeopathic medicines that promise to 'immunize' a collective group in the face of a given epidemic, without any notion of its efficacy, effectiveness, and safety, represents a risk to public health as it can induce the disregard of these people for the hygienic and prophylactic measures proven to be effective since they might feel 'protected' by these medicines.

Criticized by Hahnemann himself in the 19th century, empiricism is more serious today, a time when the scientific method is accessible and can be applied by all. Wrapped in countercultural obscurantism, many homeopathic physicians support their conduct only in their 'personal experience', disregarding the positive advances of contemporary science and rejecting knowledge indispensable to the development of homeopathic science.

On the other hand, in order to improve the homeopathic model in its various areas of activity, physicians and researchers need to adopt an impartial and prejudice-free posture, allowing rational and scientific homeopathy to have space to propose, discuss, and apply its research projects in medical schools and university hospitals, so that it can act in a complementary and adjuvant way in numerous health disorders.

Seeking to contemplate these objectives, in March 2020, we make available to the Brazilian and international homeopathic community the "Protocolo de pesquisa clínica para avaliar a eficácia e a segurança de medicamento homeopático individualizado no tratamento e na prevenção da epidemia de COVID-19",[5] in which we discuss, in a broad way, the various aspects involving the homeopathic treatment of epidemics, including the current epidemic of COVID-19:

Homeopathic treatment of epidemics: "Epistemological premises of the homeopathic model", "Guidelines for homeopathic treatment in epidemic diseases", and "Evidence of the effectiveness of homeopathy in epidemic diseases";

Selection of individualized homeopathic medicines of the epidemic genius of COVID-19 for the 3 phases of the current epidemic: "COVID-19 epidemic", "Study of the epidemic genius of the current COVID-19 pandemic", "Homeopathic medicines of the epidemic genius for the prevention or treatment of mild to moderate disease", "Homeopathic medicines of the epidemic genius for the treatment of severe disease" and "Homeopathic medicines of the epidemic genius for the treatment of critical states";

Ethical and scientific validation of the efficacy and safety of possible drug hypotheses, so that they are used, *a posteriori,* in the treatment and prevention of the population on a large scale: "Ethical and bioethical aspects of research in human beings" and "Randomized, double-blind, placebo-controlled clinical trial".

At the request of homeopathic researchers from several countries, the protocol has also been translated into English, so that it can be made available and applied by all ("Clinical research protocol to evaluate the effectiveness and safety of individualized homeopathic medicine in the treatment and prevention of the COVID-19 epidemic")[6].

Since the publication of the Portuguese version, we have been seeking an opportunity to apply this protocol to patients hospitalized in wards and ICUs of public and private hospitals, disseminating it to colleagues and researchers from numerous educational and research institutions. However, we are still waiting for positive feedback from researchers who have shown interest in it.

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RAPID COMMUNICATION

# Ankle-brachial Index and associated factors in individuals with coronary artery disease

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## SUMMARY

OBJECTIVE: *Analyzing the association between ABI and the main risk factors for coronary artery disease in coronary patients.*

METHODS: *Were selected 156 adult patients from a hospital in Maceió, Alagoas. Were evaluated with risk factors age, obesity, hypertension, diabetes mellitus, smoking, and dyslipidemia. PAOD screening was performed by the ankle-brachial index (ABI). The Mann-Whitney, chi-square, and Fisher's exact tests were used. Confidence Interval of 95% and a significance of 5%.*

RESULTS: *67.3% (n=105) males, 52.6% (n=82) elderly, 23.1% (n = 34) obese, 72.4% 6% (n=113) hypertensive, 34.6% (n=54) diabetics, 53.2% (n=83) smokers, 34.6% (n=54) dyslipidemic and 70.5% (n=110) with a family history of CAD. 16.7% (n=26) of the individuals presented PAOD. Three factors were associated with PAOD: age group ≥ 60 years (OR:3.656; p=0.005), diabetes mellitus (OR:2.625; p=0.024) and hypertension (OR:5,528; p=0.008). No significant difference was observed in the variables smoking, dyslipidemia, family history of CAD, and obesity.*

CONCLUSION: *The independent risk factors for PAOD were age, diabetes mellitus, and systemic arterial hypertension.*

KEYWORDS: *Ankle-brachial index. Peripheral vascular diseases. Risk factors.*

## INTRODUCTION

Cardiovascular diseases (CVDs) represent a public health problem with high rates of morbidity and mortality, causing 17.9 million deaths per year worldwide[1]. CVDs include coronary artery disease (CAD), cerebrovascular disease (CBVD), peripheral arterial occlusive disease (PAOD), and aortic atherosclerosis. CAD represents approximately a third of half of the total number of CVD cases[2]. Individuals with CAD are often diagnosed with PAOD, increasing their cardiovascular risk[3,4].

PAOD is a presentation with manifestations that are often asymptomatic[5] and can be diagnosed by the ankle-brachial index (ABI). This noninvasive method can provide early therapeutic interventions to reduce mortality and the risk of cardiovascular events[6].

ABI is the ratio between the systolic pressure of the ankle and the arm. When there is stenosis or obstruction near the site of pressure measurement, the index value in individuals with PAOD is less than or equal to 0.9. The ABI accuracy detects stenosis greater than

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or equal to 50% of the leg arteries with 75% sensitivity and 86% specificity[6,7].

Considering the magnitude of cardiovascular diseases worldwide, the importance of early identification of high-risk groups, and the need for intervention strategies, this study aimed to analyze the association between the ankle-brachial index and the main risk factors for coronary artery disease in individuals with coronariopathies.

## METHODS

### Study design

This is a cross-sectional observational study.

### Time and place of the study

The study was carried out in the Hospital Foundation of the Sugar and Alcohol Agro-industry of Alagoas, in Maceió - AL, involving patients treated between 2011 and 2014.

### Study population

The study population consisted of 156 patients, based on the following inclusion criteria: i) adult individuals with coronary artery disease (vessel with stenosis diameter ≥50% on cardiac catheterization examination), ii) with an indication for myocardial, percutaneous, or surgical revascularization, iii) asymptomatic or not for peripheral arterial occlusive disease. The following exclusion criteria were adopted: (i) individuals who had peripheral lesions that prevented the measurement of the ABI, such as lesions in a lower limb.

### Study variables

The following variables were analyzed: gender (male and female), age (<60 and ≥60), body mass index (BMI) (underweight, healthy, overweight, obesity grade I, II, and III), systemic arterial hypertension (SAH) (hypertensive and non-hypertensive), diabetes *mellitus* (diabetic and non-diabetic), smoking (smokers and nonsmokers), dyslipidemia (dyslipidemic and not dyslipidemic), family history of CAD (FH CAD) (with FH CAD and without FH CAD), and ankle-brachial index (ABI) (≤0.90 and >0.90).

The BMI was calculated based on the ratio between the body mass (kg) divided by the squared height ($m^2$). The cutoff values adopted for assessing the nutritional status were the ones proposed by the WHO: low weight (BMI <18.5 kg/$m^2$); appropriate weight (18.5≤ BMI <25 kg/$m^2$); overweight (25≤ BMI <30 kg/$m^2$); grade I obesity (30.0≤ BMI <35 kg/m2); grade II obesity (35.0≤ BMI <40 kg/m2); and grade III obesity (BMI ≥40.0 kg/$m^2$).

The following parameters were considered for the diagnosis of comorbidities and risk factors:

- SAH: arterial pressure >140/90 mmHg[8];
- DM: fasting glucose ≥126 mg/dl or if already in use insulin or any oral anti-diabetic drug[9];
- Dyslipidemia: total cholesterol levels ≥200 mg/dl and/or triglycerides ≥150 mg/dl[10];
- Smoker: an individual who smoked at least one cigarette per day over the previous month;
- FH CAD: self-reported (history of angina, myocardial infarction, coronary angioplasty, myocardial revascularization surgery, or sudden death of father, mother, siblings, and uncles).

### Research procedures

Initially, the individuals were approached and invited to participate in the research. At that moment, we explained the objectives and procedures of the research, and they signed the Informed Consent Form (ICF). In the next step, demographic data were collected using a form designed specifically for this purpose. In the third step, we took measurements of weight and height and measured the systolic pressure in the ankle and arm for the BMI and ABI calculations, respectively.

The measurement of the ABI was taken while the patient was in dorsal decubitus. The systolic blood pressure (SBP) was measured in both the upper limb and lower limb. The measurement of the SBP for calculating the ABI was done with a Microlife BP3AC1-1PC device. The ABI calculation was obtained by the ratio of the higher systolic blood pressure (SBP) of the posterior tibial artery and/or dorsal artery of the foot, with the higher SBP of the brachial arteries, bilaterally, always considering the lower ABI. The ABI was considered abnormal when ≤0.90.

### Statistical treatment

The data were stored in a Microsoft Excel® database and analyzed using the statistical package SPSS 22.0 (SPSS Inc., Chicago, USA). The normality of the data was initially evaluated using the Kolmogorov-Smirnov test. Continuous variables were described as mean and standard deviation and categorical variables as simple and relative frequencies. The ABI was categorized into ≤0.90 and >0.90 for the association

analysis. The comparison of the ABI values, based on the presence/absence of risk factors, was performed using the Mann-Whitney U-test. The association was tested by the chi-square or Fisher's exact test, as indicated. We also calculated the odds ratio. We considered a confidence interval of 95% (95% CI) and 5%. significance.

### Ethical aspects

The research was approved by the Research Ethics Committee of the Hospital Foundation of the Sugar and Alcohol Agro-industry of Alagoas, Decision No. 001/2011.

## RESULTS

Of the 156 patients studied, the mean age was 60.1 years (SD ± 10.0), and 67.3% (n=105) were males. Among the risk factors, 41% (n=64) were overweight and 23.1% (n=36) obese (the average weight was 72.7±13.8), 72.4% (n=103) were hypertensive, 34.6% (n=54) had diabetes *mellitus*, 53.2% (n=83) were smokers, and 34.6% (n=54) had dyslipidemia; 70.5% (n=110) had a history of coronary artery disease, and 16.7% (n=26) had ABI ≤0.90 and were, therefore, diagnosed with PAOD (Table 1).

Among the risk factors evaluated, the Mann-Whitney U-test showed that the ABI median values were lower among the elderly, diabetic, and hypertensive patients (p<0.001). No significant difference was observed in the ABI values regarding the variables smoking, dyslipidemia, family history of CAD, and obesity (Figure 1).

The factors associated with PAOD (ABI ≤0.90) were age greater than or equal to 60 years (OR 3.656; 95% CI 1.38-9.69), presence of diabetes (OR 2.625; 95% CI 1.11-6.18), and systemic arterial hypertension (OR 5.528; 95% CI 1.25-24.51) (Table 2).

## DISCUSSION

The study analyzed the association between ABI and the main risk factors for PAOD. The prevalence of PAOD was 16.7% (n=26) and the main factors associated with it were age, diabetes *mellitus,* and systemic arterial hypertension.

Among the elderly population, the development of PAOD is attributed to changes in the blood vessel walls, interfering in the perfusion of tissues with a reduction of nutrients and oxygen. These changes make the vessels more rigid, resulting in increased peripheral resistance[11]. In a study conducted in Africa involving 483 patients, 68.60% of those with PAOD were aged over 60 years (OR 2.03; p=0.004)[12]. Similar results were also observed in Brasil, where the average age of the population with ITB ≤0.9 was 73 years, with a significant association (OR 1.07; p<0.001)[13].

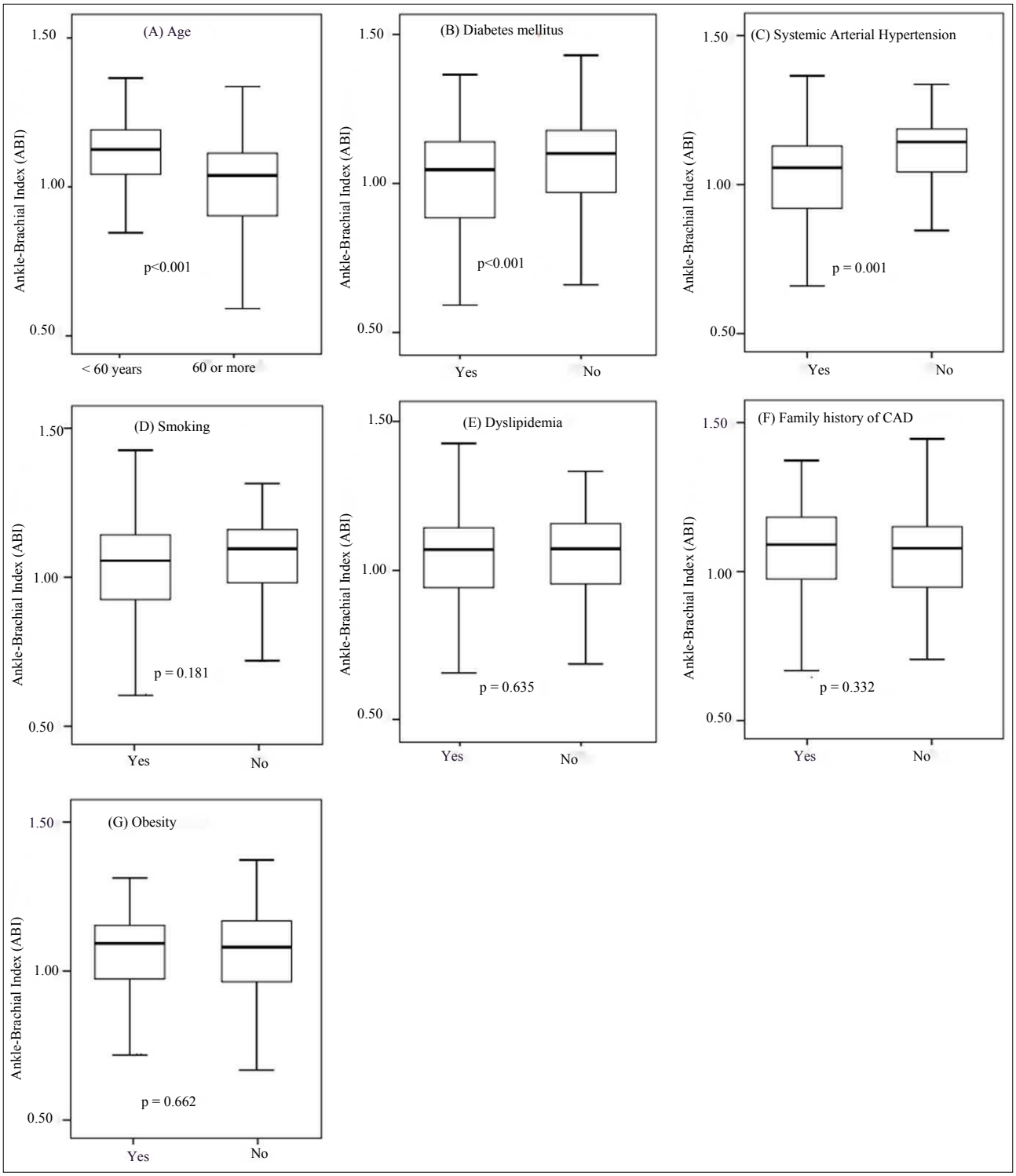
The second risk factor for PAOD relates to the presence of diabetes *mellitus*. The prolonged state of hyperglycemia in diabetes results in damage to the endothelial cells of blood vessels, thrombosis, and lipid deposition, with the additional formation of atherosclerotic plaque[14]. In a national study with 1,610

**TABLE 1.** SOCIODEMOGRAPHIC CHARACTERIZATION OF INDIVIDUALS WITH CORONARY ARTERY DISEASE (CAD) INCLUDED IN THE STUDY, ALAGOAS, BRASIL, 2019. (N=156)

| Variable | n | % |
|---|---|---|
| Sex | | |
| Male | 105 | 67.3 |
| Female | 51 | 32.7 |
| Age range | | |
| <60 | 74 | 47.4 |
| ≥60 | 82 | 52.6 |
| Mean ± SD | 60.1 ± 10.0 | |
| Body mass index (BMI) | | |
| Low weight | 2 | 1.3 |
| Normal | 54 | 34.6 |
| Overweight | 64 | 41.0 |
| Obesity grade 1 | 28 | 18.0 |
| Obesity grade II | 8 | 5.1 |
| Obesity grade III | 0 | 0.0 |
| Mean ± SD | 72.7 ± 13.8 | |
| Systemic arterial hypertension (SAH) | | |
| Hypertensive | 113 | 72.4 |
| Not hypertensive | 43 | 27.6 |
| Diabetes mellitus | | |
| Diabetic | 54 | 34.6 |
| Non-diabetic | 102 | 65.4 |
| Smoking | | |
| Smoker | 83 | 53.2 |
| Non-smoker | 73 | 46.8 |
| Dyslipidemia | | |
| Dyslipidemic | 54 | 34.6 |
| Not dyslipidemic | 102 | 65.4 |
| Family history of CAD (FH CAD) | | |
| With FH CAD | 110 | 70.5 |
| No FH CAD | 46 | 29.5 |
| Ankle-brachial index (ABI) | | |
| ≤0.90 | 26 | 16.7 |
| >0.90 | 130 | 83.3 |

Legend: CAD: Coronary artery disease.

**FIGURE 1**




individuals, 41.2% of patients with PAOD had diabetes (OR 8.77; p<0.001)[15]. An investigation by Saleh et al.[16] conducted in the Middle East involving 2,120 patients found diabetes as a factor associated with an increased risk for PAOD, however, with a lower OR than that found in our study (OR 1.827; p=0.04).

Hypertension is a third factor associated with a low ABI. It is believed that high-pressure levels result in a dysfunction of blood vessel endothelial cells, increasing the PAOD risk[17]. In a study conducted with 100 patients of a tribe in India, hypertensive individuals presented an odds ratio 3.71 times higher of developing PAOD when compared to normotensive individuals[17]. Similar results were also observed in pre-hypertensive individuals, whose OR was 3.28, in a comparative study with normotensive individuals[18].

Although smoking is another risk factor, only 20.5% (n=17) of smokers presented PAOD (ABI ≤0.90),

with no significant association (p=0.173). This non-significance also was reported by Sarmento et al.[13], whose smoking rate was 18.8%. Data from the 2018 Vigitel survey show advances in the reduction of smoking in Brasil: between 2006 and 2017, the proportion of smokers decreased from 15.7% to 10.1%, and adults who smoke 20 or more cigarettes per day decreased from 4.6% to 2.6%[19].

In a retrospective cohort study conducted in Matsumoto, Japan, with 3,056 patients hospitalized for cardiovascular disease between 2005 and 2012, 41% of individuals with ABI ≤0.90 presented dyslipidemia[20], corroborating our study, in which 38.46% of individuals with PAOD were dyslipidemic. However, although dyslipidemia is a risk factor, the data did not present statistical significance. It is possible that the size of the POAD population could have influenced the results of the regression.

Most individuals with POAD had a family history of CAD (61.53%; n=16), but there was no significant association (OR 0.613; CI 0.25-1.47). Similar results were observed in a cross-sectional study with 250 individuals in a district of Izmir, Turkey, in which 49.2% (n=123) of individuals with POAD had a family history of CAD[21], and in research performed in Porto Alegre-RS, in which the ratio was 56.6% (n=17)[22].

Although the literature points to obesity as an important risk factor, in our study, only 26.92% (n=7) of individuals with PAOD were obese, with no significant association. Similar results were reported in a recent Italian study involving 319 patients, in which the odds ratio was 0.98 (p=0.20)[23], and in the study conducted by Kock et al.[24] on 93 elderly patients treated in the specialty outpatient clinic of the University of Southern Santa Catarina (p=0.551).

Even when considering the methodology adopted, the study has limitations, among which stand out the size of the population, time of diagnosis, and severity of the cases. In this study, only 26 individuals presented PAOD, which may have compromised the statistical results.

**TABLE 2.** RISK FACTORS FOR PERIPHERAL ARTERIAL OCCLUSIVE DISEASE (PAOD) IN THE POPULATION STUDIED. ALAGOAS, BRASIL, 2019. (N=156)

| Variable | ABI | | p-value[1] | OR[2] | CI 95% |
|---|---|---|---|---|---|
| | ≤0.90 n=26 (16.7%) | >0.90 n=130 (83.3%) | | | |
| Sex | | | | | |
| Male | 15 (14.3) | 90 (85.7) | 0.252 | 0.606 | 0.26-1.43 |
| Female | 11 (21.6) | 40 (78.4) | | | |
| Age range* | | | | | |
| <60 | 6 (8.1) | 68 (91.9) | 0.005 | 3.656 | 1.38-9.69 |
| ≥60 | 20 (24.4) | 62 (75.6) | | | |
| Diabetes mellitus* | | | | | |
| Yes | 14 (25.9) | 40 (74.1) | 0.024 | 2.625 | 1.11-6.18 |
| No | 12 (11.8) | 90 (88.2) | | | |
| Systemic arterial hypertension (SAH)* | | | | | |
| Yes | 24 (21.2) | 89 (78.8) | 0.008 | 5.528 | 1.25-24.51 |
| No | 2 (4.7) | 41 (95.3) | | | |
| Smoker | | | | | |
| Yes | 17 (20.5) | 66 (79.5) | 0.173 | 1.832 | 0.76-4.41 |
| No | 9 (12.3) | 64 (87.7) | | | |
| Dyslipidemias | | | | | |
| Yes | 10 (18.5) | 44 (81.5) | 0.652 | 1.222 | 0.51-2.91 |
| No | 16 (15.7) | 86 (84.3) | | | |
| Family history of CAD | | | | | |
| Yes | 16 (14.5) | 94 (85.5) | 0.272 | 0.613 | 0.25-1.47 |
| No | 10 (21.7) | 36 (78.3) | | | |
| Obesity | | | | | |
| Yes | 7 (19.4) | 29 (80.6) | 0.610 | 1.283 | 0.491-3.35 |
| No | 19 (15.8) | 101 (84.2) | | | |

Legend: *Statistical significance (p<0.05); [1] Chi-square or Fisher exact; [2] Odds Ratio

## CONCLUSION

The study showed an association between the presence of PAOD and age, the presence of diabetes *mellitus* and arterial hypertension. Therefore, the utilization of the ABI to identify and stratify the risks of asymptomatic PAOD in CAD patients is a tool that should be valued in clinical practice. In addition, further studies with a larger population should be conducted to clarify the effects of dyslipidemia, smoking, family history, and obesity on the risk of PAOD.

### Contribution of the authors

Carlos Dornels Freire de Souza, Saulo Henrique Salgueiro de Aquino, Isabelle Tenório Melo, Francisco de Assis Costa: Participated in the development of the concept, planning of the study, data collection and analysis, discussion of the results, scientific writing, as well as in the review and approval of the final version of the work.


## RESUMO

OBJETIVO: *Analisar a associação entre o ITB e os principais fatores de risco para doença arterial coronariana em indivíduos coronariopatas.*

MÉTODOS: *Foram selecionados 156 pacientes adultos de um hospital de Maceió, Alagoas. Foram avaliados como fatores de risco idade, obesidade, hipertensão, diabetes mellitus, tabagismo e dislipidemia. A triagem da DAOP foi realizada pelo índice tornozelo-braquial (ITB). Foram utilizados os testes de Mann-Whitney, qui-quadrado e exato de Fisher. Intervalo de Confiança de 95% e significância de 5%.*

RESULTADOS: *67,3% (n=105) do sexo masculino, 52,6% (n=82) idosos, 23,1% (n=34) obesos, 72,4% (n=113) hipertensos, 34,6% (n=54) diabéticos, 53,2% (n=83) tabagistas, 34,6% (n=54) dislipidêmicos e 70,5% (n=110) com história familiar de DAC; 16,7% (n=26) dos indivíduos apresentaram DAOP. Três fatores foram associados à DAOP: faixa etária ≥60 anos (OR:3,656; p=0,005), diabetes mellitus (OR:2,625; p=0,024) e (OR:5,528; p=0,008). Não foi observada diferença significativa nas variáveis tabagismo, dislipidemia, história familiar de DAC e obesidade.*

CONCLUSÃO: *Os fatores de risco independentes para DAOP foram idade, diabetes mellitus e hipertensão arterial sistêmica.*


PALAVRAS-CHAVE: *Índice tornozelo-braço. Doenças vasculares periféricas. Fatores de risco.*

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ORIGINAL ARTICLE

# Psychological distress and its associated risk factors among university students

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## SUMMARY

OBJECTIVE: *Psychological distress is an important mental health problem among university students. The goal of this study was to determine psychological distress and its associated risk factors among students in the Anhui province.*

METHODS: *A cross-sectional study was conducted in a sample of 1304 students. In this study, a self-administered questionnaire consisting of the general demography and General Health Questionnaire (GHQ-12) was completed. Psychological distress was assessed using the GHQ-12-item questionnaire. A dichotomous category split was imposed on the GHQ-12 for the purpose of analysis. A GHQ-12 score of 4 or higher indicated psychological distress. The data were analyzed by SPSS 20.0 system.*

RESULTS: *A total of 1304 samples were analyzed in this study. The results indicated that the education level of the father and mother was associated with the students' psychological distress (P<0.001). A significant association was found between high-intensity exercise and low-intensity exercise and psychological distress. However, no significant difference was identified between gender and psychological distress (P=0.173).*

CONCLUSION: *The education level of parents, high-intensity exercise, and low-intensity exercise were associated with psychological distress. Our results suggest that it is indispensable to raise awareness of psychological disorders and its associated risk factors among university students. Further studies are required to develop appropriate interventions for high-risk groups.*

KEYWORDS: *Stress, psychological. Risk factors. Students. Universities.*

## INTRODUCTION

Psychological distress is common worldwide[1,2]. The characteristics of psychological distress include lack of enthusiasm, desperation about the future, and symptoms of anxiety[3]. The prevalence of psychological distress varies with country. About 50% of university students in Italy suffer from psychological distress[4], about 40% in the UK[5], and 50% in Spain[5]. It is predicted that a quarter of the global population will be affected by depressive symptoms at some stage in their life. More than 1/3 of undergraduates suffer from some type of dysfunction due to psychological distress, and nearly 1/10 students have considered attempting suicide, according to the American National College Health Assessment[6].

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Psychological distress has become an important public health problem.

Psychological distress among undergraduates was associated with a variety of factors across various domains such as economics, social communication, academic pressure, and coping skills. The rapid development of higher education and high expectations has brought great pressure to students[7,8]. However, discussions about psychological distress are limited and mostly conducted in Western societies[9].

Psychological distress and its related factors vary across the globe. It is more prevalent among females than males10, and family support has been inextricably linked with it[11]. However, there are few studies on the mental health of Chinese college students[12].

Psychological distress is an important mental health problem among university students[9]. The objective of this study was to determine the risk factors of psychological distress. The results indicated that the education level of parents, low- and high-intensity exercise were associated with psychological stress.

## METHODS

### Samples

The presented study was conducted with a cross-sectional design. A self-reported questionnaire was completed by 1310 university students. Written informed consent was obtained from all subjects.

### Measurement instruments

The general demographic questionnaire, General Health Questionnaire (GHQ) scale, low-intensity and high-intensity exercise were used to measure the mental health of students in this study. The demographic characteristics of respondents mainly included gender, age, education level of the father and mother, location, household income, and exercise. GHQ was used to measure mental health[13], the Likert four scale[14] was adopted to calculate the score of GHQ. This scale consisted of 12 items, and the score of each item ranged from 1 to 4. The total score of the GHQ-12 was the sum of the score of each item. A total GHQ-12 score of 4 or above was defined as psychological distress.

Low-intensity exercise was defined as at least 20 minutes or more of sports such as walking or shadowbox. In terms of low-intensity exercise frequency, n=232 (17.8%) "never exercised", while n=718 (55.1%) exercised "1 to 2 times per week", n=270 (20.7%) exercised "3 to 4 times per week", and n=84 (6.4%) "More than 5 times per week". High-intensity exercise was defined as at least 20 minutes or more of sports such as playing ball or running.

### Statistical analysis

Statistical analyses were performed using SPSS 20.0 (Inc. Chicago, IL, USA). Descriptive analysis was conducted for the distribution of characteristics of the subjects included. The Chi-squared test was applied to analyze the correlation of psychological distress with its associated risk factors.

## RESULTS

The descriptive statistics of the subjects are shown in Table 1. Out of the total 1304 subjects, 463 were male and 841 were female. A total of 903 (69.2%) respondents were from rural areas. A total of 1072 (82.2%) participants reported practicing low-intensity exercises at least once a week (Table 1). In addition, a total of 1062(81.4%) subjects showed psychological distress. Table 2 shows the association of psychological distress with the characteristics of the subjects. The results indicated that the education level of parents was significantly associated with psychological distress (P=0.001). Another interesting finding was that the students whose parents had middle-school or lower education were more likely to have psychological distress. A significant association of low-intensity exercise (P=0.034) and high-intensity exercise (P=0.003) with psychological distress was also found in this work. The results also identified that the frequency of exercise per week was associated with psychological distress. However, no significant association was detected between psychological distress and gender (P=0.162).

The distribution of the GHQ-12 score is shown in Figure 1.

## DISCUSSIONS

The aim of the current study was to determine the psychological distress and its associated risk factors among university students. The study found that factors affecting psychological distress included education level of parents, low-intensity and high-intensity exercise. Our results also showed that more than half of the participants in our study presented psychological distress, and about 81.4% of 1304 scored 4 or above in the GHQ-12. The prevalence of psychological distress in studies from other countries was lower than

our results. For example, about 55.5% in Singapore[15] and 46.2% in Malaysia[16] had psychological distress. The possible reason may be that the instruments used to measure psychological stress are different. Therefore, predictors of psychological stress among students need further investigation.

The finding of this study was that the prevalence of psychological distress among female students is higher than among males, though no statistical significance was identified. This is similar to that found by another study in Australian undergraduate students[17]. Whereas prospective symptom checklist -90 studies showed that Chinese male college students have more psychological distress[18]. This study indicates that we should pay attention to regional, cultural, and corresponding measurement tools when studying gender differences and psychological stress.

Another finding of the study was that the education level of parents was associated with the psychological stress of students, which was consistent with the results of an American study[17]. Although the education level of parents and income levels are often correlated, in a nationally representative longitudinal study of young adults in the US, the effect of parents' low education on adult depression symptoms was self-abasement, whereas the effect of parental low income was not inferior[17]. Students whose parents were less educated were prone to psychological stress[19].

Additionally, an association of low-intensity and high-intensity exercise with psychological distress was found in the present study. Evidence from a previous study identified that high-intensity exercise was helpful for reducing psychological stress[20]. The useful submission from the findings was that self-reported exercise was credible for epidemiology studies.

Some limitations may also exist in the study. A shortcoming of the cross-sectional design was the failure to explore the cause-result relationship. Thus, further longitudinal studies are still required to examine the impact of low-intensity and high-intensity exercise

**TABLE 1.** SOCIODEMOGRAPHIC CHARACTERISTICS OF THE STUDY SAMPLE (N = 1304)

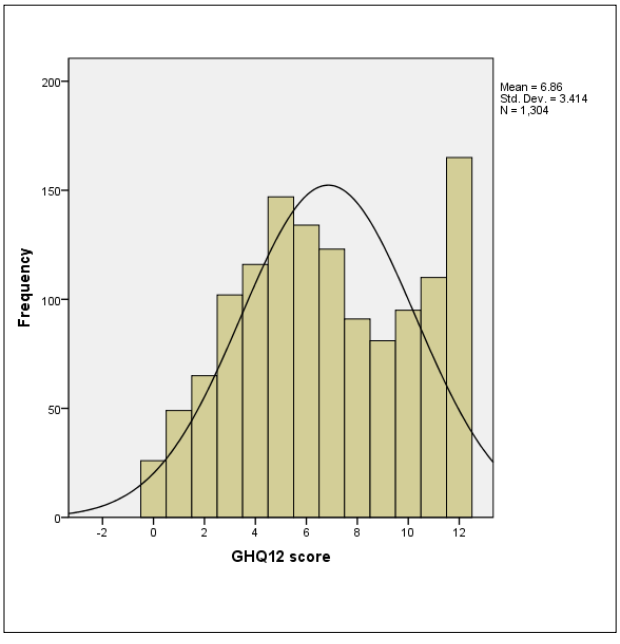
| | Variable | Frequency | Percentage (%) |
|---|---|---|---|
| Gender | Male | 463 | 35.5 |
| | Female | 841 | 64.5 |
| Grade | One | 680 | 52.1 |
| | Two | 373 | 28.6 |
| | Three | 189 | 14.5 |
| | Four | 61 | 4.7 |
| | Graduate year 1 | 1 | 0.1 |
| Father education | Primary school and low | 243 | 18. |
| | Middle school | 895 | 68.6 |
| | College and above | 165 | 12.7 |
| Mother education | Primary school and low | 583 | 44.7 |
| | Middle school | 619 | 47.5 |
| | College and above | 100 | 7.7 |
| Location | Rural area | 903 | 69.2 |
| | Urban area | 400 | 30.7 |
| Income | < 10000 | 327 | 25.1 |
| | 10000-30000 | 426 | 32.7 |
| | 30000-60000 | 390 | 29.9 |
| | > 60000 | 156 | 12.0 |
| Low-intensity exercise | never | 232 | 17.8 |
| | 1 to 2 times per week | 718 | 55.1 |
| | 3 to 4 times per week | 270 | 20.7 |
| | More than 5 times per week | 84 | 6.4 |
| High-intensity exercise | never | 522 | 40.0 |
| | 1 to 2 times per week | 604 | 46.3 |
| | 3 to 4 times per week | 127 | 9.7 |
| | More than 5 times per week | 51 | 3.9 |
| GHQ dichotomy | < 4 | 242 | 18.6 |
| | ≥4 | 1062 | 81.4 |

**TABLE 2.** PSYCHOLOGICAL DISTRESS AND ITS ASSOCIATED RISK FACTORS EVALUATION VALUE

| Variable | | GHQ < 4 | GHQ≥4 | Chi-Square value | P-value |
|---|---|---|---|---|---|
| Gender | male | 70 | 393 | 1.957[a] | 0.162 |
| | female | 104 | 737 | | |
| Grade | One | 81 | 599 | 1.397 | 0.237 |
| | Two | 61 | 312 | | |
| | Three | 19 | 170 | | |
| | Four | 13 | 48 | | |
| | Graduate year 1 | 0 | 1 | | |
| Father education | Primary school and below | 23 | 220 | 11.740 | 0.001 |
| | Middle school | 115 | 780 | | |
| | College and above | 36 | 129 | | |
| Mother education | Primary school and below | 59 | 524 | 12.073 | 0.001 |
| | Middle school | 94 | 525 | | |
| | College and above | 21 | 79 | | |
| Location | Rural area | 110 | 793 | 3.066[a] | 0.080 |
| | Urban area | 63 | 337 | | |
| Income | < 10000 | 41 | 286 | 0.810 | 0.368 |
| | 10000-30000 | 57 | 369 | | |
| | 30000-60000 | 50 | 340 | | |
| | > 60000 | 26 | 130 | | |
| Low-intensity exercise | never | 24 | 208 | 4.514 | 0.034 |
| | 1 to 2 times per week | 95 | 623 | | |
| | 3 to 4 times per week | 38 | 232 | | |
| | More than 5 times per week | 17 | 67 | | |
| High-intensity exercise | never | 53 | 469 | 8.666 | 0.003 |
| | 1 to 2 times per week | 88 | 516 | | |
| | 3 to 4 times per week | 24 | 103 | | |
| | More than 5 times per week | 9 | 42 | | |

Note: "a" represents Pearson Chi-Square

**FIGURE 1.** THE DISTRIBUTION OF GHQ-12 SCORES AMONG PARTICIPANTS




on psychological stress. Additionally, the population of this study is small and relatively uniform, future studies should recruit more students from different universities and regions.

## CONCLUSIONS

The education level of parents, high-intensity, and low-intensity exercise were associated with psychological distress. Our results suggest that it is indispensable to raise awareness about psychological disorders and its associated risk factors among university students. Further studies should be developed.

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## Disclosure

The authors declare no conflict of interest.

## Author Contributions

Conceived and designed the experiments; Baohong Xue and Dexun Zhao. Performed the experiments; Tingting li, Xu Zhang, Rui Wang, and Dexun Zhao. Analyzed the data; Lianping He. Wrote the paper; Tingting Li and Mingming Chen.


## RESUMO

OBJETIVO: *O estresse psicológico é um importante problema de saúde mental entre estudantes universitários. O objetivo deste estudo foi determinar o estresse psicológico e seus fatores de risco associados entre os estudantes na província de Anhui.*

MÉTODOS: *Um estudo transversal foi realizado entre uma amostra de 1.304 indivíduos. Nesse estudo, foi preenchido um questionário autoaplicável que consiste na demografia geral e no Questionário Geral de Saúde (GHQ-12). O problema psicológico foi avaliado utilizando o questionário GHQ de 12 itens. Uma divisão dicotômica de categoria foi imposta ao GHQ-12 para efeito de análise. Uma pontuação de quatro ou mais no GHQ-12 mostrava que um indivíduo tem problemas psicológicos. Os dados foram analisados pelo software SPSS 20.0.*

RESULTADOS: *Um total de 1.304 amostras foi analisado neste estudo. Os resultados indicaram que o nível de educação do pai e da mãe estava associado com estudantes em estresse psicológico (P<0,001). Foi encontrada uma associação significativa entre o exercício de alta intensidade e o exercício de baixa intensidade com o estresse psicológico. No entanto, não foi identificada qualquer diferença significativa entre o gênero e o estresse psicológico (P=0,173).*

CONCLUSÃO: *O nível de educação dos pais, exercícios de alta intensidade e exercícios de baixa intensidade foram associados com estresse psicológico. Nossos resultados sugerem que é indispensável aumentar a sensibilização para as perturbações psicológicas e para os fatores de risco associados aos estudantes universitários. São necessários mais estudos para desenvolver intervenções adequadas para grupos de alto risco.*


PALAVRAS-CHAVE: *Estresse psicológico. Fatores de risco. Estudantes. Universidades.*

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ORIGINAL ARTICLE

# Multidisciplinary teams: perceptions of professionals and oncological patients

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## SUMMARY

*Multidisciplinary teams are increasingly employed to treat cancer patients. This study aimed to evaluate the perception of physicians, other health care professionals, and hospitalized oncological patients regarding the multidisciplinary teams of the public and private sector. In total, 18 doctors were interviewed; 63 health professionals and 120 cancer patients. Satisfaction with the work of the multidisciplinary team was positive among patients and physicians (averages of 89.4% and 66.82% respectively), but higher among patients ($p < 0.0001$), among women rather than men (averages of 77.5% and 85.21% respectively, $p < 0.0001$), elderly individuals in comparison with adults (averages of 91.98% and 76.01% respectively, $p < 0.0001$), and in the public sector in comparison with the private sector (averages of 83.12 and 70.74 respectively, $p < 0.0001$). The results demonstrate that despite the difference between groups, patients and members of multidisciplinary groups were satisfied with multidisciplinary care, and some groups, such as elderly women from public services, may especially benefit from multi-professional groups.*

KEYWORDS: *Patient care team. Integrality in Health. Medical Oncology.*

## INTRODUCTION

The current health care model has proven unable to explain and respond to the population's health and disease processes[1]. Thus, the current General Work Program has prioritized strategies to ensure healthy living and promote general well-being, aiming to achieve universal health coverage[2]. In this strategy, practices should not be limited to the disease but take into account historical-cultural factors[3].

In the search for promoting the health of cancer patients, a multidisciplinary team of professionals, consisting of doctors, nurses, physical therapists, nutritionists, speech therapists and/or occupational therapists interact with a common goal. The coordination, communication, and decision-making between the members of the health team and patients undergoing cancer treatment can be improved when this type of approach is exploited[4]. However, since the concept of a multidisciplinary team is relatively new, there is no clear definition of its format[5]. Patient satisfaction has been shown to be positive when the teamwork is organized, multidisciplinary, agile, and efficient in care[6]. In this context, communication is extremely relevant in the therapeutic relationship between the team and the patient and aims to provide trust so that an effective assistance relationship can be achieved[7].

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Among healthcare systems worldwide, the Single Health System (SUS) is one of the greatest public ones; it is universal and the only one to ensure full assistance that is completely free[8]. However, the system presents major structural problems that hinder health promotion[9]. Such problems make SUS, which was conceived as a free and universal system, in, reality, a public system[10].

There are public and private policies that determine the procedures and processes to be offered for cancer patients during their treatment and follow-up. One of the more complex processes in the care of cancer patients is a multidisciplinary approach. This work evaluated the satisfaction of patients and health professionals involved in multidisciplinary teams both in the private and public sectors.

## METHODS

From June 2017 to July 2018, the perception of patients and healthcare professionals was evaluated through a questionnaire regarding their multidisciplinary activities in the period of cancer patient hospitalization. The patients selected were diagnosed with some type of neoplasia (lung, sarcoma, central nervous system, digestive tract, head and neck, hematological, gynecological, urological, colorectal or hidden), hospitalized for 24 hours or more in one of the following public or private hospitals in the state of São Paulo: Hospital de Ensino Padre Anchieta (public), Hospital Estadual Mario Covas (public), Hospital Alemão Oswaldo Cruz (private), and Instituto Brasileiro de Controle ao Câncer (private), and were followed-up by a multidisciplinary team (physicians, nurses, pharmacists, physical therapists, speech therapists, nutritionists, psychologists, and social workers)

Each member of the multidisciplinary team responded to a questionnaire containing eight questions to evaluate the perception of communication between the members of the multidisciplinary team, the benefits of multidisciplinary meetings, the work dynamics, and the interaction between different health professionals during the treatments. Oncologic patients also received a questionnaire with eight questions that sought to evaluate the patient's perception regarding the respect and concern of the multidisciplinary team with their health status, and if they were informed about their health condition and the possible treatments. The questions on satisfaction and dissatisfaction were to be answered with a "yes" or "no", and the level of acceptance was calculated per individual in percentages.

The normality of the samples was tested using the Kolmogorov-Smirnoff test. The quantitative variables with non-normal distribution were tested using the Mann-Whitney test, and categorical variables were analyzed by the chi-square test. The comparison between the level of acceptance of each group assessed and the categorical variables of gender, age (adult or elderly), and type of assistance (public or private) were analyzed by one-way ANOVA. All analyzes were performed using the R software.

## RESULTS

We included 81 members of multidisciplinary teams (18 of the medical team, eight of the nursing team, 21 pharmacists, two physical therapists, 11 speech therapists, 17 nutritionists, two psychologists, and two social workers), composed exclusively by adult individuals (87.7% men and 17.2% women). We evaluated 120 patients (52.5% men, 47.5% women; 55.8% adults and 44.2% elderly), with different types of neoplasm (lung [10], sarcoma [3], central nervous system [5], digestive tract [11], head and neck [10], hematological [18], gynecological [17], urological [15], colorectal [10], hidden [2]), and only 5.8% of the patients were treated in the private service, against 94.2% in the public service. We observed significant differences in gender and age between members of the multidisciplinary team and the group of patients ($Chi^2$=19.32; $p < 0.001$; $Chi^2$=48.58; $p \leq 0.001$) (Table 1).

We observed greater satisfaction with multidisciplinary care among the patients than among the members of the multidisciplinary team (averages of 89.4% and 66.82%, respectively, F=96.726, $p \leq 0.001$); among women than among men (mean of 77.5% and 85.21%, respectively, F=7.5697, $p \leq 0.001$); among elderly people than adults (average of 91.98% and 76.01%, respectively, F=30.668, $p \leq 0.001$); and in public than private care (average of 83.12% and 70.74%, respectively, F=15.896, $p \leq 0.001$). We did not observe significant differences in satisfaction among patients according to their types of neoplasia and staging (Diagnosis: F=0.87188, p=0.56168, Staging: F=0.74794, p=0.58925).

## DISCUSSION

The optimal medical management includes discussions about the *status* of the disease and treatment

plan[11,12]. Communication between the patients and the team is essential to ensure that these discussions are fruitful for the patients[13]. In this study, the patients showed a high level of satisfaction with the multidisciplinary team, which may reflect a good understanding of their individual therapeutic plan. In the literature, important factors of patient perception include empathy, the provision of hope, and active listening for effective communication with the patient[14].

The satisfaction of physicians in relation to the multidisciplinary team was lower than that of patients, but still positive (66.82%), which may reflect good communication within the team. We noticed that among the experts there is greater recognition of the importance of the multidisciplinary team and of communication as an essential element in patient care and for families under palliative care[15,16]. However, studies show that doctors believe that, in the context of a multidisciplinary approach, more precise information is provided to patients, but, despite that, interestingly, they do not show a clear preference for a multidisciplinary environment[17]. Therefore, the unclear preference for participation in multidisciplinary teams should be further investigated. Perhaps the participation in multidisciplinary teams requires additional time and effort from its members, which could hinder its more widespread acceptance by health professionals.

The patients who showed greater satisfaction with the multidisciplinary team were female, elderly, and treated by public services. Between genders, female patients with cancer are more prone to suffer from psychosocial problems[18], which could explain the perception of greater satisfaction among female patients due to the attention they receive from the multidisciplinary team. As to the level of acceptance among the elderly, evidence of interest and concern by the professionals are aspects that increase satisfaction[19,20].

There is a significant association of care provided by the Unified Health System (SUS) with some demographic profiles, such as the predominance of women, children, black and brown patients, low schooling, and income[21]. In relation to patients' satisfaction with the multidisciplinary team in connection with the type of health care system, patients from the public sector presented the greatest satisfaction. In relation to the members of the multidisciplinary team, studies

**TABLE 1.** SOCIODEMOGRAPHIC CHARACTERISTICS AND ACCEPTANCE BY THE MULTIDISCIPLINARY TEAM AND GROUP OF PATIENTS

| Characteristics | Multidisciplinary team N=81 | Patients N=120 | Test | p-value | |
|---|---|---|---|---|---|
| Gender N (%) | Male | 67 (82.7) | 63 (52.5) | 19.32[a] | 0.001* |
| | Female | 14 (17.2) | 57 (47.5) | | |
| Care N (%) | Private | 40 (49.3) | 7 (5.8) | 51.19[a] | 0.001* |
| | Public | 41 (50.6) | 113 (94.2) | | |
| Age group N (%) | Adult | 81 (100) | 67 (55.8) | 48.58[a] | 0.001* |
| | Elderly | 0 (0) | 53 (44.2) | | |
| Level of approval | Good | 66.82 | 89.27 | -8.91[B] | 0.001* |
| | Bad | 31.79 | 10.63 | | |
| **Good level of approval - Team** | | | | | |
| Age | Adult | 66.82 | NE | NE | NE |
| | Elderly | - | NA | | |
| Care | Public | 67.99 | NE | 0.798[C] | 0.374 |
| | Private | 65.63 | NE | | |
| Gender | Male | 66.60 | NE | 0.127[C] | 0.722 |
| | Female | 67.86 | NE | | |
| **Good level of approval - Patient** | | | | | |
| Age | Adult | NA | 91.98 | 2.15[C] | 0.145 |
| | Elderly | NA | 87.13 | | |
| Care | Public | NA | 100 | 2.65[C] | 0.106 |
| | Private | NA | 88.61 | | |
| Gender | Male | NA | 89.09 | 0.014[C] | 0.907 |
| | Female | NA | 89.47 | | |

[a] Chi-square test; [b] Mann-Whitney test; [c] Anova One-way test; * p>0.001; NA - Not applicable

have shown that professionals who work in SUS have professional satisfaction regarding their relationships with patients and colleagues, but may be dissatisfied with the environment and work conditions, agility in examinations and measurements, among other things[22]. Probably, the satisfaction among patients cared by SUS may reflect greater attention received by each patient, considering the sum of visits from each team professional in a context of assistance to a larger number of patients.

The introduction of a multidisciplinary team is an important factor to improve survival rates[23,24]. Studies on the perception of patients and multidisciplinary teams can promote a reflection on actions to improve their functioning and care itself, as was the case, for example in the United Kingdom, where, after changes in the work plan, there was extremely high satisfaction among patients (94%)[5].

## CONCLUSION

This study demonstrates a positive perception from cancer patients and the medical staff in relation to multidisciplinary teams, including factors that can interfere in perception, such as gender, age, and type of care (public and private). Elderly women who were assisted by public services seem to be the ones who derive more satisfaction from this approach.


## RESUMO

*Equipes multidisciplinares têm sido cada vez mais empregadas no tratamento de pacientes com câncer. Este estudo buscou avaliar a percepção de médicos, profissionais e pacientes oncológicos internados em relação à sua interação com a equipe multidisciplinar tanto no setor público quanto no privado. Entrevistamos 18 médicos, 63 profissionais da área da saúde e 120 pacientes oncológicos. Em relação ao trabalho da equipe multidisciplinar, a percepção foi positiva entre os pacientes e os médicos (médias iguais a 89,4% e 66,82%, respectivamente), mas maior entre os pacientes (p<0,001), maior entre as pacientes mulheres do que entre os homens (médias de 77,5% e 85,21%, respectivamente, p<0,001), maior entre os idosos do que entre os adultos (médias de 91,98% e 76,01%, respectivamente, p<0,0001), e maior no setor público do que no setor privado (médias de 83,12% e 70,74%, respectivamente, p<0,0001). Os resultados demonstram que apesar da diferença entre grupos, tanto pacientes como membros dos grupos multidisciplinares apresentaram satisfação com o atendimento multidisciplinar, e alguns grupos, como mulheres idosas cuidadas em serviços públicos, poderão especialmente ter um impacto maior de grupo multiprofissionais.*


PALAVRAS-CHAVE: *Equipe de assistência ao paciente. Integralidade em saúde. Oncologia.*

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ORIGINAL ARTICLE

# Comparison of Cohen and Lich-Gregoir ureteral reimplantation in the surgical management of primary unilateral vesicoureteral reflux in children

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## SUMMARY

OBJECTIVE: *Vesicoureteral reflux (VUR) represents one of the most significant risk factors for acute pyelonephritis in children. Various intravesical and extravesical techniques have been described for the surgical correction of VUR. The aim of our study was to compare the results of open intravesical and extravesical procedures for unilateral primary VUR in children.*

METHODS: *Between January 2012 and August 2018, 38 children with primary VUR who underwent open ureteral reimplantation surgery were retrospectively reviewed. The Cohen (intravesical) and the Lich-Gregoir (extravesical) approach were grouped as groups A and B, respectively. The groups were compared for age, gender, preoperative reflux grade, presence of lower urinary tract symptoms, operation time, discomfort and pain, analgesic requirements, duration of hematuria, postoperative complications, and hospital stay. All the parameters were statistically compared.*

RESULTS: *There were 38 patients in this study. Group A had 18 patients, and group B had 20 patients. The mean operative time was significantly shorter in group B than in group A. The mean hospital stay was also shorter in group B. The urethral foley stay period was 4.7±0.9 days 2±0 days (p = 0.000*), respectively, for group A and B. Macroscopic hematuria was seen in group A. The objective pain scale was worse after intravesical surgery. Analgesic requirements were higher in group A (p =0.131).*

CONCLUSION: *Intravesical and extravesical ureteroneocystostomy methods are equally successful and feasible in the treatment of primary unilateral VUR. The Cohen technique is associated with a longer and more painful hospital stay, gross hematuria, and longer operative time, compared to the Lich-Gregoir technique.*

KEYWORDS: *Vesicoureteral reflux. Ureter/surgery. Pain measurement. Replantation.*

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## INTRODUCTION

Vesicoureteral reflux (VUR) is described as urinary reflux from the bladder to the upper urinary tract. In the treatment of VUR, various intravesical and extravesical techniques have been described. Among these, the Cohen and Lich-Gregoir techniques are the most commonly used in published data. The most concerning issue in VUR is still nephropathy with renal scarring and subsequent hypertension leading to end-stage renal disease[1]. The main purpose of any treatment is to prevent renal damage. Although conservative treatment using antibiotic prophylaxis is widely accepted, most patients with reflux do not develop renal damage and do not require any treatment[2,3]. Each method has specific advantages and disadvantages. In both techniques, the purpose is to lengthen the intramural part of the ureter by a submucosal embedding of the ureter. Currently, success rates vary between 92% and 98% for open ureteral reimplantation[2]. There have been perfect research on ureteral reimplantation aiming to define the advantages and disadvantages of each technique; however, there are insufficient studies comparing both techniques in the literature. In our study, our purpose is to compare the results of extravesical (Lich-Gregoir) and intravesical (Cohen) techniques for unilateral primary VUR in children.

## METHODS

In a tertiary academic center, 38 children with primary unilateral VUR who underwent open ureteral reimplantation surgery were included in this retrospective study between January 2012 and August 2018. Local ethics committee approval and written informed consent were obtained from all participants. The present study conforms to the principles of the Declaration of Helsinki. The exclusion criteria included bilateral ureteroneocystostomy (UNC), need for ureteral tapering, repeat procedures, megaureter, and a diagnosis of neurogenic bladder. The Cohen procedure was attributed to group A, and the Lich-Gregoir procedure to group B. Conventional voiding cystourethrography (VCUG) including two fillings was used for the evaluation of the patients (Figure 1). Reflux was classified as grades I-V according to the International Classification System of the International Reflux Study Committee[4]. The indication for ureteral reimplantation (intravesical or extravesical) was similar, and the risk classification was made according to the EAU / ESPU guidelines[5]. Open surgery indications were recurrence of VUR after endoscopic injection, symptomatic high-grade reflux refractory to conservative treatment, complications due to antibiotics, progressive renal scarring, reflux nephropathy, and parental preference. The bladder was evaluated by cystoscopy before surgery (Figure 2). Renal scans were performed in all patients. We evaluated the clinical data of both groups, including age, gender, preoperative reflux grade, presence of lower urinary tract symptoms (LUTS), operation time, discomfort and pain, analgesic requirements, duration of hematuria, postoperative complications and hospital stay.

**FIGURE 1**

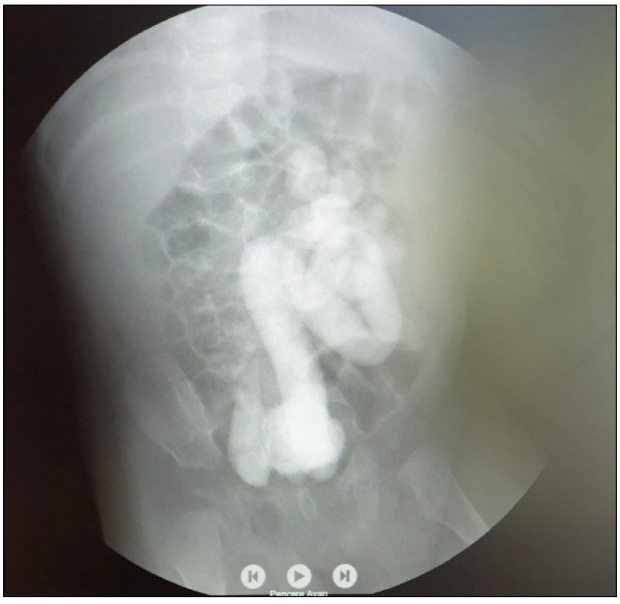
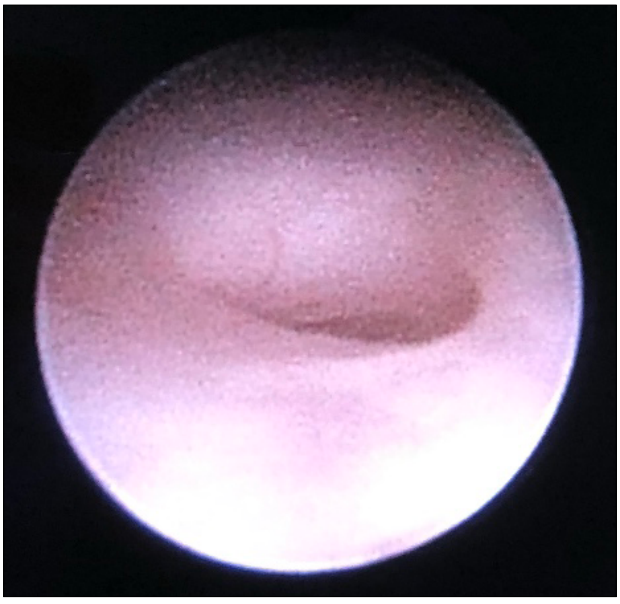


**FIGURE 2**



Anticholinergic drug usage and the presence of LUTS were also documented. Patients who had LUTS in the preoperative period received urotherapy initially. The success of the surgery was identified by the absence of reflux via VCUG six months after the surgery. All the parameters were statistically compared.

### Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics ver. 21 (IBM Co., USA). The Student t-test and Shapiro Wilks tests were applied to compare the parameters of each group. In this study, $p < 0.05$ was considered statistically significant.

### Ethical issues

Diyarbakır Gazi Yaşargil Training and Research Hospital Ethics Committee, Turkey, approved this study.

## RESULTS

There were 38 patients (male/female, 13/25) in this study. Group A included 18 patients and group B, 20. Demographic data are shown in Table 1. The mean ages of groups A and B were 3.4±1.8 (1-7) years and 5.5±2.9 (2-9), respectively (p= 0.012*). The mean reflux grades in groups A and B were similar, 3.7±0.8 (range 3-5) and 3.9±0.8 (range 3-5), respectively (p= 0.640). The split ipsilateral renal function (DMSA) was also similar for groups A and B, 39.3±4.6% vs. 38.6±4.7%, respectively (p= 0.658). There was no statistically significant difference between groups A and B in terms of prior endoscopic injection (Group A 8/18; Group B 7/20, p= 0.811). The operative and postoperative data are shown in Table 2. The mean operative time of group B was significantly shorter than that of group A (85±11.4 min vs. 72.6±10.4 min, respectively p=0.001*). The mean hospital stay was also shorter in group B (2±0.4 days and 4.6±0.9 days, respectively, p=0.000*). The urethral foley stay period was 4.7±0.9 and 2±0 days (39.3±4.6% vs. 38.6±4.7%), respectively, for groups A and B. Gross hematuria was observed only in group A, lasting for a mean of 2.5±1.3 days (p=0.000*). The objective pain scale (OPS) was worse after intravesical ureteral reimplantation (5.7±1.4 vs. 4.6±1.2, respectively, p = 0.011*). However, there was no statistically significant difference between groups A and B regarding the mean need for analgesics (96.2±59.4 mg. vs. 73.6±26.1 mg., respectively, p=0.131). The mean follow-up times (Table 3) of the groups were similar (29.9±18.9 months vs. 28.4±17.3 months, respectively, p=0. 801). No intraoperative complications were observed in both groups. We did not encounter any major postoperative complications such as febrile urinary tract infections or pyelonephritis, and severe hydronephrosis during the follow

**TABLE 1.** DEMOGRAPHIC DATA

| | Group A (N=18) | Group B (N=20) | P |
|---|---|---|---|
| | Mean±SD | Mean±SD | |
| Age (years) | 3,4±1,8 | 5,5±2,9 | 0,012* |
| Sex (Male/Female) (n) | 6/12 | 7/13 | 0,538 |
| Kidney function (percent) | 39,3±4,6 | 38,6±4,7 | 0,658 |
| Reflux grade | 3,7±0,8 | 3,9±0,8 | 0,640 |
| Prior endoscopic injection (n) | 8/18 | 7/20 | 0,811 |

Independent Student t-test *p<0.05

**TABLE 2.** OPERATIVE AND POSTOPERATIVE DATA

| | Group A (N=18) | Group B (N=20) | P |
|---|---|---|---|
| | Mean±SD | Mean±SD | |
| Operation time (minutes) | 85±11,4 | 72,6±10,4 | 0,001* |
| Hospital stay (days) | 4,6±0,9 | 2±0,4 | 0,000* |
| Urethral foley stay (days) | 4,7±0,9 | 2±0 | 0,000* |
| Objective pain scale (OPS) | 5,7±1,4 | 4,6±1,2 | 0,011* |
| Gross hematuria (days) | 2,5±1,3 | 0 | 0,000* |
| Analgesic requirement (mg) | 96,2±59,4 | 73,6±26,1 | 0,131 |

Independent Student t-test *p<0.05

up. Afebrile cystitis with positive urine culture was observed in a total of three children in up to 1 year postoperatively in group A. No reflux persistency was observed 1 year after ureteral reimplantation, in both groups.

## DISCUSSION

Vesicoureteral reflux is the most common uropathy in children[6]. Although a spontaneous resolution is common in primary reflux, surgical intervention may be required in persistent reflux, recurrent pyelonephritis, renal scar, or febrile urinary tract infection (UTI) patients. To correct reflux, both intravesical and extravesical approaches are highly successful and reduce the occurrence of febrile UTI[6,7]. Currently, success rates range between 92% and 98% for open ureteral reimplantation[2]. In the last ten years, a decrease in the incidence of ureteral reimplantation has been observed in the world. This may be due to a reduction in the number of VCUGs performed and an increase in endoscopic interventions for the treatment of primary VUR[8]. Endoscopic therapies are associated with lower patient morbidity and, possibly, lower costs[9]. Extravesical reimplantation is generally used in Canada and Europe[6,10,11]. However, intravesical reimplantation has become more popular for unilateral VUR in the United States[6]. In recent years, the use of minimally invasive techniques in urology has increased. In the literature, laparoscopic and robotic ureteral reimplantation have equivalent success rates to open surgery[12]. Both intravesical and extravesical techniques have excellent success rates of over 90% to correct VUR, and both these techniques have their own advantages and disadvantages. Most studies have evaluated the advantages and disadvantages of these techniques, retrospectively[6,10,11].

In general, the intravesical approach is thought to be more invasive than the extravesical because of the need to open the bladder[6,10,11]. Macroscopic hematuria is a typical postoperative finding that sometimes requires long-term monitoring and catheterization[6-11]. In our study, hematuria was not seen in group B, but we observed a mean duration of gross hematuria of 2.5±1.3 days in group A. It is thought that bladder incision is responsible for hematuria, postoperative pain, and bladder spasms[13]. Ellsworth et al.[11] reported that the extravesical technique causes fewer episodes of bladder spasm and is less painful than the intravesical technique.

Chen et al.[14] compared three different surgical techniques: open intravesical, open extravesical, and laparoscopic extravesical. They also included bilateral VUR patients in their study, in contrast to ours. They found that the mean operative time was significantly shorter in the Lich-Gregoir group than in the Cohen group, 58 minutes vs. 113 minutes, respectively ($p < 0.001$). In addition, the hospital stay was also longer for the Cohen group than for the Lich-Gregoir, 4.9 days vs. 3.0 days ($p < 0.05$)[14]. In our study, the mean hospital stay was also shorter in group B, in agreement with the literature (1.2 ± 0.8 and 5.8±1 days, respectively, $p = 0.007$). We think extravesical ureteral reimplantation appears to be more advantageous than intravesical ureteral reimplantation in terms of hospital stay. Esposito et al. compared the open Cohen technique, the endoscopic subureteric injection procedure, and the laparoscopic extravesical ureteral reimplantation, according to Lich-Gregoir. They reported that the operative time in the Cohen group was 109 minutes. Although the success rates of these three techniques were similar, the Cohen group had a longer hospital stay and higher analgesic requirements[15]. In our study, the mean operative time was significantly shorter in group B than in group A, in line with these studies (85±11.4 minutes vs. 72.6±10.4 minutes, respectively p=0.001*).

Postoperative pain and analgesic demand are other important parameters. Oswald et al.[16] reported that the extravesical approach needs less pain medication

**TABLE 3.** FOLLOW UP

| | Group A (N=18) | Group B (N=20) | P |
|---|---|---|---|
| | Mean±SD | Mean±SD | |
| Follow up (months) | 29,9±18,9 | 28,4±17,3 | 0,801 |
| Afebrile cystitis (n, %) | 3 (16.6%) | - | 0,080 |
| reflux persistency | - | - | |
| hydronephrosis | - | - | |
| pyelonephritis | - | - | |

Independent Student t-test *p<0.05

and anticholinergics postoperatively. Arlen et al.[17] found no difference between surgical techniques and analgesic demand. Harel et al.[18] compared the results of open intravesical ureteral reimplantation and robotic extravesical ureteral reimplantation and found that robotic extravesical ureteral reimplantation has less analgesic demand and postoperative pain than open ureteral reimplantation. In their study, in the robotic surgery group, 87% of the patients were discharged from the hospital on the operation day. In our study, OPS scores were higher in group A (5.7±1.4 vs. 4.6±1.2, respectively, p = 0.011*), as was the need for analgesics ( 96.2±59.4 mg. vs. 73.6±26.1 mg., respectively, p = 0.131); however, these were not statistically significant. The extravesical approach is less painful than intravesical approaches.

Routine stent placement after the Cohen technique is debatable in the literature. Most authors still use stents after Cohen ureteral reimplantation, while others do not [19,20]. Uvin et al.[20] reported that the use of temporary ureteral double J stenting did not cause postoperative infections in children. We did not insert a double J stent after the Cohen technique routinely.

The effect of endoscopic injections prior to open UNC on success rates is another argument in the literature. Lee et al.[21] reported that there were no significant differences in operative time, hospitalization time, postoperative complications, and success rates among open ureteral reimplantation techniques after previous failed endoscopic injection for primary VUR. Previous endoscopic injection surgery had no negative effect on our surgical results.

The main limitation of our study is the retrospective analysis of patient's data. However, there are a limited number of studies comparing these two surgical techniques in the literature. The main advantage of our study is to record pain scores and the level of analgesic requirements after surgery. We believe our study contributes to the current literature because it is a direct comparison of the two most common surgical techniques in a very specific population, including unilateral primary VUR patients.

## CONCLUSIONS

Intravesical and extravesical ureteral reimplantation are highly effective methods to treat VUR, with success rates of up to 98%[6]. On the other hand, the open intravesical technique is more invasive and causes more comorbidities than the extravesical one[11]. The extravesical technique is a rather easy procedure that requires less operative time, has a shorter hospital stay, and averts gross hematuria. Those children who had extravesical surgery experienced less postoperative pain and required fewer analgesics. Both techniques are applicable in urology practice. However, both techniques could be performed by the surgeons depending on their surgical experience.

## COMPLIANCE WITH ETHICAL STANDARDS

### Author contributions

All authors have made substantial contributions to the article and assume full responsibility for its content; all those who have made substantial contributions to the article have been named as authors.

### Funding

No financial or nonfinancial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

### Conflict of interest

The authors declare that they have no conflict of interest.

### Ethical approval

This is a retrospective study that was conducted at the Diyarbakır Gazi Yaşargil Training and Research Hospital, Turkey, and was approved by the Diyarbakır Gazi Yaşargil Training and Research Hospital Ethics Committee. The study is in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

### Informed consent

Informed consent was obtained from all individual participants included in the study.

### Author's contributions

Cemil Aydin, MD, Assist. Prof./ Writer, Data collection, Design, Analysis. Ali Akkoc, MD, Assist. Prof./ Concept and design. Ramazan Topaktaş, MD / Acquisition of data. Aykut Bugra Sentürk, MD, Assist. Prof./ Concept and design. Zeynep Banu Aydin, MD/ Radiologic evaluation, analysis or interpretation of data. Ahmet Ürkmez, MD, Assist. Prof./ Critical revision for important intellectual content. Muhammet Yaytokgil, MD, Analysis or interpretation of data.

## RESUMO

OBJETIVO: *O Refluxo Vesicoureteral (RVU) representa um dos mais importantes fatores de risco para pielonefrite aguda em crianças. Diversas técnicas intra e extravesicais já foram descritas para a correção cirúrgica do RVU. O objetivo do nosso estudo é comparar os resultados de procedimentos extravesicais e intravesicais abertos para o tratamento de RVU primário unilateral em crianças.*

METODOLOGIA: *Entre janeiro de 2012 e agosto de 2018, 38 crianças com RVU primário foram submetidas a cirurgia aberta de reimplante ureteral. Esses casos foram retrospectivamente revisados. As abordagens de Cohen (intravesical) e Lich-Gregoir (extravesical) foram agrupadas nos grupos A e B, respectivamente. Os grupos foram comparados quanto à idade, sexo, grau de refluxo pré-operatório, presença de sintomas no trato urinário inferior, tempo de operação, desconforto e dor, necessidade de analgésicos, duração de hematúria, complicações pós-operatórias e tempo de internação. Todos os parâmetros foram comparados estatisticamente.*

RESULTADOS: *No total, 38 pacientes foram incluídos neste estudo. O grupo A teve 18 pacientes e o grupo B, 20. O tempo médio de operação foi significativamente menor no grupo B do que no grupo A. O tempo médio de internação também foi menor no grupo B. O tempo de uso do foley uretral foi de 4,7 ± 0,9 dias e 2±0 dias (p = 0,000*) , respectivamente, para o grupo A e B. Hematúria macroscópica foi observada no grupo A. A pontuação na escala objetiva de dor foi pior após a cirurgia intravesical. A necessidade de analgésicos foi maior no grupo A (p = 0,131).*

CONCLUSÃO: *As técnicas extravesicais e intravesical de ureteroneocistostomia são igualmente bem-sucedidas e viáveis para o tratamento de RVU primário unilateral. A técnica de Cohen está associada a um período de internação mais longo e mais doloroso, hematúria e maior tempo operatório, em comparação com a técnica de Lich-Gregoir.*


PALAVRAS-CHAVE: *Refluxo vesicoureteral. Ureter/cirurgia. Medição da dor. Reimplante.*

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ORIGINAL ARTICLE

# Cefazolin sodium pentahydrate combined with vacuum sealing drainage in the treatment of open fracture complicated with soft tissue injury

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## SUMMARY

OBJECTIVE: *To investigate the clinical efficacy of cefazolin sodium pentahydrate combined with vacuum sealing drainage (VSD) in the treatment of open fracture complicated with soft tissue injury.*

METHODS: *Sixty-three patients with open fracture complicated with soft tissue injury were divided into observation (n = 33) and control (n = 30) groups. After surgical reduction, fixation, and repair of the fractures, the control group was treated with VSD for 10 days, and the observation group was treated with cefazolin sodium pentahydrate based on VSD for 10 days. The infection control time was recorded. After treatment, the pain of patients was evaluated. Before and after treatment, the serum levels of C-reactive protein (CRP), interleukin (IL)-6, IL-8, tumor necrosis factor α (TNF-α), cortisol, epinephrine, norepinephrine, and glucose were detected. After 6 months of treatment, the total effective rate of the treatment was evaluated.*

RESULTS: *The infection control time and Visual Analogue Scale score after treatment in the observation group were significantly lower than in the control group, respectively (P < 0.05). After the treatment, the serum levels of CRP, IL-6, IL-8, TNF-α, cortisol, epinephrine, norepinephrine, and glucose in each group were significantly lower than before the treatment (P < 0.05), and each index in observation was significantly lower than in the control group (P < 0.05).*

CONCLUSIONS: *In the treatment of open fractures complicated with soft tissue injury, cefazolin sodium pentahydrate combined with VSD can effectively reduce inflammation and stress, thus improving the treatment efficacy.*

KEYWORDS: *Fractures, open. Soft tissue injuries. Cefazolin. Negative-pressure wound therapy.*

## INTRODUCTION

In modern society, the incidence of accidents caused by high-energy factors is increasing year by year. Fractures, especially open ones, have become a common and frequently-occurring injury. Open fractures are often accompanied by soft tissue injury, large-area skin defect, and tendon exposure. Soft tissue injury has brought great challenges to the treatment of fractures and is also the key to determine the curative effect. The speed and degree of soft tissue healing determine the outcome of fracture healing and

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limb function preservation[1,2]. At present, open dressing change and skin grafting are often used to promote wound healing. However, many patients are complicated with slow growth of adjacent wound granulation tissue, insufficient blood supply, and local release of toxic substances from necrotic tissue, leading to the infection[3,4]. In addition, the long-term wound exposure, cross-infection, and nosocomial infection are also important factors of further infection[5]. In recent years, the vacuum sealing drainage (VSD) technique has been widely used in orthopedics. It has a definite effect in promoting granulation growth, reducing tissue edema, and improving wound microcirculation. VSD has now become the standard treatment method for some wounds[6,7]. However, some complications may occur when VSD is used alone, such as blockage of the drainage tube and anaerobic bacteria growth caused by anaerobic environment due to wound closure, which leads to the frequent replacement of dressings[8]. Cefazolin sodium pentahydrate is an upgraded variety of the traditional cefazolin sodium. It can further extend the strong anti-gram-positive bacteria performance of cefazolin sodium, and greatly reduce the incidence of adverse reactions, especially allergic ones9. Given this, this study investigated the clinical efficacy of cefazolin sodium pentahydrate combined with VSD in the treatment of open fractures complicated with soft tissue injury. The objective was to provide a reference for further applications of this strategy in the clinic setting.

## METHODS

### Patients

Sixty-three patients with open fracture complicated with soft tissue injury admitted to our hospital from March 2013 to June 2017 were selected. There were 48 males and 25 females. The age of patients was 18-63 years, with an average of 40.56±6.12 years. The course of injury was 1-25 h, with an average of 3.99±1.43 h. There were 8 cases caused by crashing objects, 15 caused by falling, 22 caused by traffic accidents, and 18 caused by mechanical contusion. There were 26 cases of upper limb injuries and 37 cases of lower limb injuries. According to the Gustilo classification, there were 16 cases of type II, 33 cases of type III A, and 14 cases of type III B. The inclusion criteria were as follows: i) the imaging findings showed the limb fractures; ii) the fracture conformed to the Gustilo classification of open fracture; iii) there was exudate in the wound; iv) there was defined trauma history. The exclusion criteria were as follows: i) allergy to experimental drugs; ii) serious heart, lung, liver, or other important organ dysfunction. This study was approved by the Medical Ethics Committee of the General Hospital of The Yangtze River Shipping, and all the participants signed the informed consent.

### Treatment

After admission, the patients in two groups actively received fluid infusion and antibiotics treatment. The wound was cleaned and disinfected before surgery, and the necrotic tissues or foreign materials were removed. The surgical reduction, fixation, and repair of the fracture were performed according to imaging findings. After the above treatment, the VSD material was cut into the shape of the wound size, and the drainage strip was made by inserting multi-side porous silica gel material into the VSD material. The length of each drainage strip was less than 2 cm. The drainage strips were connected by a three-way joint, and the skin around the wound was disinfected with alcohol. Then, the wound and the drainage strips were sealed together using translucent film. The other outlets of the drainage strips were connected to the negative pressure machine. The pressure of the machine was set at 120-400 mmHg. The continuous drainage was performed for 10 days. If the surgery was successful and the sealing worked well, the VSD material was removed after about 10 days. If the VSD did not reach a good state, it needed to be re-performed in time. From the time of the VSD beginning, the patients in the observation group received an intravenous drip of cefazolin sodium pentahydrate (Shenzhen Jiuxin Pharmaceutical Co., Ltd., Shenzhen, China), with a dose of 2.0 g/day, for successive 10 days. The patients in the control group received routine treatment only.

### Observation of wound situation

During the treatment, the situation of the wound was observed. The standard of infection control was as follows: i) the bacterial culture results of the sample in three consecutive drainages were negative; ii) the fresh granulation tissue grew well, and the blood supply was good; iii) there was no obvious inflammation such as swelling and exudation around or in the wound. The duration from the beginning of the treatment to the occurrence of the above situations was regarded as the infection control time.

### Evaluation of pain

After the treatment, the pain of patients was evaluated using the Visual Analogue Scale (VAS) score as follows: 0 points: no pain; 1-3 points: mild pain; 4-6 points: moderate pain; 7-9 points: severe pain; 10 points: the most severe pain.

### Measurement of inflammatory factors and stress indexes

Before and after the treatment, 5 ml of circulating venous blood was collected and serum was obtained after centrifugation. The serum levels of C-reactive protein (CRP), interleukin (IL)-6, IL-8, and tumor necrosis factor α (TNF-α) were detected by enzyme-linked immunosorbent assay. The serum levels of cortisol, epinephrine, and norepinephrine were detected by high-performance liquid chromatography and electrochemical methods. The level of glucose was detected by the glucose oxidase method.

### Follow up and evaluation of total treatment efficacy

The patients were followed up for 6 months. The total curative effect was evaluated at the end of the follow up as follows: i) cured: X-ray examination showed that the bone destruction was repaired; the dead bone disappeared; the local swelling and pain disappeared; the systemic symptoms disappeared; the sinus ulcer was healed; the limb function recovered; ii) markedly effective: X-ray showed that partial bone destruction was repaired and the lesion was improved; the local swelling and pain disappeared; the systemic symptoms were alleviated; the sinus ulcer was healed; the limb function was improved; iii) effective: X-ray showed that the bone destruction tended to be repaired and the lesion was stable; the local and systemic symptoms were improved; the sinus ulcer was not healed, with sinus tract residue; iv) ineffective: X-ray showed that the lesion continued to develop; the local and systemic symptoms could not be controlled. The total effective (cured + markedly effective + effective) rate was calculated.

### Statistical analysis

SPSS statistical package (SSPS Inc., Chicago, USA) version 20.0 was used to perform the statistical analysis. The measurement data were presented as mean±SD, and the comparison between the two groups and between before and after treatment was performed using the t-test. The enumeration data were presented as a number, and the comparison was performed using the chi-square ($\chi^2$) test. $P < 0.05$ was defined as statistically significant.

## RESULTS

General data of the subjects in the two groups

The general data of the subjects in the observation and control groups are shown in Table 1. Each index of age, gender, injury course, cause of injury, injury site, and Gustilo classification had no significant difference between two groups ($P > 0.05$).

**TABLE 1.** GENERAL DATA OF SUBJECTS IN THE TWO GROUPS.

| Group | Observation | Control | t/$\chi^2$ | P |
|---|---|---|---|---|
| n | 33 | 30 | | |
| Age (years) | 41.22±5.19 | 39.78±4.73 | 1.147 | 0.256 |
| Gender (male/female, n) | 20/13 | 18/12 | 0.002 | 0.961 |
| Injury course (h) | 3.75±1.33 | 4.12±1.63 | 1.125 | 0.265 |
| Cause of injury (n) | | | 0.607 | 0.895 |
| Crashing object | 5 | 3 | | |
| Falling | 7 | 8 | | |
| Traffic accident | 12 | 10 | | |
| Mechanical contusion | 9 | 9 | | |
| Injury site (n) | | | 0.038 | 0.845 |
| upper limb | 14 | 12 | | |
| lower limb | 19 | 18 | | |
| Gustilo classification (n) | | | 0.174 | 0.917 |
| Type II | 8 | 8 | | |
| Type IIIA | 17 | 16 | | |
| Type IIIB | 8 | 6 | | |

### Comparison of infection control time and VAS score between the two groups

The infection control time in the observation group was 2.32±0.44 days, which was significantly shorter than the 10.45±2.78 days in the control group ($P < 0.05$). After the treatment, the VAS score in the observation group was 2.32±0.44 points, which was significantly lower than the 2.66±0.55 points in the control group ($P < 0.05$).

### Comparison of serum inflammatory factors between the two groups

Before the treatment, the serum levels of CRP, IL-6, IL-8, and TNF-α had no significant difference between observation and control groups, respectively ($P > 0.05$). After the treatment, the serum levels of CRP, IL-6, IL-8, and TNF-α in each group were significantly lower than those before treatment, respectively ($P < 0.05$). In addition, after the treatment, each index in the observation group was significantly lower than those in the control group ($P < 0.05$) (Figure 1).

### Comparison of serum stress indexes between the two groups

Before the treatment, there was no significant difference in serum levels of cortisol, epinephrine, norepinephrine, or glucose between the observation and control groups, respectively ($P > 0.05$). After the treatment, the serum levels of cortisol, epinephrine, norepinephrine, and glucose in each group were significantly lower than those before the treatment ($P < 0.05$). In addition, after the treatment, each index in the observation group was significantly lower than that in the control group ($P < 0.05$) (Figure 2).

### Comparison of adverse reactions between the two groups

During the treatment, the main adverse reactions of patients were gastrointestinal reactions, low fever, rash, and others. The incidence of adverse reactions in the observation and control groups was 2.67% and 4.45%, respectively, with no significant difference between the two groups ($P > 0.05$).

### Follow up results

After 6 months from the treatment, in the observation group, there were 11, 16, 5, and 1 cases with cured, remarkably effective, effective, and ineffective treatment outcomes, respectively. In the control group, there were 9, 14, 4, and 3 cases with cured, remarkably effective, effective, and ineffective treatment outcomes in the control group, respectively. The total effective rates in the observation and control groups were 96.97% and 90.00%, respectively, with no significant difference between the two groups ($P > 0.05$).

## DISCUSSION

In open fractures, the injured tissues are exposed to air for a long time. This is prone to cause the incomplete removal of remnants and necrotic tissues and ischemia of the wound margin. Therefore, the chance of wound infection is higher than in closed injur[ies10]. In the traditional treatment of open fractures complicated with soft tissue injury, based on the surgical reduction, fixation, and repair of fracture, the strict debridement, thorough hemostasis, smooth drainage, and prophylactic application of antibiotics are often conducted. However, the incidence of postoperative infections in traditional treatment is still high[11]. In VSD, based on traditional debridement, the wound is filled with the dressing to close the dead cavity. A continuous negative pressure sealing environment is constructed by drainage through silica gel tubes and closure of the wound with physiological-permeability adhesive film. This can thoroughly remove the necrosis and exudates[12]. The VSD material has good histocompatibility and is not easy to adhere to. At the same time, VSD can reduce the number of dressing changes, the chances of cross-infection, and the pain and economic burden of patients[13]. Cefazolin sodium pentahydrate is developed based on cefazolin sodium. Its chelating crystal structure is more refined and stable. All sulfur-containing groups are firmly encapsulated in the crystal, which can effectively prevent the falling off of sulfur-containing groups and their contact with rubber plugs, producing toxic substances[14]. Cefazolin sodium pentahydrate has a more remarkable antimicrobial effect and higher safety compared with cefazolin sodium. There are fewer reports on the application of cefazolin sodium pentahydrate for patients with open fractures complicated with soft tissue injury. This study investigated the clinical efficacy of cefazolin sodium pentahydrate combined with VSD in the treatment of open fractures complicated with soft tissue injury. Results showed that, compared with using VSD alone, cefazolin sodium pentahydrate combined with VSD could shorten the infection control time and decrease the VAS score. This indicates

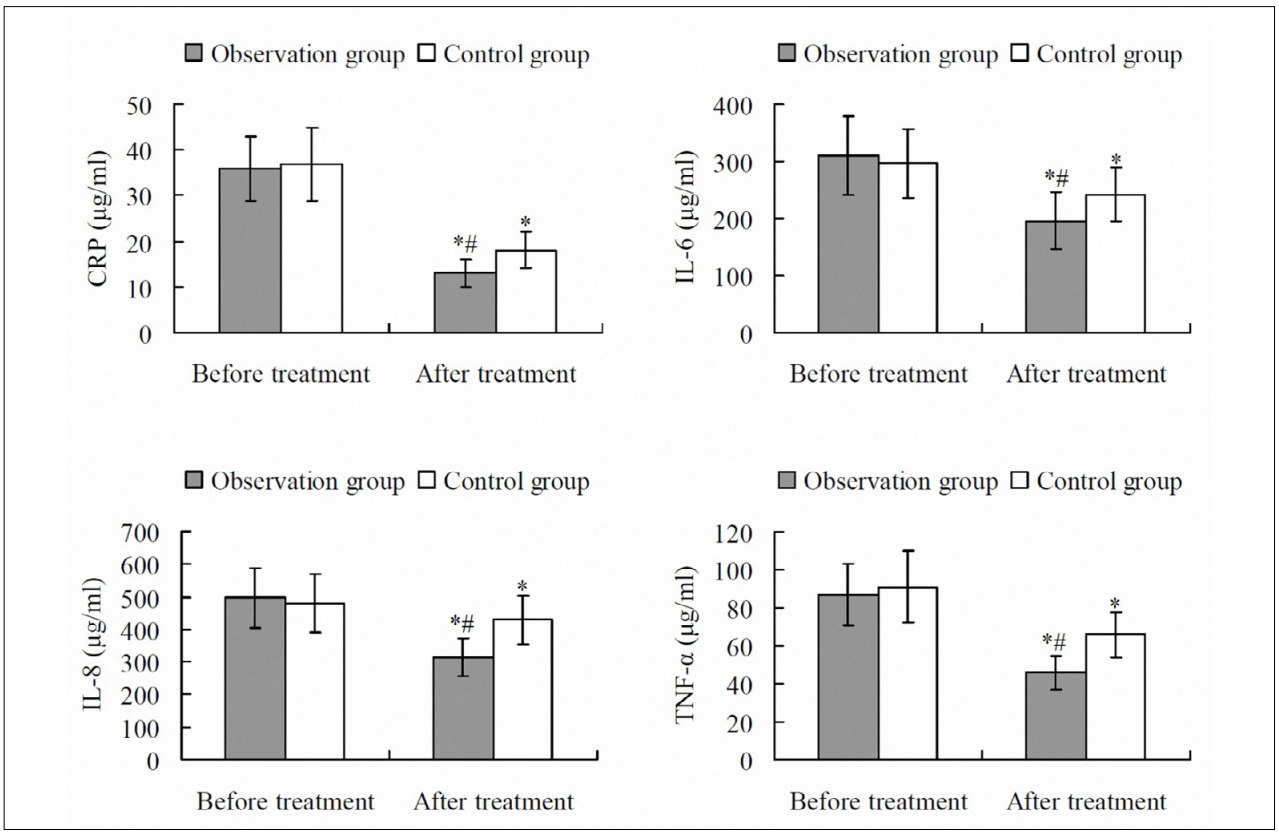


**FIGURE 1.** SERUM INFLAMMATORY FACTORS BEFORE AND AFTER TREATMENT IN THE TWO GROUPS. *P < 0.05 COMPARED WITH BEFORE THE TREATMENT; #P < 0.05 COMPARED WITH THE CONTROL GROUP. CRP, C-REACTIVE PROTEIN; IL-6, INTERLEUKIN 6; IL-8, INTERLEUKIN 8; TNF-α, TUMOR NECROSIS FACTOR α.

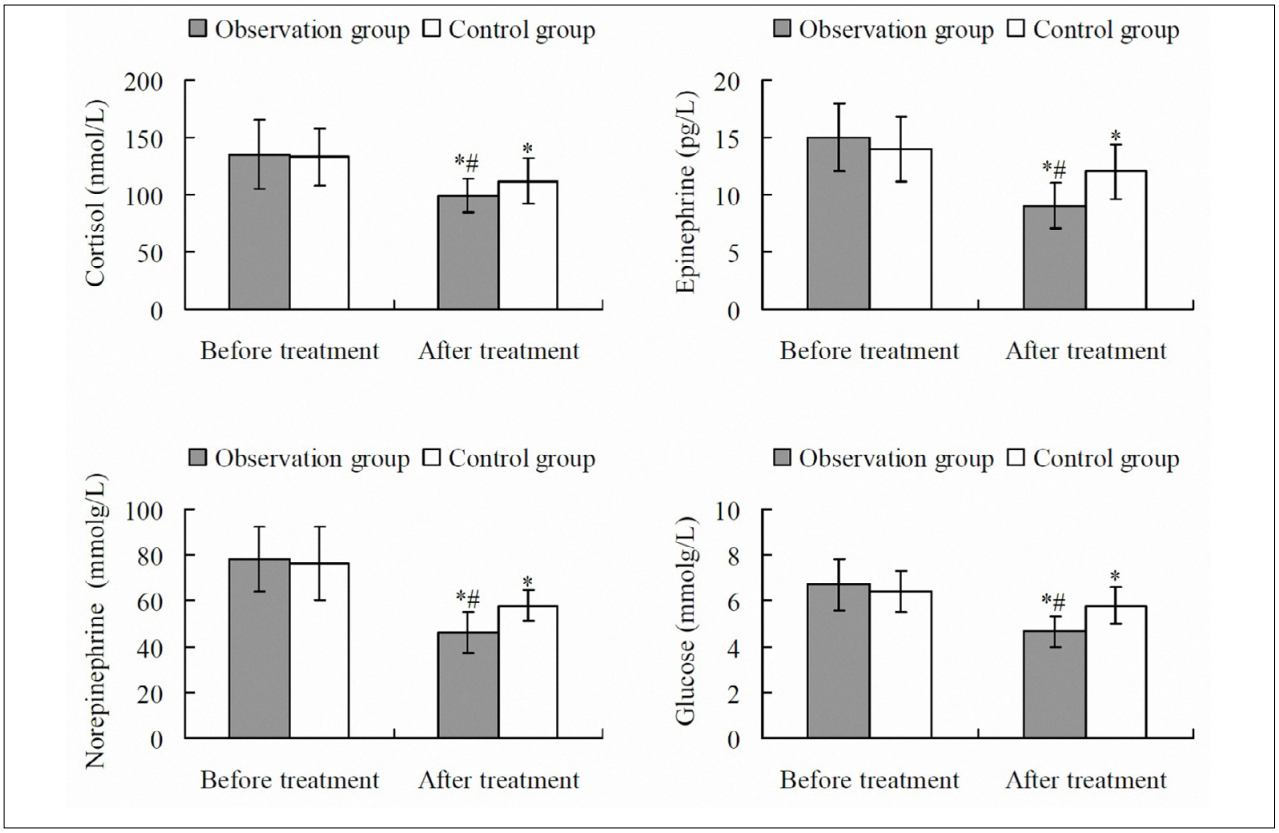


**FIGURE 2.** SERUM STRESS INDEXES BEFORE AND AFTER THE TREATMENT IN THE TWO GROUPS. *P < 0.05 COMPARED WITH BEFORE THE TREATMENT; #P < 0.05 COMPARED WITH THE CONTROL GROUP.

that, in treating open fractures complicated with soft tissue injury, the combination of cefazolin sodium pentahydrate and VSD can clearly improve the efficacy, compared with using VSD alone.

In open fracture patients, due to tissue injury, surgical trauma, and postoperative infection, the serum levels of inflammatory factors dramatically increase. CRP, IL-6, IL-8, and TNF-α are common inflammatory factors synthesized by peripheral macrophages, lymphocytes, fibroblasts, and other immune cells. Moreover, they interact with each other. The increase in the level of one inflammatory factor can promote the synthesis and secretion of other inflammatory factors through a cascade reaction[15]. These inflammatory factors can promote the release of prostaglandin E2, collagenase, and a large number of proteoglycan enzymes to destroy the cartilage matrix and aggravate the inflammatory reaction, which is not conducive to the prognosis of patients[16]. Results of this study showed that, after the treatment, the serum levels of inflammatory factors in each group were significantly lower than before the treatment, each index in the observation group was significantly lower than that in the control group. This suggests that the combination of cefazolin sodium pentahydrate and VSD can further reduce the inflammation reaction.

Trauma, surgery, and inflammatory reaction can induce a systemic stress response. Cortisol is an important hormone in the body, which can effectively maintain normal physiological functions and plays an important role in regulating mood and health, cellular immunity, and inflammation. When the body is in a state of stress, cortisol levels rise significantly to maintain the stability of blood pressure[17]. In addition, excessive cortisol secretion can induce increased glycogen decomposition, leading to an increase in blood glucose level[18]. Under a stress state, the excitability of the sympathetic nerves is increased, and the synthesis and secretion of epinephrine and norepinephrine are significantly increased[19]. In the present study, after the treatment, the serum levels of cortisol, epinephrine, norepinephrine, and glucose in the observation group were significantly lower than in the control group. This indicates that the combination of cefazolin sodium pentahydrate and VSD can further decrease the stress response in patients with open fractures complicated with soft tissue injury.

In conclusion, in the treatment of open fractures complicated with soft tissue injury, cefazolin sodium pentahydrate combined with VSD can effectively reduce inflammation and stress, thus improving the treatment effect. It is a safe and efficient treatment strategy and is worthy of further study and application. This study still has some limitations. The sample size is relatively small, and a larger sample size will make the results more convincing. In our next studies, the sample size should be further increased for more satisfactory outcomes. In addition, there may be changes of other factors involved in open fractures complicated with soft tissue injury, which need to be further clarified.

## Declaration of conflict of interest

None.

## Authors' contributions

Biao Che and Kai Zou designed the study. Wenjie Lou and Zhongbin Yu participated in data collection. Biao Che and Song Qin performed statistical analyses. Wenjie Lou drafted the manuscript. Biao Che and Kai Wang critically revised the manuscript. All authors read and approved the final manuscript.

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**RESUMO**

OBJETIVO: *Investigar a eficácia clínica do cefazolin penta-hidrato de sódio combinado com drenagem por vedação a vácuo (VSD) no tratamento da fratura exposta complicada com lesão nos tecidos moles.*

MÉTODOS: *Sessenta e três doentes com fratura exposta complicada com lesões nos tecidos moles foram divididos em grupos de observação (n=33) e controle (n=30). Após redução cirúrgica, fixação e reparação da fratura, o grupo de controle foi tratado com VSD durante dez dias e o grupo de observação foi tratado com cefazolina penta-hidrato de sódio com base no VSD durante dez dias. O tempo de controle de infecção foi gravado. Após o tratamento, a dor dos doentes foi avaliada. Antes e após o tratamento, foram detectados os níveis séricos de proteína C-reativa (CRP), interleucina (IL)-6, IL -8, fator de necrose tumoral alfa (TNF-α), cortisol, epinefrina, norepinefrina e glicose. Após seis meses de tratamento, a taxa efetiva total de tratamento foi avaliada.*

RESULTADOS: *O tempo de controle da infecção e a pontuação da Escala Visual Analógica após o tratamento no grupo de observação foram significativamente inferiores ao do grupo de controle, respectivamente (P<0,05). Após o tratamento, os níveis séricos de CRP, IL-6, IL-8, TNF-α, cortisol, epinefrina, norepinefrina e glicose em cada grupo foram significativamente menores do que antes do tratamento, respectivamente (P<0,05), e cada índice de observação foi significativamente inferior ao do grupo de controle (P<0,05).*

CONCLUSÃO: *No tratamento da fratura exposta complicada com lesões nos tecidos moles, o cefazolin penta-hidrato de sódio combinado com VSD pode efetivamente reduzir a inflamação e o estresse, melhorando assim a eficácia do tratamento.*

PALAVRAS-CHAVE: *Fraturas expostas. Lesões dos tecidos moles. Drenagem a vácuo. Cefazolina. Tratamento de ferimentos com pressão negativa.*

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ORIGINAL ARTICLE

# Reduction of functional cardiovascular reserve in the stages of chronic kidney disease

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## SUMMARY

OBJECTIVE: *Patients with chronic kidney disease (CKD) present reduced oxygen consumption at peak exercise ($VO_2$ peak). No studies have evaluated objective measures of the cardiovascular reserve, besides $VO_2$ peak and $VO_2$ at the anaerobic threshold ($VO_2$ AT), and compared these measures among ckd patients at different stages of the disease.*

METHODS: *Fifty-eight patients [pre-dialysis group (PD)=26, hemodialysis group (HD)=20, and post-kidney transplant group (KT)=12] were included. The following measures of cardiovascular reserve were obtained: 1) peak heart rate (HR); 2) peak systolic blood pressure (SBP); 3) $VO_2$ peak and % predicted; 4) $VO_2$ AT and % of predicted $VO_2$; 5) peak circulatory power; 6) ventilatory efficiency for the production of carbon dioxide ($VE/VCO_2$ slope); 7) oxygen uptake efficiency slope (OUES); and 8) recovery of gas exchange.*

RESULTS: *The $VO_2$ peak and $VO_2$ AT in the PD, HD, and KT groups were reduced to 86% and 69%, 70% and 57%, and 79% and 64% of the predicted value, respectively. Patients in the HD group had lower $VO_2$ peak (17.5±5.9 vs. 23.2±8.2 [p-value=0.036]) and $VO_2$ AT (14.0±5.2 vs. 18.3±4.7 [p-value=0.039]) compared to patients in the KT group. OUES was significantly lower in the HD group compared to the KT group (p-value=0.034). Age in the PD, HD, and KT groups and sedentary lifestyle in the KT group were predictors of $VO_2$ peak.*

CONCLUSIONS: *CKD patients presented a reduction in cardiovascular reserve regardless of the stage of the disease. However, hemodialysis patients presented a greater reduction of cardiovascular reserve when compared to post-kidney transplant patients.*

KEYWORDS: *Renal insufficiency, chronic. Exercise test. Kidney transplantation. Renal dialysis.*

## INTRODUCTION

The cardiopulmonary exercise test (CPET) is considered a standard reference in the evaluation of cardiopulmonary and metabolic responses to aerobic exercise in patients with cardiovascular diseases[1]. Patients with chronic kidney disease (CKD) are at high risk for cardiovascular disease[2]. Complex changes in the cardiovascular system of CKD patients result in structural and functional changes that may lead

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to reduced tolerance to exercise and quality of life, increased morbidity, and finally, premature death[3].

Exercise capacity depends on the health of the cardiovascular system in maintaining the transport of oxygen and carbon dioxide between the cellular and pulmonary systems[4]. A reduction in exercise capacity limits the range of physical activities a patient can perform. Several measures of the functional cardiovascular reserve, in addition to those traditionally used, can be obtained from a CPET and have been used to evaluate patients with heart failure[5,6].

Several studies have already demonstrated a reduction in the functional cardiovascular reserve through a reduction of oxygen uptake at peak exercise ($VO_2$ peak) in CKD patients[7-10]. However, we are not aware of any previous studies that evaluated objective measures of the cardiovascular reserve, besides $VO_2$ peak and $VO_2$ at the anaerobic threshold (AT), and compared these measurements among CKD patients at different stages of the disease. Therefore, the objective of this study was to evaluate measures of functional cardiovascular reserve in CKD patients at different stages of the disease [pre-dialysis (PD), hemodialysis (HD), and post-kidney transplant (KT)] and to determine the predictors of $VO_2$ peak in these groups of patients. We hypothesized that although these patients have CKD in common, measurements of functional cardiovascular reserve would be significantly different in the different stages of CKD. The knowledge of these changes and differences may guide the treatment and implementation of preventive measures for other diseases, especially cardiovascular ones, which may occur due to renal disease.

## METHODS

### Study design

A secondary analysis was carried out using the dataset of research performed with patients who were submitted to pre-dialysis treatment, hemodialysis, or kidney transplant under follow-up at the Nephrology Unit of the Charity Hospital of Ijuí-RS. The pieces of research were cross-sectional studies conducted between 2012 and 2014. The researcher responsible for the dataset approved its use.

Patients were included in this study if they were at least 18 years old and had all data from the evaluation protocol in the databases, which included complete clinical evaluation, laboratory analysis, and cardiopulmonary testing.

### Study population

A total of 241 patients were followed up at the Nephrology Unit of the Charity Hospital of Ijuí-RS and screened between 2012 and 2014. From this total, 72 patients were included in previous research, of which 58 had complete biochemical and exercise capacity data and, therefore, were analyzed in this study (Fig. 1).

### Data collection and variables

Clinical and demographic data were recorded, including age, sex, CKD etiology, time of current treatment, weight, height, body mass index (BMI), and presence of cardiovascular risk factors [sedentary lifestyle, systemic arterial hypertension (SAH), diabetes mellitus (DM), alcoholism, and smoking]. The laboratory data of creatinine, urea, potassium, hemoglobin, and hematocrit were collected from recent hematological and biochemical tests whose values were recorded on the medical records of the patients who were registered in the databases.

The CPET or maximum incremental exercise test was performed on a treadmill (Imbrasport, Porto Alegre, Brasil), with the following ramp protocol: initial speed of 1 $km.h^{-1}$ and final speed of 6 $km.h^{-1}$; and initial inclination of 0% and final inclination of 10%. Exhausted gases were analyzed every 20 seconds through a gas analyzer (total metabolic analysis system, TEEM 100, Aero Sport, Ann Arbor, Michigan). Blood pressure was measured every 3 minutes with a sphygmomanometer. Heart rate (HR) was determined using the R-R interval from 12 electrocardiogram leads. The CPET variables were calculated as described by Dall'Ago et al.[11]. In summary, the $VO_2$ peak was defined as the highest value achieved during the test for 20 seconds, and peak circulatory power was calculated as the product of $VO_2$ peak and peak systolic blood pressure (peak SBP). The recovery kinetics of oxygen uptake ($T_{1/2}VO_2$) was evaluated as the time required for a 50% decrease from the $VO_2$ peak and calculated using the least-squares model, according to Dall'Ago et al.[11]. The oxygen uptake efficiency slope (OUES) was calculated as the slope of the linear regression line between $VO_2$ and the logarithm of ventilation (VE)[12]. The evaluation of ventilatory efficiency was calculated using the linear regression model relating the VE and carbon dioxide production ($VCO_2$) during the exercise. For this, data from the entire cardiopulmonary test were used, from the beginning to the peak of the exercise. The slope values of the $VE/VCO_2$ ratio line were used for the analysis of ventilatory efficiency.

The first ventilatory threshold (also known as the anaerobic threshold) was determined by reviewing the gas exchange curves and was the heart rate in which the ventilatory equivalent for oxygen increases systematically without an increase in the ventilatory equivalent for carbon dioxide[1]. The prediction equation of the maximal oxygen uptake ($VO_2$ max), proposed by Almeida et al.[13] for the Brazilian population, was used. All patients continued taking their usual medication prescribed by their physicians.

### Statistical analysis

Normality was measured using the Kolmogorov-Smirnov test. Depending on the distribution of the variable, continuous data were described through the mean and standard deviation or median and interquartile range and compared by ANOVA (Tukey) or Kruskal-Wallis test, as appropriate. Categorical variables were presented as a percentage and were compared by Chi-square test or Fisher's exact test, as appropriate.

The $VO_2$ peak (in $mL.kg^{-1}.min^{-1}$) adjusted for age and body mass index was the outcome variable of primary interest in this study and, therefore, was used as a dependent variable for regression modeling analyses. To identify important predictors of $VO_2$ peak, a sequence of regression modeling analyzes were performed. Patient data were analyzed separately to determine the variables that were predictive of the $VO_2$ peak within each group. Significantly different variables between groups were first analyzed in a univariate linear regression model. Then, those significantly associated in the univariate analysis (p-value<0.05) were included in a multiple linear regression model. All data were stored and analyzed in the Statistical Package for the Social Sciences (SPSS) software for windows v. 20.0. A significance level of 5% was adopted.

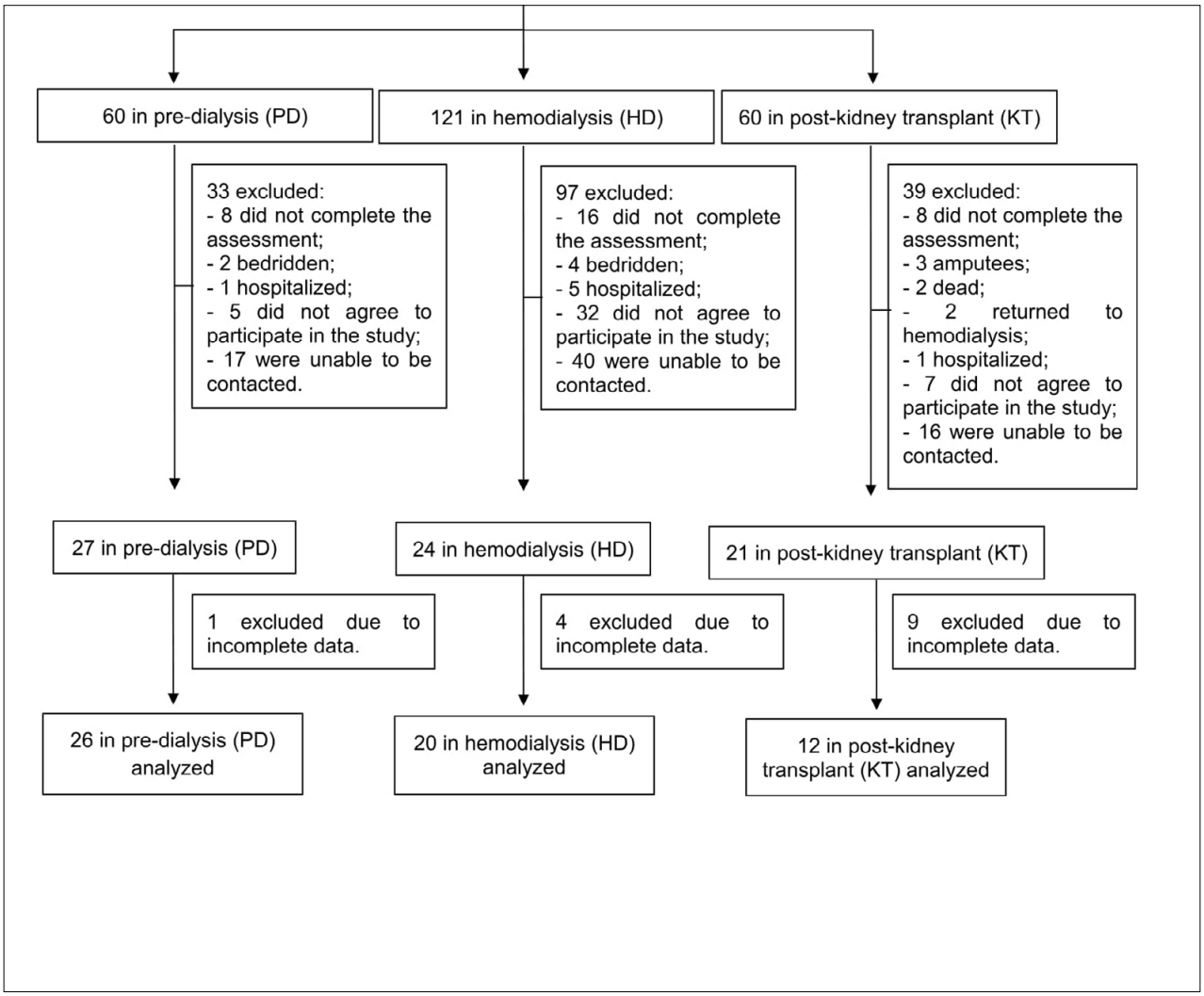


**FIGURE 1**

## RESULTS

### Characteristics of the patient population

Fifty-eight patients were included in this study. The characteristics of these patients are shown in Table 1. The CKD patients of the three groups had similar (a) sociodemographic and clinical characteristics: age (p-value=0.202), sex (p-value=0.526), BMI (p-value=0.790), time of CKD (p-value=0.084); and (b) prevalence of comorbidities such as: hypertension (p-value=0.340), DM (p-value=0.768), smoking (p-value=0.237), and alcoholism (p-value=0.146).

Biochemical data differed significantly between the PD, HD, and KT groups (Table 1). Creatinine and urea levels were higher in patients in the HD group when compared to patients in the PD group (p-value<0.001; p-value=0.005) and KT group (p-value<0.001; p-value<0.001), respectively. Additionally, creatinine and urea levels were higher in patients in the PD group when compared to patients in the KT group (p-value=0.050; p-value=0.012), respectively. Potassium was significantly higher in the PD group when compared to the HD (p-value=0.050) and KT (p-value=0.042) groups. Hemoglobin and hematocrit levels were lower, and consequently the percentage of patients with anemia was higher in the HD group when compared to the PD (p-value=0.001; p-value=0.001) and KT groups (p-value<0.001; p-value<0.001).

### Functional cardiovascular reserve

Metabolic data of the CPET for the three groups are presented in Fig. 2. When compared to patients in the KT group, patients in the HD group had lower $VO_2$ peak (17.5±5.9 vs. 23.2±8.2 [p-value=0.036]), corresponding to 70.5% vs. 79.5% of the predicted $VO_2$ peak, and $VO_2$ AT (14.0±5.2 vs. 18.3±4.7 [p-value=0.039]), corresponding to 56.7% vs. 63.7% of the predicted $VO_2$ peak. Patients in the PD group presented lower peak circulatory power values when compared to those in the HD group (p-value=0.002). The OUES was significantly lower in the HD group when compared to the KT group (p-value=0.034).

### Independent predictors of $VO_2$ peak

The increase in age was negatively associated with $VO_2$ peak in patients in the PD group (b=-0.13; p-value=0.034), HD group (b=-0.33; p-value=0.002), and KT group (b=-0.66, p-value=0.011). A sedentary

**TABLE 1.** CHARACTERISTICS OF THE STUDY POPULATION IN THE DIFFERENT STAGES OF CHRONIC KIDNEY DISEASE

| Variables | PD (n = 26) | HD (n = 20) | KT (n = 12) | p-value |
|---|---|---|---|---|
| Age, years | 61.2 ± 16.3 | 56.2 ± 11.3 | 53.3 ± 8.6 | 0.202 |
| Males, n (%) | 17 (65.4) | 14 (70.0) | 10 (83.3) | 0.526 |
| BMI, $kg.m^{-2}$ | 27.8 ± 4.3 | 26.8 ± 4.3 | 27.4 ± 5.3 | 0.790 |
| Treatment time[a], months | 12.0 [5.5 – 36.0] | 36.0 [14.5 – 50.2] | 31.0 [20.5 – 207.5] | 0.084 |
| Comorbidities, n (%) | | | | |
| SAH | 23 (88.5) | 15 (75.0) | 11 (91.7) | 0.340 |
| DM | 13 (50.0) | 8 (40.0) | 6 (50.0) | 0.768 |
| Sedentary lifestyle[b] | 21 (80.8) | 17 (85.0)§ | 5 (41.7)‡ | 0.015* |
| Smoking | 4 (15.4) | 1 (5.0) | 0 (0.0) | 0.237 |
| Alcoholism | 8 (30.8) | 7 (35.0) | 0 (0.0) | 0.146 |
| Biochemical parameters | | | | |
| Creatinine, $mg.dL^{-1}$ | 3.2 ± 1.5† | 9.3 ± 2.5§ | 1.5 ± 0.3‡ | <0.001* |
| Urea, $mg.dL^{-1}$ | 106.6 ± 43.3† | 160.1 ± 46.4§ | 55.3 ± 15.0‡ | <0.001* |
| Potassium, $mEq.L^{-1}$ | 8.8 ± 11.7† | 5.2 ± 0.8 | 4.4 ± 0.4‡ | 0.004* |
| Hemoglobin, $g.dL^{-1}$ | 12.3 ± 2.1† | 9.7 ± 1.6§ | 13.8 ± 1.5 | <0.001* |
| Hematocrit, % | 37.6 ± 6.0† | 29.8 ± 5.0§ | 41.7 ± 4.6 | <0.001* |
| Anemia[c], n (%) | 13 (50.0)† | 20 (100.0)§ | 4 (33.3) | <0.001* |

PD: pre-dialysis group; HD: hemodialysis group; KT: post-kidney transplant group; BMI: body mass index; CKD: chronic kidney disease; SAH: systemic arterial hypertension; DM: diabetes mellitus. a: Treatment time, months: this variable refers to the time of conventional treatment through the use of medication in the PD group, the time of hemodialysis treatment in the HD group, and the time since kidney transplant for the KT group. b: The patient was considered sedentary if he/she reported not performing any physical activity at least 3 times a week for at least 30 minutes. c: Anemia was defined according to World Health Organization criteria (hemoglobin <13 g.dL-1 in men and <12 g.dL-1 in women). Values for categorical variables are presented as frequency (percentage); values for continuous variables are presented as mean ± standard deviation or median [interquartile range]; the p-value was calculated by the Tukey test or Kruskall-Wallis test for continuous variables and Chi-square test or Fisher's exact test for categorical variables. * p-value ≤0.05. † p-value = 0.05 when compared to the PD and HD groups (Mann-Whitney test or Fisher's exact test). ‡ p-value = 0.05 when compared to the PD and KT groups (Mann-Whitney test or Fisher's exact test). § p-value = 0.05 when compared to the HD and KT groups (Mann-Whitney test or Fisher's exact test).

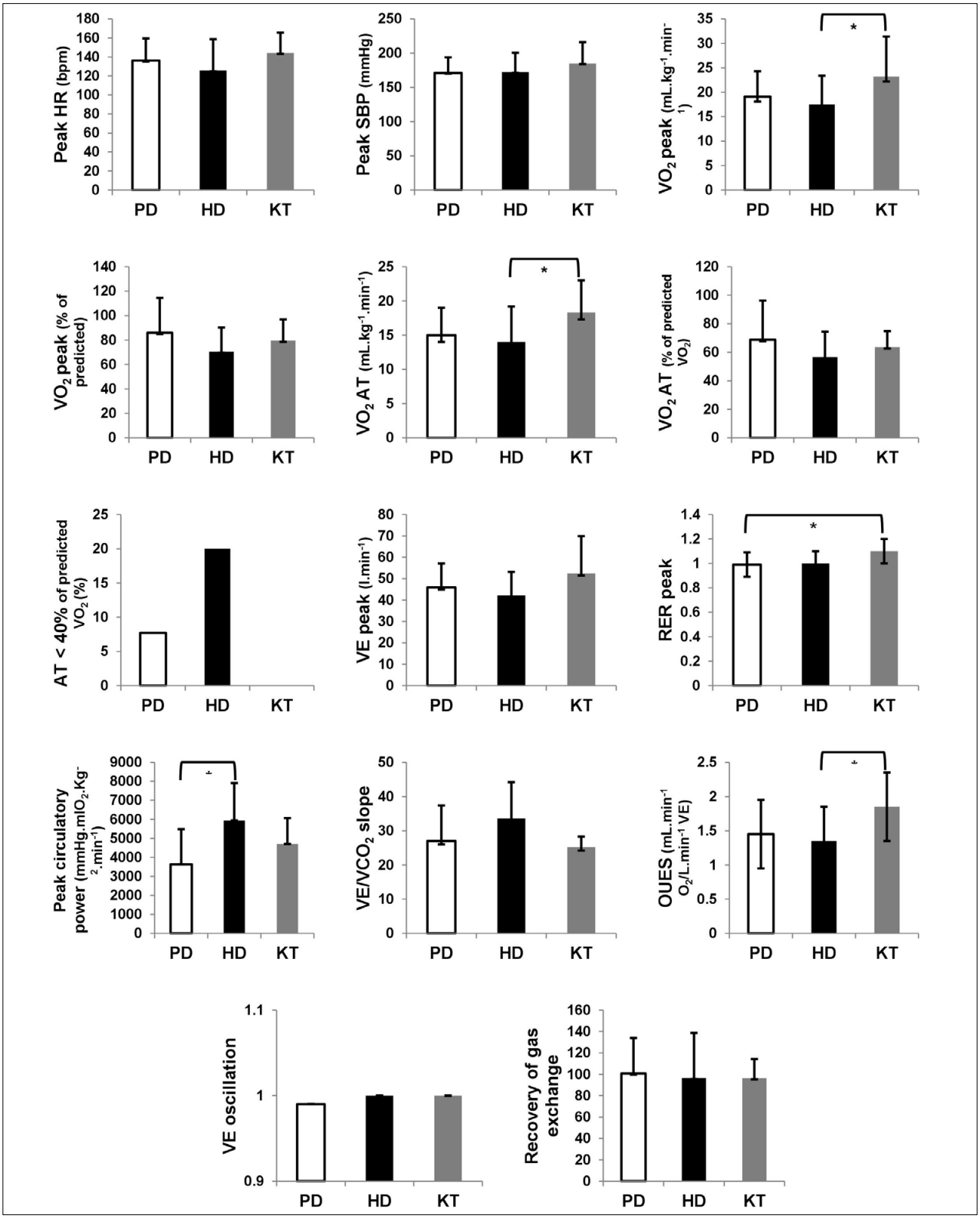


**FIGURE 2**

lifestyle was negatively and significantly associated with $VO_2$ peak in patients in the KT group (b=-11.63, p-value= 0.007), but not in the PD (b=-1.85, p-value=0.487) and HD (b=-2.67, p-value=0.483) groups. The analysis of the multiple linear regression model for the KT group was performed. In the post-kidney transplant patient population, the constant $VO_2$ peak was 54.59 mL.kg$^{-1}$.min$^{-1}$ (adjusted $R^2$=0.76; p-value<0.001). Higher age (b=-0.51 [95% CI=-0.85 – -0.18], p-value=0.007) and sedentary lifestyle (b=-9.28 [95% CI= -14.83 – -3.72], p-value=0.004) were significant predictors of lower $VO_2$ peak.

## DISCUSSION

To our knowledge, this is the first study to evaluate measures of functional cardiovascular reserve in CKD patients and their association with the stages of kidney disease. Studies involving objective measures of the functional cardiovascular reserve are common for patients with heart disease[5,6], but for CKD patients, such studies are rare. In this study, we detected that $VO_2$ peak and $VO_2$ AT in pre-dialysis, hemodialysis, and post-kidney transplant patients were reduced to 86% and 69%, 70% and 57%, and 79% and 64% of the predicted value, respectively. A previous study has shown that reduced $VO_2$ peak and $VO_2$ AT values were associated with an increased risk of premature death in CKD patients[14]. The present study further demonstrated that these parameters were significantly reduced in patients in the HD group compared to patients in the KT group. Other findings were that a) patients in the PD group had lower values of circulatory power when compared to those in the HD group, and b) OUES was significantly lower in the HD group when compared to the KT group.

OUES and circulatory power are variables which are evaluated less frequently than other traditional indices. Reduced OUES values[5,15] and circulatory power[16,17] predict a worse prognosis in heart disease. Despite the great potential of these variables for clinical evaluation[16-18], we did not find its use in the population of CKD patients, so our data are pioneering and can serve as a comparison for future studies. When comparing our OUES data with those from another population that also had a chronic limiting disease, such as patients with heart failure (1.96 $ml.min^{-1}$)[5], our patients performed worse regardless of the stage of CKD; only the KT group had slightly similar values.

$VO_2$ peak, $VO_2$ AT, and OUES were significantly better in post-kidney transplant patients, confirming their better exercise capacity when compared to patients in the HD group. These findings corroborate the literature that shows that kidney transplant is the only treatment that offers better survival compared to other renal replacement therapies. A successful kidney transplant reduces the risk of cardiovascular mortality when compared to maintaining dialysis therapy[14,19,20]. A recent study has demonstrated an improvement in the survival of patients with reduced functional cardiovascular reserve after kidney transplant[14].

Although $VO_2$ peak, $VO_2$ AT, and OUES were better in the post-kidney transplant patients, all the other measures of the functional cardiovascular reserve were not significantly different from the patients in the PD and HD groups. This evidences that the improvement in exercise capacity is not complete, and that it depends on other factors such as the adoption of a healthy lifestyle with regular practice of exercise. For the KT patients, a sedentary lifestyle was a significant independent predictor of lower $VO_2$ peak. Physical training has been shown to improve $VO_2$ peak in patients undergoing long-term hemodialysis[21].

Comparable reduced $VO_2$ peak values (18.8 $mL.kg^{-1}.min^{-1}$)[10]; (18.5 $mL.kg^{-1}.min^{-1}$)[21]; (18.6 $mL.kg^{-1}.min^{-1}$)[7] were documented in previous studies in CKD patients undergoing hemodialysis, but other measures of the cardiovascular reserve were not available for comparison[7,22]. A comparison with data from Sietsema et al.[7,22] reveals that our patients' hemoglobin levels were lower (11.2 and 11.8 $g.dL^{-1}$), although the dialysis time was similar (41.5 and 32.0 months). Our patients were older and had a higher BMI, which may result in a lower $VO_2$ peak; however, the $VO_2$ peak was comparable across studies.

The hemoglobin levels of patients in our study were lower (11.8 $g.dL^{-1}$) when compared to the study of Ting et al.[10], despite dialysis time (32.0 months), age (53.3 years), and BMI (27.2 $kg.m^{-2}$) being similar. This study evaluated other objective measures of cardiovascular reserve such as $VO_2$ peak (73.4% of predicted), $VO_2$ AT (11.2 $mL.kg^{-1}.min^{-1}$), $VO_2$ AT (43.9% of predicted $VO_2$), $VE/VCO_2$ slope (29.3), and HR peak (132.8 bpm), which were also relatively similar to those found in our study; however, our HD patients presented worse performance, except in $VO_2$ AT.

Patients in the studied HD group presented a higher prevalence of anemia and significantly lower hemoglobin and hematocrit levels when compared to patients in the PD and KT groups. It is known that the presence of anemia in CKD is determined by different factors such as relative erythropoietin (EPO) deficiency, iron deficiency, inflammation, hyperparathyroidism, blood loss, decreased half-life of red blood cells, and deficiency of folic acid and vitamin B12[23].

Creatinine and urea are markers traditionally used to characterize the impairment of glomerular function. In our study, the values of these two markers for all three groups support the values of erythrocyte parameters since the greater the renal damage, the lower the EPO production, and consequently, the lower the erythrocyte production leading to an anemic state[24]. Thus, even using recombinant

human erythropoietin, hemodialysis patients present a greater degree of anemia, and a greater degree of functional impairment. Pre-dialytic patients still have higher hemoglobin concentrations due to better renal integrity. Patients after renal transplantation, due to the production of the grafted organ, are able to produce a greater amount of EPO and, therefore, have higher hemoglobin levels.

Hemoglobin and iron are involved in the processes of releasing oxygen to tissues, so they may affect exercise capacity. A recent study in patients with heart failure observed a significant reduction in exercise capacity in parallel to reduced hemoglobin levels, and in patients with anemia and iron deficiency, exercise capacity was significantly lower than in patients with isolated anemia or iron deficiency[25]. We observed a significant difference in hemoglobin levels between the PD, HD, and KT groups, and in the $VO_2$ peak and $VO_2$ AT between the HD and KT groups. However, in a subgroup analysis, we did not observe a significant difference in $VO_2$ peak between patients with and without anemia (p-value=0.390); additionally, there was no correlation between hemoglobin levels and $VO_2$ peak (r=0.189; p-value=0.250) and $VO_2$ AT (r=0.174, p-value=0.290). This evidences that in this population, regardless of the CKD stage, anemia did not significantly affect the measures of cardiovascular reserve and was not a predictor of $VO_2$ peak.

This study is characterized by the initial exploration of measures of functional cardiovascular reserve in CKD patients and by comparing these measures between the different stages of the disease. Like any study, it has some limitations. First, although the literature indicates that measures of the functional cardiovascular reserve are prognostic markers in patients with heart failure, the cross-sectional nature and relatively small sample size of the present study did not allow us to expand the prognostic utility of both indices. Therefore, further prospective evaluations in this population are required to use these measures as prognostic markers.

## CONCLUSIONS

Our study shows that patients with CKD present a reduction of functional cardiovascular reserve regardless of the stage of the disease they are in. However, hemodialysis patients presented a greater reduction of cardiovascular reserve when compared to post-kidney transplant patients. Since a sedentary lifestyle was an independent predictor of the lowest $VO_2$ peak in post-kidney transplant patients, the importance of physical training to improve functional cardiovascular reserve is emphasized, especially in these patients.

### Authors' contributions

Schneider J designed the study, analyzed the data, and wrote the manuscript. Fontela PC reviewed the analysis of the data and the manuscript and provided intellectual content of critical importance to the work described. Frizzo MN, Franz LBB, and Oliveira OB reviewed the manuscript. Winkelmann ER designed the study, reviewed the analysis of the data, and wrote the manuscript. All authors approved the final version of the manuscript.


## RESUMO

OBJETIVO: *Pacientes com doença renal crônica (DRC) apresentam redução no consumo de oxigênio no pico do exercício ($VO_2$ pico). Nenhum estudo avaliou medidas objetivas da reserva cardiovascular, além do $VO_2$ pico e do $VO_2$ no limiar anaeróbio (LA), e comparou essas medidas entre pacientes com DRC nos diferentes estágios da doença.*

MÉTODOS: *Cinquenta e oito pacientes [grupo pré-diálise (PD)=26, grupo hemodiálise (HD)=20 e grupo pós-transplante (PT)=12] foram incluídos. As seguintes medidas da reserva cardiovascular foram obtidas: 1) frequência cardíaca (FC) pico; 2) pressão arterial sistólica (PAS) pico; 3) $VO_2$ pico e % do predito; 4) $VO_2$ LA e % do $VO_2$ predito; 5) potência circulatória pico; 6) eficiência ventilatória para a produção de dióxido de carbono ($VE/VCO_2$ slope); 7) eficiência ventilatória para o consumo de oxigênio (Oues); 8) recuperação das trocas gasosas.*

RESULTADOS: *O $VO_2$ pico e o $VO_2$ LA nos grupos PD, HD e PT foram reduzidos para 86% e 69%, 70% e 57%, e 79% e 64% do valor previsto, respectivamente. Pacientes do grupo HD obtiveram $VO_2$ pico (17,5±5,9 vs. 23,2±8,2 [p=0,036]) e $VO_2$ LA (14,0±5,2 vs. 18,3±4,7 [p=0,039]) mais baixo, comparado aos pacientes PT. A Oues foi significativamente menor no grupo HD comparado ao grupo PT (p=0,034). Idade nos grupos PD, HD e PT, e sedentarismo no grupo PT foram preditores do $VO_2$ pico.*

CONCLUSÃO: *Pacientes com DRC apresentam redução da reserva cardiovascular independentemente do estágio da doença. No entanto, pacientes em hemodiálise apresentam uma redução mais acentuada da reserva cardiovascular quando comparados aos pacientes pós-transplante.*


PALAVRAS-CHAVE: *Insuficiência renal crônica. Teste de esforço. Transplante de rim. Diálise renal.*

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ORIGINAL ARTICLE

# miR-125a-5p inhibits cancer stem cells phenotype and epithelial to mesenchymal transition in glioblastoma

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## SUMMARY

OBJECTIVE: *Glioblastoma (GBM) is a common type of cancer with high mortality. Epithelial to mesenchymal transition (EMT) plays a vital role in the development of glioblastoma. The aim of this study is to evaluate the role of miR-125a-5p in glioblastoma and in the tumorigenesis of chemotherapeutic drug-resistant cancer stem-like cells in brain glioma.*

METHODS: *The role of miR-125a-5p in the regulation of CSCs, EMT, migration, and invasion in glioblastoma was measured in this study.*

RESULTS: *We showed the roles of miR-125a-5p in the regulation of CSCs, EMT, migration, and invasion in glioblastoma. miR-125a-5p can inhibit the CSCs phenotype and EMT in glioblastoma cells. In addition, its over-expression can significantly regulate CSCs-associated genes and EMT-associated gene expression in glioblastoma cells.*

CONCLUSIONS: *We concluded that miR-125a-5p is one of the key microRNAs regulating CSCs and EMT programs in glioblastoma. The results suggested that miR-125a-5p might be a novel therapy target for glioblastoma.*

KEYWORDS: *Glioblastoma. Neoplastic stem cells. MicroRNAs.*

## INTRODUCTION

Glioblastoma (GBM) is one of the most common and lethal primary malignant tumors with a median survival of about one year[1-3]. A subgroup of glioblastoma cells, known as stem cell-like cells in GBM were identified and proved to be responsible for the initiation of glioma and the resistance of GBMs to clinical therapies[4,5]. The epithelial-mesenchymal transition (EMT) and its reverse process, named the mesenchymal-epithelial transition (MET), play crucial roles in embryogenesis[6]. For example, the mesoderm generated by EMTs develops into multiple tissue types and, later in development, mesodermal cells generate epithelial organs, such as the kidney and ovary through MET[7]. The EMT of glioblastoma partly contributes to the development of resistance to chemotherapy or radiotherapy[8,9]. Thus, understanding the mechanism underlying cancer stem cells (CSCs) and EMT in glioblastoma for novel drug targets as well as designing new therapeutic strategies should open an opportunity for cancer treatment.

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miRNAs are small (19–25 nucleotides) noncoding, single-stranded RNAs that control gene expression by targeting mRNA transcripts and leading to their translational repression or degradation[10,11]. Multiple genes regulated by miRNAs play crucial roles in biological processes of tumor progression, including migration, invasion, EMT, and cancer stem cell[12-14]. Recently, a study indicated that miR-125a-5p could inhibit glioblastoma cell proliferation and promote cell differentiation[15].

In this study, we showed the roles of miR-125a-5p in the regulation of CSCs, EMT, migration, and invasion in glioblastoma. miR-125a-5p can inhibit CSCs phenotype and EMT in glioblastoma cells. In addition, its over-expression can significantly regulate CSC–associated genes and EMT-associated gene expression in glioblastoma cells. Thus, we concluded that miR-125a-5p is one of the key microRNAs regulating CSCs and EMT programs in glioblastoma. The results indicate that miR-125a-5p might be a novel target for glioblastoma therapy.

## METHODS

### Glioblastoma Cell Line

Human glioblastoma U87MG cells were purchased from the MD Anderson Cancer Center (Houston, TX, USA). Complete medium (RPMI 1640 supplement with 10% FCS, Gibco, Grand Island, NY, USA) was used for cell culture, and the cells were maintained in a humidified atmosphere containing 5% $CO_2$ at 37ºC.

### Pre-miR-125a-5p/control miR and Transfection

Pre-miR-125a-5p and control-miR were purchased from Ambion (Austin, TX, USA). A final concentration of 50 nM of pre-miR-125a-5p and its respective negative control (control-miR) were used for each transfection. For transfection experiments, the cells were cultured in serum-free medium without antibiotics at 60% confluence for 24h and then transfected with the transfection reagent (Lipofectamine 2000, Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. After incubation for 6h, the medium was removed and replaced with the normal culture medium for 48h, unless otherwise specified.

### Real-time PCR for miRNA

The total RNA from the cultured cells, with efficient recovery of small RNAs, was isolated using the mirVanamiRNA Isolation Kit (Ambion, Austin, TX, USA). Detection of the mature form of miRNAs was performed using the mirVanaqRT–PCR miRNA Detection Kit, according to the manufacturer's instructions (Ambion, Austin, TX, USA). The U6 small nuclear RNA was used as an internal control.

### Sphere Growth

Cells ($10^3$/ml) in serum-free RPMI1640/1mM Na-pyruvate were seeded on 0.5% agar precoated, 6-well plates. After the first week, half the medium was replaced every third day. Single spheres were picked and counted.

### Western Blot Analysis

Western blot analysis was performed as described before. Mainly, after incubation with primary antibody anti-CD133 (1:500; Abcam, Cambridge, MA, USA), anti-body anti-OCT-4 (1:500; Abcam, Cambridge, MA, USA), anti-Nanog (1:500; Abcam, Cambridge, MA, USA), anti-E-Cadherin (1:500; Abcam, Cambridge, MA, USA), anti-Vimentin (1:500; Abcam, Cambridge, MA, USA), anti-MMP2 (1:500; Abcam, Cambridge, MA, USA), anti-MMP6 (1:500; Abcam, Cambridge, MA, USA) and anti-β-actin (1:500; Abcam, Cambridge, MA, USA) overnight at 4ºC, IRDyeTM-800 conjugated anti-rabbit secondary antibodies (Li-COR, Biosciences, Lincoln, NE, USA) were used for 30 min at room temperature. The specific proteins were visualized by Odyssey™ Infrared Imaging System (Gene Company, Lincoln, NE, USA).

### Reverse transcription-polymerase chain reaction and real-time for mRNA

Total RNA was isolated from cells or tissues using Trizol reagent (Invitrogen, Carlsbad, CA, USA). cDNA was synthesized from 1 µg of total RNA in a 20 µl reverse transcription (RT) system. Real-time PCR for Vimentin, Fibronectin, and E-Cadherin was done with a Power SYBR Green PCR Master Mix (Applied Biosystems, Carlsbad, CA, USA) according to the manufacturer's protocol. The housekeeping gene Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as the RNA loading control. The PCR primer sequences are as follows:

GAPDH:
Forward-5'-ATTCAACGGCACAGTCAAGG-3',
Reverse-5'-GCAGAAGGGGCGGAGATGA-3';

Vimentin:
Forward-5′-GACAATGCGTCTCTGGCACGTCTT-3′,
Reverse-5′-TCCTCCGCCTCCTGCAGGTTCTT-3′;

Fibronectin:
Forward-5'-TTTTGACAACGGGAAGCATTATCAGATAA-3',
Reverse-5-TGATCAAAACATTTCTCAGCTATTGG-3';

E-Cadherin:
Forward-5′-TCA ACG ATC CTG ACC AGC AGT TCG-3′,
Reverse- 5′-GGT GAA CCA TCA TCT GTG GCG ATG-3′.

### Immunofluorescence Analyses

For cell immunofluorescence analyses, cells were plated on glass coverslips in six-well plates and transfected as indicated. After 48h of the transfection, coverslips were stained with the mentioned anti-Vimentin. The Alexa Fluor 488 goat anti-rabbit IgG antibody was used as a secondary antibody (Invitrogen, Carlsbad, CA, USA). Coverslips were counterstained with DAPI (Invitrogen-Molecular Probes, Eugene, Oregon, USA) for visualization of the nuclei. Microscopic analysis was performed with a confocal laser-scanning microscope (Leica Microsystems, Bensheim, Germany). Fluorescence intensities were measured in a few viewing areas for 300 cells per coverslip and analyzed using ImageJ 1.37v software (http://rsb.info.nih.gov/ij/index.html).

### Wound Healing Assay

It was performed as described before[16].

### Statistical Analysis

Data are presented as mean±standard deviation. Student's t-test (two-tailed) was used to compare the two groups ($P<0.05$ was considered significant) unless otherwise indicated ($x^2$ test).

## RESULTS

### miR-125a-5p is downregulated in glioblastoma

In an attempt to identify miR-125a-5p expression between glioblastoma tissues and adjacent normal tissues, we performed real-time PCR in glioblastoma tissues versus normal tissues. MicroRNA was isolated from 31 pairs of glioblastoma tissues and adjacent normal tissues. We found that miR-125a-5p was significantly decreased in glioblastoma tissues compared with adjacent normal tissues.

### miR-125a-5p inhibits the formation of stem cell-like population and regulates CSCs-associated gene expression in glioblastoma cells

To assess the role of miR-125a-5p in glioblastoma, we transfected U87MG cells with pre-miR-125a-5p or control miR, and then real-time PCR was performed. We found that miR-125a-5p was significantly increased in the cells transfected with pre-miR-125a-5p (Figure1A).

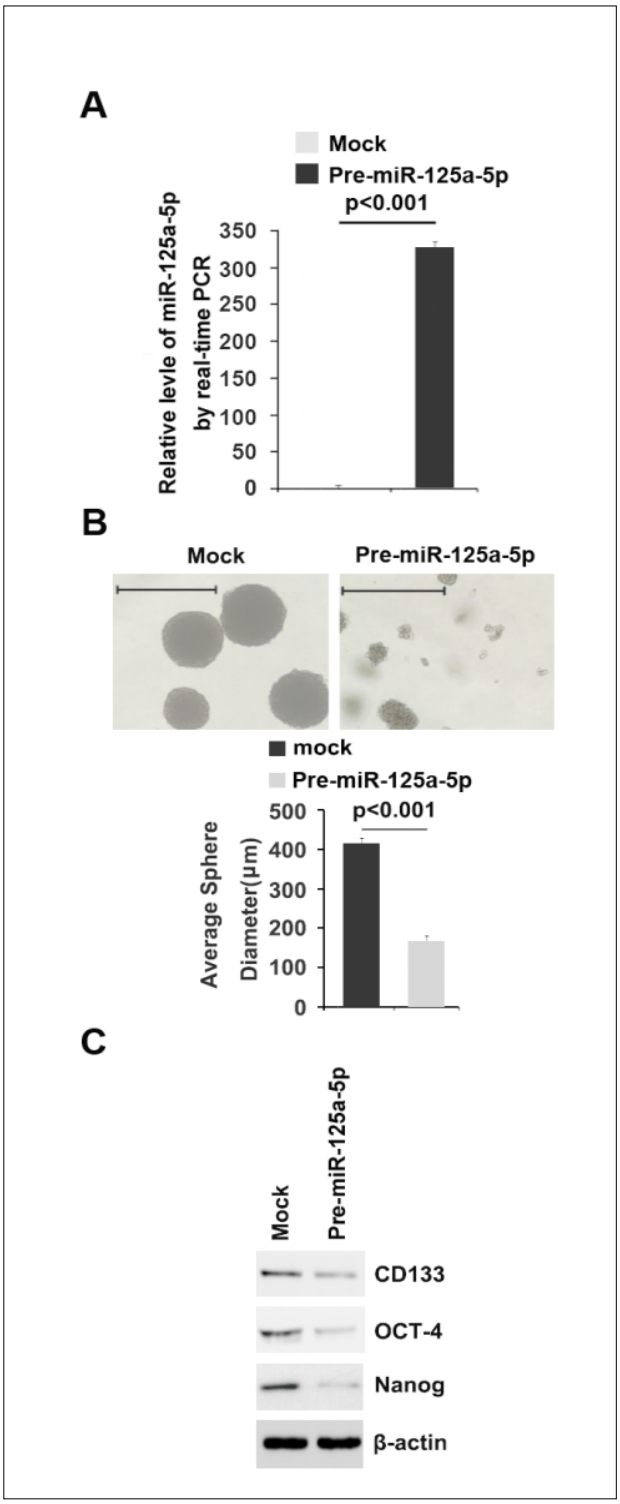
To determine whether miR-125a-5p could affect stem-like cell characteristics, we performed a sphere-forming assay to assess the capacity of CSC or CSC-like cells to self-renewal in this study. We found that the formation of spheres was decreased by miR-125a-5p in U87MG cells (Figure1B). We also performed western blot to detect whether CSCs markers - CD133, OCT-4, and Nanog were affected by miR-125a-5p in the cells. The results showed that CD133, OCT-4, and Nanog protein were significantly decreased by miR-125a-5p in U87MG cells (Figure1C).

### miR-125a-5p inhibits epithelial-mesenchymal transition (EMT) in glioblastoma cells

Increased formation of stem cell-like population can result in EMT of cancer cells[17]. Thus, miR-125a-5p could inhibit EMT in glioblastoma cells. To determine whether U87MG cells with stem-like cell characteristics phenotype could have changed the MET, we transfected U87MG cells with pre-miR-125a-5p and then observed that its overexpression caused significant changes in the cell's morphology (MET, mesenchymal to epithelial transition) (Figure2A).

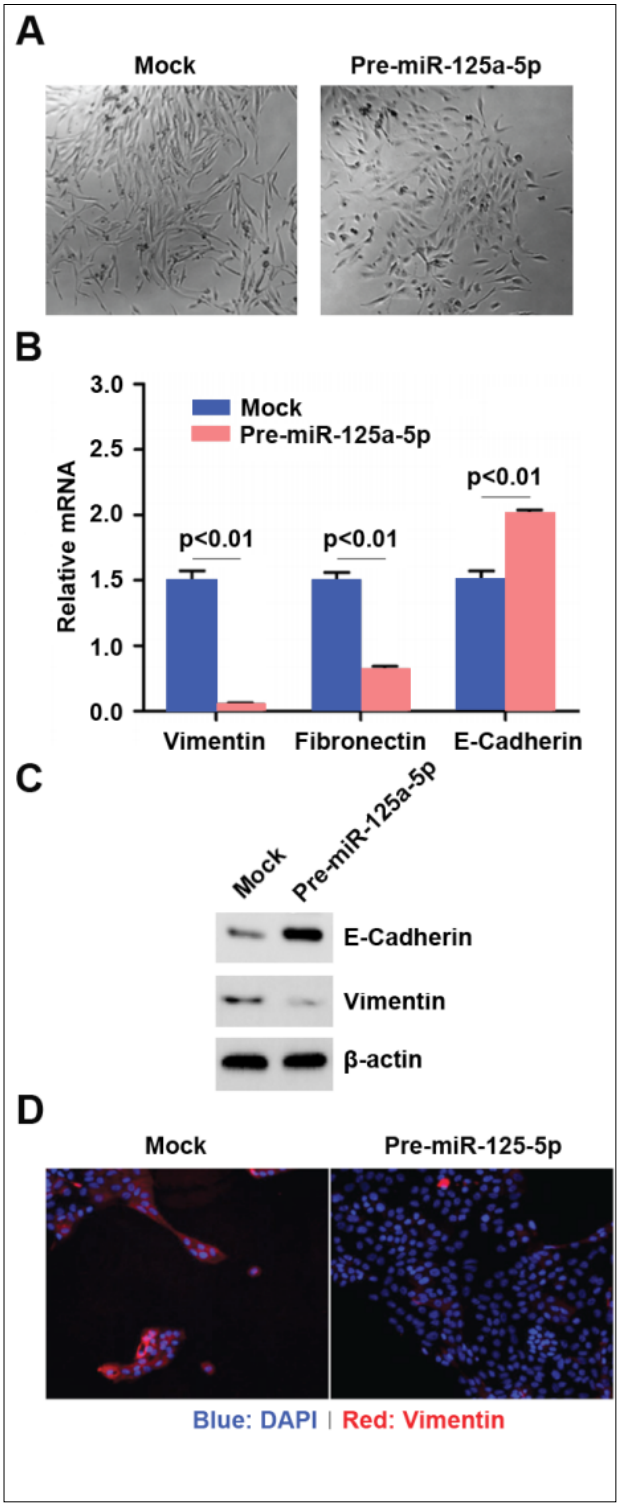
To further verify that the changes in cell morphology were caused by the MET expression levels of epithelial and mesenchymal markers were compared in U87MG cells transfected with pre-miR-125a-5p with the cells transfected with control miR. The results of real-time PCR revealed that the E-cadherin mRNA (epithelial marker) was induced, and Vimentin as well as Fibronectin mRNA (mesenchymal markers) were suppressed by miR-125a-5p in U87MG cells (Figure2B). To further analyze whether miR-125a-5p could affect E-cadherin and Vimentin, we performed western blotting to detect their expression in the cells transfected with pre-miR-125-5p. The results demonstrated that E-cadherin was promoted, and Vimentin was suppressed by miR-125a-5p (Figure2C). In order to further show the effect of miR-125a-5p on Vimentin protein, we performed

**FIGURE1.** MIR-125A-5P INHIBITS THE FORMATION OF STEM CELL-LIKE POPULATION AND REGULATES CSCS-ASSOCIATED GENES EXPRESSION IN GLIOBLASTOMA CELLS




**A.** Real-time PCR for miR-125a-5p in U87MG cells transfected with pre-miR-125a-5p or control miR (mock). U6 was a loading control. n=3. **B.** Sphere growth for U87MG cells transfected with pre-miR-125a-5p and control miR (mock). Bars=1000μm. n=3. **C.** Western Blot for CD133, OCT-4, and Nanog in U87MG cells transfected with pre-miR-125a-5p and control miR (mock). β-actin was a loading control. n=3

**FIGURE 2.** MIR-125A-5P INHIBITS EPITHELIAL-MESENCHYMAL TRANSITION (EMT) IN GLIOBLASTOMA CELLS




**A.** Images for U87MG cells transfected with pre-miR-125a-5p and control miR (mock). n=3. **B.** Real-time RT–PCR for Vimentin, Fibronectin, and E-cadherin mRNA in U87MG cells transfected with pre-miR-125a-5p or control miR (mock). GAPDH was a loading control. n=3. **C.** Western Blot for E-cadherin and Vimentin in U87MG cells transfected with pre-miR-125a-5p and control miR (mock). β-actin was a loading control. n=3. **D.** Immunofluorescence analyses for Vimentin protein in U87MG cells transfected with pre-miR-125a-5p and control miR(mock). n=3

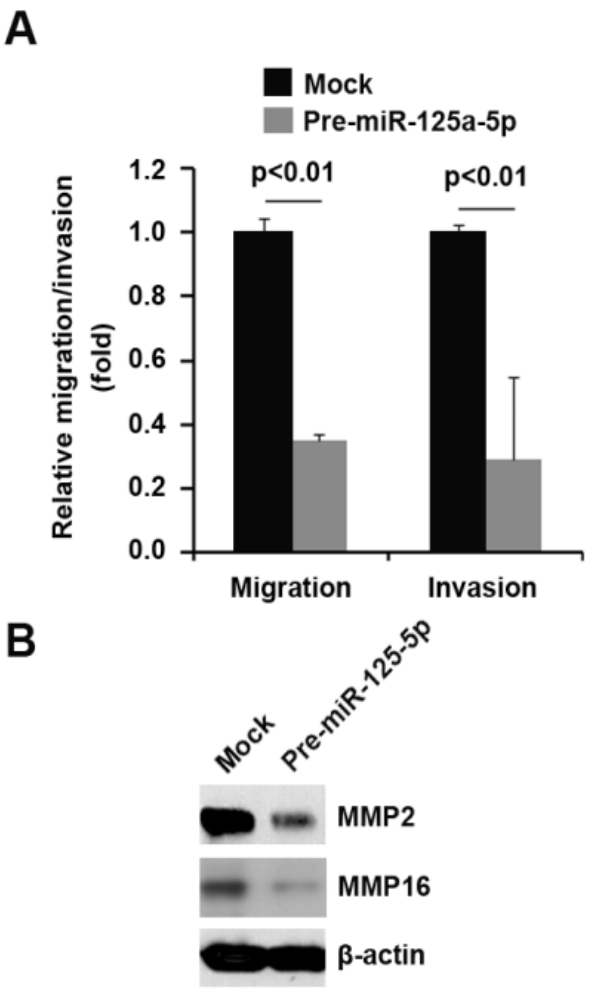
immunofluorescence analysis. Consistent with the results of western blot, we found that Vimentin expression was inhibited in the cells transfected with miR-125a-5p (Figure2D).

### miR-125a-5p can suppress migration and invasion as well as attenuate MMP2 and MMP16 protein in U87MG cells

EMT is not only associated with tumor stem-like cell characteristics but also provides those cells with a distinct advantage for migration and invasion[18]. Thus, we reasoned that miR-125a-5p could also affect invasion and migration in U87MG cells. To identify this reason, we performed an invasion and migration assay. We found that miR-125a-5p overexpression could suppress migration and invasion in U87MG cells (Figure3A). In addition, we found that MMP2 and MMP16 protein can be inhibited by miR-125-5p (Figure3B).

## DISCUSSION

Evidence has shown that altered patterns of miRNA expression correlate with the progression of glioblastoma[19]. The behavior of miRNAs is complex because they regulate hundreds of targets, resulting in the downregulation of numerous target genes, including oncogenes and tumor suppressors[20]. MicroRNAs play crucial roles in glioblastoma stem cell-like phenotypes and EMT[21]. The dynamic nature of cancer stem cells and EMT that underlie angiogenesis, metastasis, proliferation, migration, and invasion, has profound implications for glioblastoma therapy[22]. Thus, the molecular knowledge of CSCs and EMT in glioblastoma




**A.** Invasion and migration assays for U87MG cells transfected with pre-miR-125a-5p and control miR (mock). n=3. **B.** Western Blot for MMP2 and MMP16 in U87MG cells transfected with pre-miR-125a-5p and control miR (mock). β-actin was a loading control. n=3

**FIGURE 3.** MIR-125A-5P CAN SUPPRESS MIGRATION AND INVASION AS WELL AS ATTENUATE MMP2 AND MMP16 PROTEIN IN U87MG CELLS

is important because it will be helpful in the discovery of novel drug targets as well as in the design of new therapeutic strategies for improving the treatment of glioblastoma.

miR-125a-5p has been identified as a tumor suppressor gene in various cancers[15,23]. More recently, it has been reported that miRNA-125a-5p can inhibit glioblastoma cell proliferation and promote cell differentiation[15]. Consistent with these results, we showed that miR-125a-5p was downregulated in glioblastoma tissues. CD133 has been proposed as a stem cell marker, and it can affect clinical outcomes in glioblastoma[24]. More than 50% of Oct4-positive cells expressed the putative CSC markers CD133[25]. NANOG can promote gliomasphere clonogenicity, CD133(+) stem cell behavior, and proliferation[26]. In this study, we found that the overexpression of miR-125a-5p inhibited the formation of stem cell-like population and CD133, OCT-4, and Nanog protein expression. Molecular connections between the EMT program and the stem-cell state are beginning to emerge[27]. We showed that miR-125a-5p also suppressed EMT in glioblastoma cells, indicating that miR-125a-5p is one of many connections between cancer stem cells and EMT in glioblastoma.

CD133-positive tumor cells and EMT confer glioma radioresistance, chemotherapeutic-drug resistance, and it could be the source of tumor recurrence after radiation. Targeting CD133 in cancer stem cells may overcome this radioresistance and chemotherapeutic-drug resistance as well as provide a therapeutic model for malignant brain cancers[28]. Thus, we reason that miR-125a-5p may play an important role in glioma radioresistance and chemotherapeutic-drug resistance.

## DISCLOSURE

The authors report no conflicts of interest in this work.

### Author Contributions

Conceptualization, Xi-De Zhu; formal analysis, Zhen-Juan Gao; writing — original draft preparation, Xi-De Zhu; writing — review and editing, Xi-De Zhu; supervision, Qi Pang; funding acquisition, Guo-Dong Zheng


## RESUMO

OBJETIVO: *O glioblastoma (GBM) é um câncer comum e de alta mortalidade. A transição epitélio-mesênquima (EMT) desempenha um papel vital no desenvolvimento do glioblastoma. O objetivo deste estudo é avaliar o papel do miR-125a-5p no glioblastoma e a tumorigênese de células-troco cancerígenas resistentes a medicamentos quimioterápicos em gliomas cerebrais.*

METODOLOGIA: *Os papéis do miR-125a-5p na regulação de células-tronco cancerígenas, EMT, migração e invasão do glioblastoma foram medidos neste estudo.*

RESULTADOS: *Mostramos a função do miR-125a-5p na regulação das células-tronco cancerígenas, EMT, migração e invasão do glioblastoma. O miR-125a-5p pode inibir o fenótipo e a EMT de células-tronco cancerígenas em células de glioblastoma. Além disso, a sua superexpressão pode regular de forma significante genes associados às células-tronco cancerígenas e a expressão de genes associados à EMT em células de glioblastoma.*

CONCLUSÕES: *Concluímos que o miR-125a-5p é um dos principais microRNAs na regulação de células-tronco cancerígenas e programas de EMT em glioblastomas, e os resultados sugerem que o miR-125a-5p pode ser um novo alvo terapêutico em casos de glioblastoma.*


PALAVRAS-CHAVE: *Glioblastoma. Células-tronco neoplásicas. MicroRNAs.*

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ORIGINAL ARTICLE

# Comparison of the effect of ultrasound-guided thoracic paravertebral nerve block and intercostal nerve block for video-assisted thoracic surgery under spontaneous-ventilating anesthesia

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## SUMMARY

OBJECTIVE: *The aim of the current study was to compare the efficacy of two different techniques for blocking chest nerves during video-assisted thoracic surgery (VATS) under spontaneous-ventilating anesthesia.*

METHODS: *One hundred patients were recruited in this study and divided into two groups. The first, P group, underwent the TPVB approach; the second, I group, underwent the ICNB approach. Then, the rate of clinical efficacy, duration of the block procedure, and its complications were recorded for comparison of the effect of the two approaches.*

RESULTS: *No difference was found in the clinical effect of chest nerve blocks between the two groups. Two patients in the ICNB group were converted to general anesthesia due to severe mediastinal flutter (grade three). The number of patients who had grade one mediastinal flutter in the TPVB group was significantly higher than in the ICNB group. Vascular puncture was detected in four patients in the ICNB group and in one patient in the TPVB group. No other complications were observed.*

CONCLUSIONS: *No difference was found regarding the clinical efficacy in the two groups. However, ultrasound-guided TPVB was superior to ultrasound-guided ICBN during VATS for pulmonary lobectomy under spontaneous-ventilating anesthesia. Additionally, vascular puncture should receive more attention.*

KEYWORDS: *Anesthesia. Nerve block. Thoracic surgery. Video-assisted surgery.*

## INTRODUCTION

Thoracic disease is a high-risk clinical finding. Thoracoscopic pulmonary nodule resection represents the most effective and suitable treatment for pulmonary nodules and can provide essential histopathologic information for definitive diagnosis, staging, and primary treatment. However, conventional thoracoscopic surgery is performed under general anesthesia with double-lumen endotracheal intubation[1]. This requires the use of a large number of anesthetics, including sedatives, analgesics, and muscle relaxants,

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which may cause airway damage, respiratory and cardiac complications, as well as residual effects of the drug, precluding early recovery[2-4]. It has been reported that the incidence of postoperative complications is 12%-40%[3]. Pulmonary complications are the main reason for prolonging hospital and intensive care unit (ICU) stays. A nerve block can reduce the incidence of pulmonary complications[4]; therefore, this is an essential and vital anesthetic technique to ensure the rapid recovery of patients after thoracoscopic surgery[6].

A variety of techniques have been proposed to complete thoracoscopic surgery under spontaneous-ventilating anesthesia, including epidural blocks, paravertebral nerve blocks, intercostal blocks, and local incision anesthesia[7,8]. Along with the technologic advances in ultrasonographic applications over the last decade, many ultrasound-guided nerve block methods have been reported, including ultrasound-guided thoracic paravertebral nerve block (TPVB) and ultrasound-guided intercostal nerve block (ICNB). Within the thoracic paravertebral space, the spinal nerves go out of the intervertebral space and travel to the paravertebral space. The spinal nerves are divided into anterior, posterior, and sympathetic nerves. The posterior branch is divided into the back muscles and skin. The anterior branch divides into a traffic branch, then courses laterally and becomes an intercostal nerve. We directly inject the drug into the paraspinal space, which is composed of the anterior lateral pleural wall layer, the posterior rib transverse ligament, and the medial vertebral body structure[9]. The intercostal nerve is formed by the anterior branch of the thoracic nerve, which is located in the intercostal space. The muscle branches of the intercostal nerve dominate the inner and outer intercostal, thoracic transverse, upper and lower serratus, intra-abdominal and external oblique, abdominal transverse, and abdominal rectus muscles. A local anesthetic is injected approximately 0.3 cm inside the lower edge of the rib[10]. During thoracoscopic surgery, even if the ICNB is completed, it is impossible to ensure that the patient has good analgesia when incising the skin[11]. However, the paravertebral space communicates with the rib space outward, communicates with the vertebral canal inward, and communicates upward and downward with the adjacent segmental paraspinal space. Thus, drug injection into the gap can not only block the corresponding level of the paravertebral nerve but also spread to the adjacent paravertebral nerve and epidural space[12-14]. Theoretically, a TPVB has greater superiority; however, there is a paucity of clinical evidence to support this point.

We compared the effect of the two approaches in patients undergoing thoracoscopic pulmonary nodule resection.

## METHODS

### Patients

In this prospective randomized study, we enrolled 50 patients (18–50 years of age). The allocation of patients receiving a TPVB (P-group) or ICNB (I-group) was performed using a computer-generated randomization scheme. Approval of the study was obtained from the Ethics Committee of the Affiliated People's Hospital of Jiangsu University, and written informed consent was obtained from each of the participants. This study was conducted in accordance with the Declaration of Helsinki.

### Inclusion and exclusion criteria

All patients met the American Society of Anesthesiologists' physical classification class I–II and were intended to undergo thoracoscopic pulmonary nodule resection with spontaneous-ventilating anesthesia. Patients with a known allergy to LAs, an infection at the site of injection, a coagulopathy, a neuromuscular disorder, a BMI ≥ 25 kg/m$^2$, an estimated operative time>3 h, the possibility of major bleeding intra-operatively, a severe cardiopulmonary complication, a spinal or thoracic deformity, respiratory obstruction, and a foreseeable difficult airway were excluded.

### Sample size calculation

We calculated the sample size prior to the implementation of the study using a power and sample size program[15]. According to the existing literature, the pain scores were 5.4 on a scale of 1-10. We considered a pain score reduction of at least 1.5 as clinically significant[16]. If the mean of cohort 1 was 5.4, the mean of cohort 2 was 3.9, and assuming a SD of 2.4, the required sample size in each cohort was 42 with a power of 80%. The significance level was set at an $\alpha$=0.05. Thus, our study recruited 50 patients in each group to meet the sample size requirement.

### Procedure

Upon arrival to the operating room, intravenous access was established, and the patients received

invasive blood pressure monitoring, electrocardiography using lead II, and pulse oximetry monitoring. TPVBs and ICNBs are invasive operations. To improve patient comfort and promote comfortable anesthesia, this study used TPVBs or ICNB after induction of general anesthesia. The patient inhaled oxygen via face mask, followed by anesthesia induction. Dexmedetomidine was injected intravenously with 0.40 μg/kg (infusion in 15 min). The propofol target-controlled infusion (TCI) was 2.50~3.00 μg/ mL. The remifentanil target-controlled infusion (TCI) was 1.00-1.50 μg/mL. When spontaneous respirations ceased, a laryngeal mask was placed[14].

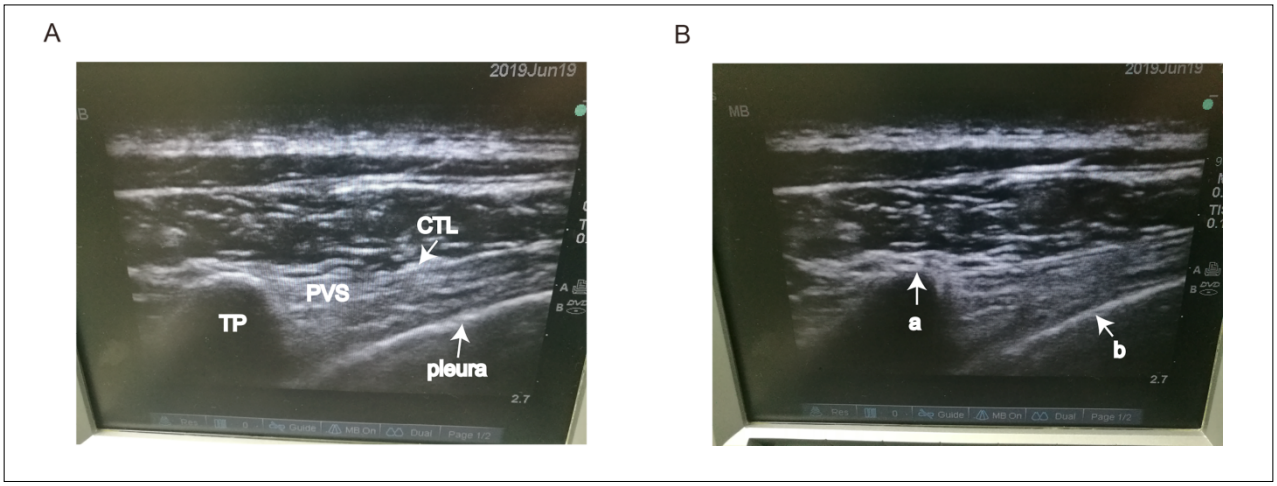
After anesthesia induction, the P group underwent ultrasound-guided TPVB (figure 1). A 22-gauge, 80-mm echogenic needle (SonoPlex cannulas; Pajunk®, Geisingen, Germany), MylabTM25 Gold (Esaote, Genova, Italy), and a linear probe (LA435: 6-18 MHz; Esaote) were used. Povidone-iodine was used to make an aseptic field. The locations of the spinous process, transverse process, and ribs were confirmed by ultrasound. The first rib was identified in the parasagittal plane, and the ribs were counted in order. The T3–4 intercostal space and the transverse process were confirmed by an in-plane intercostal approach, as described by Shibata and Nishiwaki[16]. The needle was in the thoracic paravertebral space, and 1 mL of test dose was applied to confirm the displacement of the pleura. The assistant subsequently injected 14 mL of the prepared drug. The same procedure was applied to the fifth thoracic paravertebral space. At this time, the thoracic paraspinal space was dilated, and the pleura were pushed to the ventral side by local anesthetic. In the I group, ultrasound-guided ICNB[17] (figure 2) was performed in the lateral position. A linear ultrasound probe was placed in the longitudinal plane with the superior portion of the probe rotated 15 degrees laterally at the posterior angulation of the desired rib. The three layers of intercostal muscle (external, internal, and innermost) were identified in the intercostal space between the adjacent ribs. The needle was introduced under guidance until the tip was resting within the internal layer of the intercostal muscle. At that point, the needle was meticulously advanced into the innermost layer of the intercostal muscle. After negative aspiration for air or blood, 0.25% ropivacaine was administered in divided doses at the level of the incision and two spaces above and below the incision.

After the nerve block was completed, the anesthesia was maintained with propofol (TCI, 2.50 μg/mL) and dexmedetomidine (0.20 μg/kg/·h) for continuous pumping. After the artificial pneumothorax collapsed, 0.375% ropivacaine mixed with 1.00% lidocaine was used for the thoracic vagus nerve block, 2.00% lidocaine (5.0 mL) was sprayed on the lung surface and observed for 30 sec. After the vital signs were stable, surgery commenced.

### Outcome assessment

Video-assisted thoracic surgery (VATS) for pulmonary lobectomy was performed by the same thoracic surgery team. The severity of mediastinal flutter was evaluated by the thoracic surgeon who was blinded to the chest nerve block approach used.

**FIGURE 1.** ULTRASOUND-GUIDED PARAVERTEBRAL NERVE BLOCK




(A) The transverse process (TP), costotransverse ligament (CTL), and pleura are identified, and the paravertebral space (PVS) is visualized. (B) a is transverse process; b is parietal pleura.

The mediastinal flutter was classified as follows: grade 1= slight mediastinal flutter; grade 2= moderate mediastinal flutter which would not disturb the surgery; and grade 3= severe mediastinal flutter, which would prevent surgery. Grades 1 and 2 were both considered clinically effective. Patients with grade 3 mediastinal flutter during surgery were converted to general anesthesia with the administration of non-depolarizing muscle relaxants. The duration of the block procedure and complications, such as LA intonation, vascular puncture, hematoma formation, nerve injury, and visceral injury, if any, were also recorded.

### Statistical analysis

Data are expressed as the mean ± SD for age, height, weight, operation, and duration of block procedure. An independent sample unpaired t-test was applied for comparison of age, height, weight, operation, and duration of block procedure in normal distributions, and Mann–Whitney U tests were performed for continuous ASA scores. Chi-squared tests were performed for gender, method of chest nerve block, and complications. All statistical analyses were performed using SPSS 16.0 (SPSS, Inc., Chicago, IL, USA). P-value ≤0.05 was considered as statistically significant.

## RESULTS

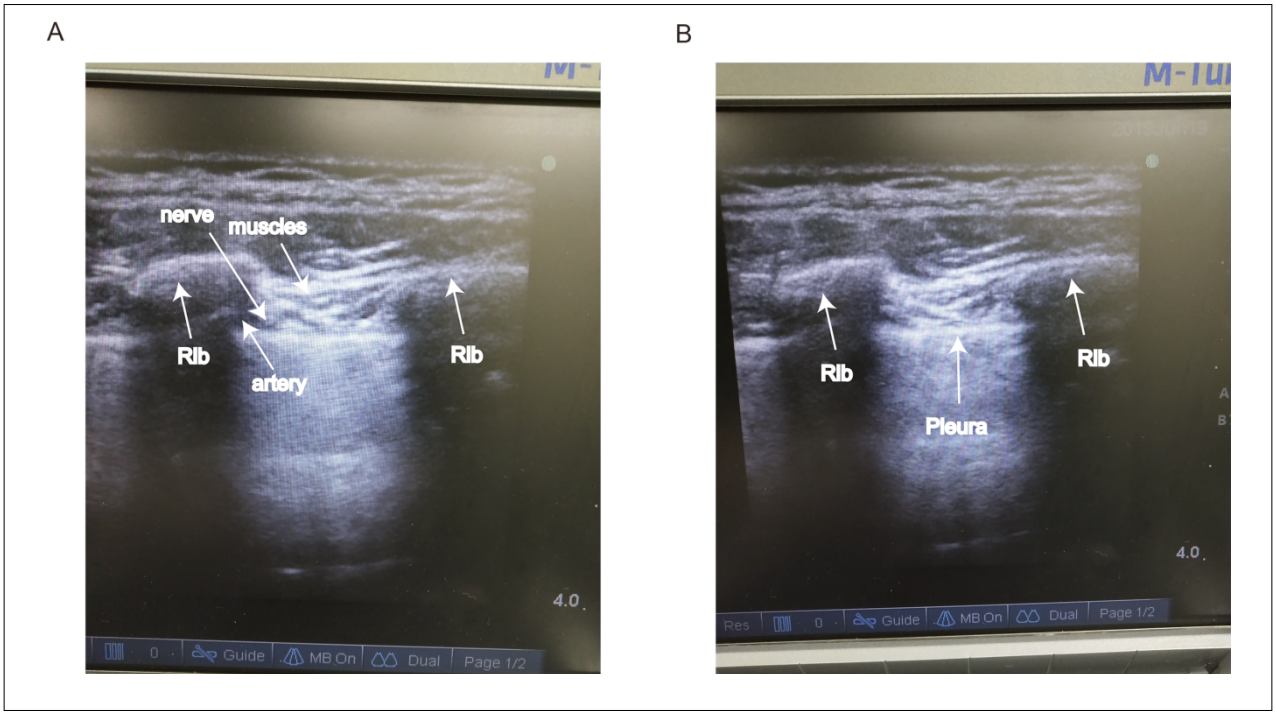
The demographics of the patients are presented in Table 1. There were no significant differences in the duration of surgery or block procedure between

**TABLE 1.** DEMOGRAPHICS OF PATIENTS

| | P-group | I-group | P-value |
|---|---|---|---|
| Age (years) | 41.2±6.1 | 40.4±6.3 | 0.55 |
| Sex | | | |
| Male | 36 | 35 | 0.62 |
| Female | 14 | 15 | |
| Height (cm) | 166.9±6.4 | 167.1±6.3 | 0.79 |
| Weight (kg) | 65.8±7.5 | 66.1±8.1 | 0.78 |
| ASA score | | | |
| I | 12 | 13 | 0.59 |
| II | 38 | 37 | |
| Site of chest nerve block | | | |
| Right | 24 | 25 | 0.56 |
| Left | 26 | 25 | |
| Duration of operation (mins) | 52±7.8 | 51±8.2 | 0.69 |
| Duration of block procedure (hs) | 8.6±2.1 | 8.8±1.8 | 0.49 |
| Complications | | | |
| Local anesthetic intonation | 0 | 0 | 1.0 |
| Vascular puncture | 1 | 4 | 0.01 |
| Hematoma | 0 | 0 | 1.0 |
| Nerve injury | 0 | 0 | 1.0 |
| Visceral injury | 0 | 0 | 1.0 |

Abbreviation: ASA, American Society of Anesthesiologists' physical status classification.

**FIGURE 2.** ULTRASOUND-GUIDED INTERCOSTAL NERVE BLOCK




(A) Depicting the positions of the intercostal muscles, artery, and adjacent ribs. (B) Ultrasound view of the intercostal space.

the two groups. No difference was found in the clinical efficacy of the chest nerve block between the two groups. Two patients in the ICNB group were converted to general anesthesia for severe mediastinal flutter (grade three). The number of patients who had grade one mediastinal flutter in the TPVB group was significantly higher than in the ICNB group. Vascular puncture was noted in four patients in the ICNB group and in one patient in the TPVB group. No other complications were observed.

## DISCUSSION

A TPVB or ICNB combined with a laryngeal mask to retain spontaneous-breathing anesthesia achieved "integral minimally-invasive," including anesthesia, avoiding damage and complications caused by endotracheal intubation, and reducing the use of anesthetics. The adverse reactions and side effects of the drug were alleviated, the influence on the function of the neuroendocrine-immune system of the body was reduced, the post-operative feeding time was shortened, the time course of antibiotics was less, the indwelling time of the drainage tube was shortened, the hospital stay was reduced, rapid recovery was achieved, and medical resources were saved, thus fostering economic and social benefits and greatly improving patient satisfaction[3,4]. We evaluated the effect of TPVB or ICNB based on the mediastinal flutter during surgery and ensured the safety of the procedure by changing the anesthesia technique in a timely fashion. The results of this study indicate that both approaches had similar clinical effectiveness, suggesting a feasible alternative for chest nerve block[18].

When TPVB and ICNB are not effective, the patient will have changes in body movement, blood pressure, and heart rate, and an increase in breathing and in the amplitude of the mediastinal flutter; thus, seriously affecting the operation[19]. The incidence of grade 1 was significantly higher in the P group than the group I, indicating that the TPVB method was superior to the ICNB. Because of the interneuronal brachialization of the intercostal space, the ICNB is also in the position of the surgical incision. The intercostal nerves of the upper and lower gaps should also be blocked at the same time. The intercostal nerve is located in the rib groove at the lower edge of the rib under the arteries and veins. The intercostal nerve and intercostal arteriovenous supply are not easily recognized via ultrasound and increase the probability of arterial injury and the incidence of pneumothorax. We could try to avoid vascular puncture using ultrasound guidance, but complete prevention cannot be assumed and might account for the four vascular puncture patients in group I. A TPVB can achieve a good analgesic effect. A local anesthetic can be injected into the paravertebral space and can spread up or down through the rib head and rib neck, spread to the opposite side through the intervertebral foramen, and outward to the intercostal space level, thereby blocking its movement, sensation, and sympathetic nerves, and exerting clinical effects[20]. This anatomic feature explains the results observed in this study.

As mentioned previously, four approaches have been proposed in different studies and are summarized in Table 2. Ultrasound-guided TPVB or ICNB was used in this study[21]. The operation was simple, the analgesia was exact, and the complications were few; however, the plasma concentration of propofol TCI required in the P group was lower than the I group, which may indicate that the paravertebral block effect is better, the stress response is lighter, and a sympathetic block is achieved. We could try to avoid vascular puncture using ultrasound guidance, but complete prevention cannot be assumed and might account for the two vascular puncture patients in the group I.

There were two limitations to the current study. One major limitation was the small sample size. In addition, a multitude of factors underlies mediastinal flutter, which is mainly caused by insufficient analgesia. In this study, however, the amplitude of the mediastinal flutter was used to reflect the block effect (good or bad); thus, the research results may be biased, seeking better indicators for the effect of the block, and make the research results more realistic.

In summary, ultrasound-guided TPVBs and ICNBs are simple and successful alternative techniques for thoracoscopic surgery. However, TPVB has more merit. In addition, attention should be paid to the problem of vascular puncture and pneumothorax.

### Acknowledgments

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### Disclosure

The authors report no conflicts of interest in this work.

## Author Contributions

Conceptualization, Yongfeng Zheng; formal analysis, Hong Wang, Zheng Cheng and Xiaodong Ma; writing—original draft preparation Yongfeng Zheng; writing—review and editing, Yongfeng Zheng and Donghua Shao; supervision, Weibao Cao; funding acquisition, Donghua Shao.


## RESUMO

OBJETIVO: *O objetivo do presente estudo é comparar a eficácia de duas técnicas diferentes para o bloqueio nervoso torácico durante cirurgia torácica vídeo-assistida (CTVA) e anestesia com ventilação espontânea.*

METODOLOGIA: *Cem pacientes foram incluídos no estudo e divididos em dois grupos. Em um (grupo P), foi utilizada a abordagem de BPVT e no outro (grupo I), a abordagem de BIC. Então, a taxa de eficácia clínica, duração do procedimento de bloqueio e suas complicações foram registradas para a comparação do efeito das duas abordagens.*

RESULTADOS: *Nenhuma diferença foi observada no efeito clínico do bloqueio nervoso torácico entre os dois grupos. Dois pacientes no grupo de BIC foram convertidos para anestesia geral devido a fibrilação mediastinal grave (grau três). O número de pacientes com fibrilação mediastinal de grau um no grupo de BPVT foi significativamente maior do que no grupo de BIC. Perfuração vascular foi detectada em quatro pacientes do grupo de BIC e em um do grupo de BPVT. Não foram observadas outras complicações.*

CONCLUSÃO: *Não houve diferença de eficácia clínica entre os dois grupos. No entanto, BPVT guiado por ultrassom foi superior ao BIC guiado por ultrassom durante CTVA para lobectomia pulmonar com anestesia em ventilação espontânea. Além disso, deve-se prestar mais atenção quanto à perfuração vascular.*


PALAVRAS- CHAVE: *Anestesia. Bloqueio nervoso. Cirurgia torácica. Cirurgia videoassistida.*

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ORIGINAL ARTICLE

# Long-term efficacy of gliflozins versus gliptins for Type 2 Diabetes after metformin failure: a systematic review and network meta-analysis

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**SUMMARY**

*After metformin failure in treatment for diabetes type 2, there is no trivial option for adjuvant medication. The last two oral class medications, gliflozins and gliptins, have different mechanisms of action but have never been compared in long run studies. The aim of the present meta-analysis is to assess the overall long-term efficacy of these drugs after metformin failure. A systematic review and meta-analysis were performed, including all trials with a duration of over 2 years, comparing gliflozins or gliptins after metformin failure in type 2 diabetes. Data Sources: Pubmed (Medline), Embase, Lilacs, and the Cochrane Library from inception through July 2016 without language restrictions. The longest study period found in the literature was 4 years. We selected 1 article on empagliflozin, 1 on dapagliflozin, and 1 on saxagliptin with missing data. After one year of treatment, over 50% of the patients presented HbA1c > 7%. Efficacy rate after 4 years of empagliflozin (23%) was better than dapagliflozin (5%) and saxagliptin (7%); however, it presented statistically non-significant values for HbA1c (7.4 and 7.3% between gliflozins), and missing data for saxaglifozin. Nonetheless, empagliflozin performed better than glimepiride in the 4-year period (standardized mean difference SMD 0.4, confidence interval CI 95% 0.23 to 0.56). The failure of the secondary treatment using gliflozins occurs in less than one year of treatment (less than 50% of the patients presenting HbA1c > 7 %). Empagliflozin offered better glycemic control compared to sulfonylureas but was similar to dapagliflozin.*

KEYWORDS: *Diabetes mellitus, type 2. Metformin. Dipeptidyl-peptidase IV inhibitors.*

## INTRODUCTION

Type 2 diabetes mellitus (T2D) accounts for more than 90% of cases of diabetes. It is a typical progressive disease characterized by the gradual deterioration of pancreatic β-cell function and basal insulin resistance[1]. Although metformin is the primary drug of choice, it fails within nearly 2 years[2]. The choice of the second drug after metformin failure considers several factors, such as weight gain, risk of hypoglycemia, side effects, and cost; however, none of the consensuses considers the time of failure of the drug in the therapeutic choice[3,4].

More recently, two new classes of glucose-lowering agents were put into the market. Gliptins (dipeptidyl peptidase-4 inhibitors) increase the incretin effect *in vitro*, prolonging the action of native GLP-I[5]. Drugs from this class have similar efficacy in reducing HbA1c

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levels, presenting satisfactory levels of safety and tolerance[6]. The newest class, gliflozins (sodium-glucose co-transporter-2 inhibitors), act by increasing urinary glucose excretion regardless of insulin secretion[7]. Their main advantages are weight loss and low risk of hypoglycemia[8].

Gliptins and gliflozins have been investigated after metformin failure in several randomized controlled trials (RCTs) and short-term meta-analysis. Their efficacy and safety were evaluated in systematic reviews and meta-analyses within a period of less than 2 years[9,10]. However, there are neither direct long-term comparisons between the two classes nor a meta-analysis to address their efficacy.

Network meta-analysis (NMA) compare the effectiveness of interventions indirectly, in the absence of head-to-head studies[11]. In addition, NMA has been acknowledged as a key health care decision-making tool that is increasingly recognized, given the possibility of classifying treatments according to efficacy and safety[11].

The primary objective of this study is to estimate the efficacy of gliflozins versus gliptins after metformin failure. A long-term perspective (more than 2 years' follow-up) was selected to reflect diabetes management better.

## METHODS

### Data Sources and Searches

A systematic literature review was conducted to identify RCTs involving gliptins and gliflozins in T2D inadequately controlled using metformin monotherapy. Details of the search strategies are in Appendix S1. This study was conducted according to the methods and recommendations from the Cochrane handbook[12].

Searches were conducted in July 2017 in electronic databases (EMBASE, MEDLINE via Pubmed, LILACS, and the Cochrane Central Register of Controlled Trials); 2016 conference proceedings [European Association of the Study of Diabetes (EASD), American Diabetes Association (ADA), American College of Cardiology (ACC)]; and clinical trial registry [clinicaltrials.gov]. An updated review of electronic databases was performed in March 2018. Language was not an exclusion criterion. The selection of the studies considering inclusion criteria and data extraction were performed by two independent reviewers, to reduce bias. The meta-analysis protocol was published on Prospero database CRD42015026155.

### Study Selection

Initially, eligible studies were RCTs of 52 weeks' duration, conducted among adults with T2D inadequately controlled on metformin monotherapy. Studies shorter than 52 weeks were excluded, as the initial effect of treatment may not be maintained in the longer-term. To have meaningful results, we aimed to compare studies presenting the longest periods possible found in the literature. Placebo- and active-controlled RCTs comparing two or more drug classes of interest were included. When the study used several doses of the drug in a fixed manner, the usual dose of clinical use was included in the analysis. The treatment efficacy (percentage of patients with HbA1c < 7%), HbA1c levels, weight variation, and frequency of hypoglycemia were analyzed.

### Data Extraction and Quality Assessment

After the identification of eligible studies, the authors independently extracted data, using standardized predefined forms. For continuous variables (HbA1c and weight variation), we extracted outcome data such as the number of participants, mean difference, and standard error (or standard deviation). For dichotomous outcomes (frequency of patients with hypoglycemia and treatment efficacy), the total number of participants and events that were randomized and received treatment. Whenever studies reported different data for follow-up duration as an outcome, the longest one available was used. In cases where the independent reviewers disagreed on the eligibility of an article or data extraction, a consensus was reached by arbitration. The quality of the study was assessed using the Cochrane risk of bias tool[12].

### Data Synthesis and Analysis

We assumed a network meta-analysis within a Bayesian approach[13], using R programming. We planned to measure heterogeneity and sensitivity analysis. Results were reported with 95% confidence intervals (CIs); we considered p values <0.05 as statistically significant.

We used the results of the systematic review to create a network of evidence of the longest effect available (4 years of treatment). As a meta comparator, the sulfonylureas were chosen.

For HbA1c, we evaluated the therapeutic efficacy in years 1, 2, 3, and 4 (percentage of patients with HbA1c < 7%) estimating a normal distribution in the absence of the data, performing a $Q^2$ test. When data was not

available, we used DigitizeIt®, a digitalization software, to capture the missing information.

A Summary of findings table was adapted to a network meta-analyses[14].

### Outcomes

From HbA1c and weight, variations from the baseline values were analyzed. Therapeutic efficacy was evaluated according to the percentage of patients presenting HbA1c < 7%.

The proportion of subjects with at least one episode of hypoglycemia (regardless of the definition) was analyzed on an odds ratio scale.

## RESULTS

From 2.496 identified records, we excluded non-human, less than 1 year duration RCTs and observational studies, leaving 164 reports for full-text assessment. After further selection (Figure 1), 3 unique RCTs fulfilled the inclusion criteria (Table 1) for the systematic review and had 4 years of duration. We selected 1 article on empagliflozin[15], 1 on dapagliflozi[16], and 1 on saxagliptin[17] with missing data. The risk of bias table is available in Appendix S2.

Studies mentioned diet and activity recommendations but did not specify any guidance on how to execute them.

The definition of metformin failure (i.e. HbA1c inclusion criteria in the individual RCTs) varied across the included trials 6.5-10%. In the study on dapagliflozin (DAPA), there was a progressive titration of the doses of dapagliflozin and glipizide up to 10 and 20 mg, respectively. In the study on empagliflozin (EMPA), there was a progressive titration of glimepiride up to 4 mg and a fixed dose of empagliflozin 25 mg. In the study on saxagliptin (SAXA), we chose an arm with 5 mg and the placebo.

Mean baseline HbA1c ranged from 7,6 to 8,1%. The mean change from baseline HbA1c observed in the individual trial arms ranged from −0.9 to −0.2%, (adjusted mean change) presented in Table 2.

**FIGURE 1.** THE PRISMA FLOW DIAGRAM FOR IDENTIFICATION AND SELECTION OF PRIMARY STUDIES INCLUDED IN THE SYSTEMATIC REVIEW AND META ANALYSIS.

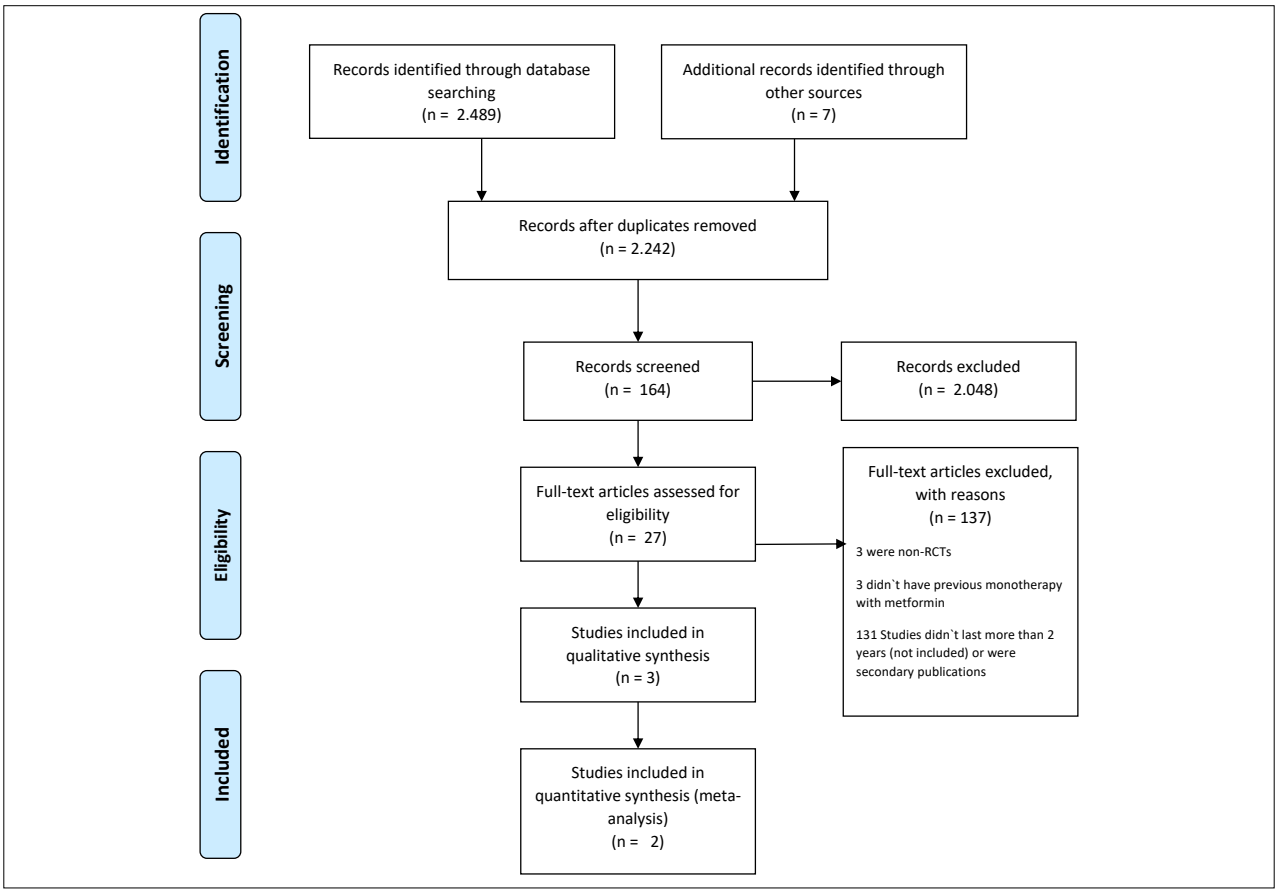


**TABLE 1.** BASELINE CHARACTERISTICS OF THE SELECTED STUDIES

| Study | Participants and baseline characteristics | Intervention / outcome |
|---|---|---|
| Del Prato et al., 2015<br>Multicenter study (n = 77)<br>ClinicalTrials Registry: NCT00660907<br>Design: 2 arms, double-blind, randomized, dapagliflozin 2.5-10 mg, comparator glipizide 5-20 mg<br>Duration: 2 years with extension of 2 years | N: 814<br>Participants: patients with T2M on metformin pre-randomization (> 1500 mg/d) or associated to another suspended medication and titration of metformin<br>Age (years): dapagliflozin + met 58 ± 9; lipizide + met 59 ± 10<br>Basal HbA1c (%): dapagliflozin + met 7.6 + 0.9; glipizide + met 7.7 + 0.9<br>Basal weight (Kg): No data available | Intervention: dapagliflozin 2.5-10 mg<br>Comparator: glipizide 5-20 mg<br>Primary outcome: mean change in HbA1c at 52 weeks<br>Secondary outcomes: weight change at 52 weeks, proportion of patients with at least 1 episode of hypoglycemia, patients with weight reduction greater than 5% |
| Salsali et al, 2016<br>Multicenter study (n = 182)<br>ClinicalTrials Registry: NCT01167881<br>Design: 2 arms, double-blind, randomized, empagliflozin 25mg, comparator glimepiride 1-4 mg<br>Duration: 2 years with extension of 2 years | N: 1549<br>Participants: patients with T2M on metformin (> 1500 mg/d).<br>Age (years): empagliflozin + met 56.2 ± 10; glimepiride + meth 55.7 ± 10<br>Basal HbA1c (%): empagliflozin+ met 7.9 ± 0.8; glimepiride + met 7.9 ± 0.9<br>Basal weight (Kg): empagliflozin + met 82.5 ± 19; glimepiride + met 83 ± 19 | Intervention: empagliflozin 25 mg<br>Comparator: glimepiride 1-4 mg<br>Primary outcome: mean change in HbA1c at 104 weeks<br>Secondary outcomes: weight change at 104 weeks, variation of systolic and diastolic blood pressure at 104 weeks |
| Rosenstock et al., 2013<br>Multicenter study (n = 154)<br>ClinicalTrials Registry: NCT00121667<br>Design: 4 arms, double-blind, randomized, saxagliptin 2.5, 5, and 10 mg, placebo as a comparator. Rescue drug pioglitazone 15-45 mg. Only included the 5 mg dose in the analysis.<br>Duration: 4 years | N: 743<br>Participants: patients with T2M on metformin (> 1500 mg/d).<br>Age (years): saxagliptin + met 54.7 ± 9; Placebo + met 54.8 ± 10<br>Basal HbA1c (%): saxagliptin + met 8.1 ± 0.1; Placebo + met 8.1 ± 0.1<br>Basal weight (Kg): No data available | Intervention: saxagliptin 5 mg<br>Comparator: placebo<br>Primary outcome: mean change in HbA1c at 25 weeks<br>Secondary outcomes: fasting blood glucose variation at 24 weeks, percentage of patients reaching HbA1c <7% at 24 weeks |

Met: metformin. Data presented in mean and standard deviation

**TABLE 2.** SUMMARY OF FINDINGS

**What is the best therapeutic option after primary failure with metformin in the long term?**
Patients: T2D with primary metformin failure
Interventions: dapagliflozin and empagliflozin
Comparator: Sulfonylureas (glipizide and glimepiride)

| Outcomes | Standardized mean difference (MD) or odds ratio (OR) and confidence interval. | | | | | |
|---|---|---|---|---|---|---|
| | Dapagliflozin | | Empagliflozin | | Sulfonylureas | |
| HbA1c (%) | MD 0,2 | -0,2 1 | MD 0,4 | -0,9 1 | | -0,4 1 |
| | (-0,2- 0,5) | (-0,0- 0,4) | (0,2- 0,6) | (-1,0- -0,8) | | (-0,6- - 0,2) |
| HbA1c < 7% in 4 years | 5% | | 23% | | 5% (2 studies) | |
| | ⊕○○○ very low | | ⊕○○○ very low | | | |
| | confidence in estimate due to relative risk | | confidence in estimate due to relative risk | | | |
| | Based in 801 patients (1 study) | | Based in 1.541 patients (1 study) | | | |
| Weight variation | MD 1,1 | -3,6 1 | MD 2,63 | -4,1 1 | | 0,8 1 |
| (Kilos) | (0,8 - 1,3) | (-4,3 - 3,0) | (2,4- 2,8) | (-4,1- -3,9) | | (-2,3- - 1,3) |
| | ⊕○○○ very low | | ⊕⊕○○ low | | | |
| | confidence in estimate due to relative risk | | confidence in estimate due to relative risk | | | |
| | Based in 801 patients (1 study) | | Based in 801 patients (1 study) | | | |
| Hypoglycemia | RC 0,05 | 30 fewer per 100 | RC 0,08 | 33 fewer per 100 | 36 per 100 | |
| (Frequency of patients) | (0,03- 0,09) | (28 fewer to 33 fewer) | (0,05- 0,13) | (31 fewer to 34 fewer) | | |
| | ⊕⊕⊕○ moderate | | ⊕⊕⊕○ moderate | | | |
| | confidence in estimate due to risk of bias | | confidence in estimate due to risk of bias | | | |
| | Based in 801 patients (1 study) | | Based in 801 patients (1 study) | | | |

1. Compared with the baseline value

Efficacy rate (HbA1c < 7%) in 1 year of treatment was 35 and 43%, for dapagliflozin and empagliflozin, respectively. In 4 years of treatment, empagliflozin (23%) was statistically significantly better than dapagliflozin (5%) and saxagliptin (7%), data presented in Appendix S3.

Only the EMPA study presented results for baseline weight. Weight variation was negative for gliflozins and positive for sulfonylureas (Table 2).

For the meta-analysis, only the DAPA and EMPA studies had a meta comparator (sulfonylurea) and were eligible. In the arms comparison of the DAPA study (dapagliflozin versus glipizide), the HbA1c variation did not present statistical significance at the end of the study. In the EMPA study (empagliflozin versus glimepiride), there was a significant reduction in the HbA1c (SMD: 0.40, CI 95% 0.23 to 0.56). In the meta-comparison between dapagliflozin and empagliflozin, there was no statistical significance, presented in Figure 2.

Comparing bodyweight variation, in the DAPA study, the weight variation was statistically significant, favoring dapagliflozin (SMD: 1.07, CI 95% 0.83 to 1,32). In the EMPA study, the analysis also showed statistical significance favoring empagliflozin (SMD: 2.63, CI 95% 2.4 to 2.85). In the meta-comparison between dapagliflozin and empagliflozin, there was statistical significance favoring empagliflozin (SMD: 1.56, CI 95% 1.22 to1.88), presented in Figure 2.

The frequency of patients with hypoglycemia was significantly higher in the sulfonylureas arms in DAPA study (OR:0.05, CI 95% 0.03 to 0.09) and in the EMPA study (OR: 0.08, CI 95% 0.05 to 0.13). In the meta-comparison between dapagliflozin and empagliflozin, there was no statistical significance (Figure 2).

Due to the low availability of studies, it was not possible to measure heterogeneity and run a sensitivity analysis.

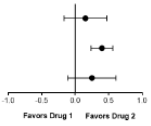
## DISCUSSION

The medical literature lacks RCTs to evaluate the efficacy of gliflozins and gliptins for T2D after monotherapy failure using metformin in the long-term. This has been the first review to address this question.

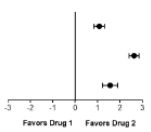
The efficacy of dapagliflozin and empagliflozin were less than 50% in one year, suggesting that glycemic control becomes insufficient within the first years of the study for most of the patients. Results recently published from the Canvas Trial Program, designed to evaluate cardiovascular outcomes, compared canagliflozin and placebo associated to basal therapy (metformin > 77% of the patients) and showed they were unable to sustain glycemic control for more than 6 years, evidencing a progressive deterioration over time[18]. Abdul-Ghani et al.[19], in 2015, suggest a three-medicament treatment in patients with diabetes recently diagnosed was more efficient to reduce HbA1c

**FIGURE 2.** A: COMPARISON OF HBA1C (%) VARIATION FROM BASELINE. B: COMPARISON OF WEIGHT VARIATION (KG) FROM BASELINE. C: COMPARISON OF THE FREQUENCY OF PATIENTS WITH HYPOGLYCEMIA. SD= STANDARD DEVIATION, MD: STANDARDIZED MEAN DIFFERENCE, OR: ODDS RATIO, CI95%L = LOWER LIMIT 95% CONFIDENCE INTERVAL, CI95%U = UPPER LIMIT 95% CONFIDENCE INTERVAL.

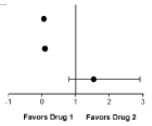
| | | | Treatmentt 1 | | | Treatmentt 2 | | | Treatment effect | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A | Treatment 1 | Treatment 2 | Mean | SD | Total | Mean | SD | Total | MD | CI95%L | CI95%U |
| Del Prato et al.[16] | DAPAGLIFLOZIN | SU | 7.550 | 0.680 | 79 | 7.550 | 0.645 | 71 | 0.151 | -0,170 | 0.471633914 |
| Ridderstrale et al.[15] | EMPAGLIFLOZIN | SU | 7.270 | 0.390 | 365 | 7.440 | 0.477 | 243 | 0.398 | 0.234 | 0.562024521 |
| | DAPAGLIFLOZIN | EMPAGLIFLOZIN | 7.550 | 0.680 | 79 | 7.270 | 0.390 | 265 | 0.248 | -0,113 | 607904928 |




| | | | Treatmentt 1 | | | Treatmentt 2 | | | Treatment effect | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| B | Treatment 1 | Treatment 2 | Mean | SD | Total | Mean | SD | Total | MD | CI95%L | CI95%U |
| Del Prato et al.[16] | DAPAGLIFLOZIN | SU | -3.650 | 4.117 | 159 | 0.730 | 4.045 | 140 | 1.073 | 0.830 | 1.315.482.303 |
| Ridderstrale et al.[15] | EMPAGLIFLOZIN | SU | -4.060 | 1.870 | 336 | 0.821 | 1.840 | 248 | 2.628 | 2.405 | 2.850.421.751 |
| | DAPAGLIFLOZIN | EMPAGLIFLOZIN | -3.650 | 4.117 | 159 | -4,060 | 1.870 | 336 | 1.555 | 1.225 | 188.461.348 |




| | | | Treatmentt 1 | | | Treatmentt 2 | | | Treatment effect | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| C | Treatment 1 | Treatment 2 | Prop | Number of Cases | Total | Prop | Number of Cases | Total | OR | CI95%L | CI95%U |
| Del Prato et al.[16] | DAPAGLIFLOZIN | SU | 0.05 | 22 | 406 | 0.51 | 210 | 408 | 0.05 | 0.03 | 0.09 |
| Ridderstrale et al.[15] | EMPAGLIFLOZIN | SU | 0.03 | 24 | 765 | 0.28 | 218 | 780 | 0.08 | 0.05 | 0.13 |
| | DAPAGLIFLOZIN | EMPAGLIFLOZIN | 0.05 | 22 | 406 | 0.03 | 24 | 765 | 1.53 | 0.80 | 2.91 |



and presented less hypoglycemia when compared to the progressive adoption of a three-medicament treatment along two years. It is possible that the time wasted up to the moment of failure in the primary treatment can be related to a significant loss of β cell functionality in the selected studies of this analysis, similar to the one found in the literature. The consensus provided by the American Diabetes Association and American Association of Clinical Endocrinology ought to consider the time of failure of the drugs, aside from weight, cost, side effect, and drug efficacy when recommending a second drug therapy.

In the selected studies, dapagliflozin and empagliflozin were compared to sulfonylureas (glipizide and glimepiride respectively) titration, allowing it to be up to half of the maximum dose. Medical literature shows scarce comparisons between sulfonylureas[20]. In the DAPA study, only 63% of the patients in the glipizide arm received the maximum titration dose of 20 mg[16]. There are no 4-year data referring to the mean dose of glimepiride in the EMPA study; however, in the 2-year publication, only 40% of the patients in the glimepiride group used the allowed maximum dose in the 4mg[21]. In a study comparing canagliflozin versus glimepiride after the failure of metformin as primary treatment, which was not included in this review, for it lasts 2 years, the titration of glimepiride was done up to the maximum recommended dose of 8 mg/d[22]. Although some publications in the medical literature point that the efficacy between half a dose and the full dose of sulfonylureas would have similar effects[20]. We can conclude that one cannot characterize therapeutic equivalence or superiority of gliflozins in the selected studies in patients who did not reach the recommended half dose of the sulfonylureas. Additionally, hypoglycemia could have been a limiting factor in the titration of the sulfonylureas.

The meta-comparison of HbA1c between both gliflozins showed no significant difference. To interpret this result, it is important to consider that the criteria for rescue and titration from each study were different. This analysis presents a low level of quality of evidence due to severe inconsistency (heterogeneity which could not be calculated) and severe inaccuracy (only 2 studies).

Both gliflozins demonstrated weight loss when compared to sulfonylureas, and in the meta-comparison, empagliflozin performed better than dapagliflozin. The variation of weight loss was maintained for 4 years for gliflozins compared to sulfonylureas (Appendix S4). Those data must be analyzed considering potential confounders, such as the progressive titration of dapagliflozin, the employed methodology for incomplete data in each study (LOCF versus MMRM), and the fact that in the DAPA study the results of weight variation included patients after the therapeutic rescue.

Hypoglycemia is a main concern in diabetes treatment, especially in patients using sulfonylureas. In this review, we demonstrated a low frequency of patients with hypoglycemia under the class of gliflozins in a 4-year period (dapagliflozin 5% and empagliflozin 3%) compared to sulfonylureas (glipizide 52% and glimepiride 28%). This result must be evaluated since each study has had its own objective and subjective criteria of hypoglycemia.

Other factors not evaluated in this systematic review that can impact the clinical use of gliflozins and gliptins are the adverse effects and cardiovascular safety. The medical literature has been showing a higher risk of urinary infection[23] and a beneficial cardiovascular profile of gliflozins[18,24].

## LIMITATIONS

A critical assumption underlying NMA is related to exchangeability, i.e., that trials selected are sufficiently similar in design, outcomes, and population. Potential limitations of this NMA network were the number of studies, the study designs, and losses during the follow-up. Other crucial factors to be considered are incomplete data of the outcomes (especially missing data of LOCF vs. MMRM strategies), selective narratives, and performance (sub dose of sulfonylureas as a comparator).

## CONCLUSION

More long-term studies are required to evaluate the efficacy of gliptins and gliflozins after the therapeutic failure of metformin monotherapy in patients with T2D.

The efficacy of the treatment, defined by the percentage of patients with HbA1c <7%, is low in the first years of treatment with gliflozins. In 4 years of treatment, the efficacy profile of empagliflozin (23%) performed better than saxagliptin (7%) and dapagliflozin (5%); however, with average values of HbA1c that were statistically non-significant.

The variation of weight loss was maintained in 4

years for gliflozins compared to sulfonylureas, being more favorable to empagliflozin.

The frequency of patients with hypoglycemia was significantly better for gliflozins compared to sulfonylureas. There was no difference in the class of gliflozins.

The results of this systematic review and meta-analysis suggest careful analysis for generalizations to other populations. Further studies are required to evaluate the efficacy of glycemic control, weight variation, and frequency of hypoglycemia in the long-term after the introduction of gliflozins and gliptins after the primary failure of metformin in patients with T2D.

## Acknowledgments

We thank Rosa Maria Fischi for technical assistance.

## Supporting information

Appendix S1 - Search strategy; Appendix S2 - Risk of bias; Appendix S3 - Proportion of patients with HbA1c < 7%; Appendix S4 – Variation of weight during 4 years of follow-up

**RESUMO**

*Após a falha da metformina no tratamento do diabetes tipo 2, não existe uma opção trivial para a medicação adicional. Os dois últimos medicamentos de classe oral, gliflozinas e gliptinas, têm mecanismos de ação diferentes, mas nunca foram comparados em estudos de longo prazo. O objetivo da presente meta-análise é a avaliação da eficácia global em longo prazo desses medicamentos após a falha da metformina. Uma revisão sistemática e meta-análise foram realizadas, incluindo todos os ensaios com uma duração de mais de dois anos, comparando gliflozinas ou gliptinas após a insuficiência de metformina no diabetes tipo 2. Fontes de dados: PubMed (Medline), Embase, Lilacs e a Biblioteca Cochrane desde o início até julho de 2016, sem restrições de idioma. O período mais longo de estudo encontrado na literatura foi de quatro anos. Foi selecionado um artigo sobre empagliflozina, um artigo sobre dapagliflozina e um artigo sobre saxagliptina com dados faltantes. Após um ano de tratamento, mais de 50% dos pacientes apresentavam HbA1c >7%. A taxa de eficácia em quatro anos de empagliflozina (23%) foi melhor que dapagliflozina (5%) e saxagliptina (7%), porém com valores estatisticamente não significativos para HbA1c (7,4% e 7,3% entre gliflozinas) e dados ausentes para a saxaglifozina. No entanto, a empagliflozina teve um desempenho melhor do que a glimepirida no período de quatro anos (diferença média padronizada SMD 0,4, intervalo de confiança IC 95% 0,23 a 0,56). A falha do tratamento secundário com gliflozinas ocorre em menos de um ano de tratamento (menos de 50% dos pacientes com HbA1c >7%). A empagliflozina ofereceu melhor controle glicêmico em comparação com as sulfonilureias, mas semelhante à dapagliflozina.*

PALAVRAS-CHAVE: *Diabetes mellitus tipo 2. Metformina. Inibidores da dipeptidil peptidase IV.*

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ORIGINAL ARTICLE

# Prescription of red cell concentrates by emergency physicians

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## SUMMARY

OBJECTIVE: *To evaluate the adequacy of the prescription of red cell concentrates by emergency physicians.*

METHODS: *A cross-sectional study based on the survey of transfusion requests records completed by emergency physicians, from May/2018 to April/2019, in an emergency hospital. Adequacy in the indication, volume, and subtype (filtered, irradiated, and washed) of prescribed erythrocytes were evaluated. To compare the qualitative data, we used the $\chi 2$ test. The significance level adopted was 5%.*

RESULTS: *One thousand and twenty-two transfusions were evaluated. The indication, volume, and subtypes were correct in 72.7%, 45.9%, and 81.6% respectively. Transfusion in symptomatic patients presented superior adequacy when compared to asymptomatic individuals with significant statistical difference (indication: 79,6% vs 67.2%, p <0.001; Volume: 63.5% vs 31.7%, p <0.001; subtype: 85.3% vs 78.7%, p 0.006). Among clinical situations, there were more errors in sepsis (39.7%) and pneumonia (36.3%). More than half of the prescriptions presented excessive volume, raising the risk of circulatory overload, observing that the mean age was 60.6 years. The specific analysis of the prescribed subtypes showed adequacy of 17.9% in the filtered, 1.7% in the irradiated, and none in the washed. Thirty transfusions should have been filtered, but the prescriber did not request the subtype.*

CONCLUSION: *One hypothesis for the observed inaccuracies is inadequate medical training on the subject, both in undergraduate and medical residency, associated with a lack of continuing education on transfusion protocols. The transfusion Committee received the results of this study with a proposal for continuing education measures on transfusion hemotherapy.*

KEYWORDS: *Erythrocyte transfusion. Blood transfusion. Emergency treatment. Prescriptions. Transfusion medicine.*

## INTRODUCTION

Richard Lower conducted, in 1665, in England, the first blood transfusion between animals[1]. This procedure, then, was tested in humans in the following decades and is currently one of the most used therapies in the world[2].

The transfusion of red cell concentrate (RCC) increased survival in different clinical situations and surgical procedures. However, it can be the cause of increased mortality when prescribed without need[3].

Recent studies show that a restrictive strategy

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(indicating RCC with lower values of hemoglobin) reduces mortality in severe patients[4,5]. Transfusion protocols indicate the red blood cell transfusion for patients with a hemoglobin count of less than 7 g/dL in most situations[6]. However, many physicians are unaware of the transfusion protocols or are resistant to apply the restrictive strategy, increasing the risks to patients and the number of RCCs prescribed[7-9].

Various transfusion reactions can occur, some potentially lethal, such as anaphylaxis, circulatory overload, and TRALI (transfusion-related acute lung injury)[10,11].

RCC transfusion is an important part of therapy in various clinical situations, especially in urgency and emergency scenarios[12-14]. Having knowledge of current protocols is essential for emergency physicians.

The objective of this study is to evaluate the adequacy of RCC prescriptions by physicians of an urgency and emergency hospital.

## METHODS

We conducted a cross-sectional study based on a survey of request forms for a hemotherapy procedure. We included patients aged over 13 years treated in the emergency room of the medical clinic of the Central Hospital and Emergency Center of São Bernardo do Campo (HPSC), SP, from May 2018 to April 2019. This is a public municipal hospital that receives urgent and emergency cases and that features a transfusion agency. Forms with incomplete data were excluded from the analysis.

The adequacy of the RCC prescription was based in three distinct forms of analysis: indication of transfusion based on the value of hemoglobin (Hb), the prescribed volume, and choice for the correct subtype (filtered, irradiated, washed). To assess the adequacy of the indication, the prescribed volume, and the choice of RCC subtypes, we used the recommendations by the Brazilian Ministry of Health from 2015[15]. To analyze the transfusions indicated for sepsis patients, we used the international guidelines for sepsis management[16].

We collected data such as age, gender, indication, pretransfusion hemoglobin, prescribed volume, choice of RCC subtype, and previous diseases. The data were entered into an Excel (Microsoft) spreadsheet and analyzed using the Statistical Package for Social Science (SPSS), version 24.0. The qualitative variables were presented in the form of an absolute number and percentage. For the comparison of the qualitative data, we used the $\chi 2$ test. The significance level adopted was 5%.

This study was approved by the Research Ethics Committee of the Faculty of Medicine of ABC (Decision No.: 3.286.784), CAAE 11199319.2.0000.0082.

## RESULTS

A total of 1,044 RCC transfusions were performed during the study period, of which 22 (2.1%) were excluded due to incomplete data. Males received 55.1% of the transfusions (Table 1). The mean age was 60.6 years (minimum of 14, and a maximum of 100 years).

Most transfusions (55.5%) were prescribed based on a laboratory indication (anemia) in asymptomatic patients. The most prevalent clinical indications were: enterorrhagia (40.9%), hemodynamic decompensation (13%), sepsis (12.8%), and lower gastrointestinal bleeding (9.7%) (Table 1). Indications were made with less than 7 g/dL in 69.3% of transfusions. Laboratory criteria had an average Hb of 6.6 g/dL, while the transfusions based on clinical criteria had an average Hb of 6.3 g/dL. The prescriptions were as follows: one pack of RCC for 313 patients, two packs for 588, three packs for 113, and four packs for eight. The average number of packs prescribed based on laboratory indication was 1.8 and, based on clinical indication, 1.9 (Table 1).

A total of 185 specific subtypes of RCC were requested. In 45 transfusions, two or three subtypes were prescribed simultaneously. The subtype most frequently requested was irradiated RCC (119), followed by filtered RCC (56), and washed RCC (10) (Table 1).

The indication for transfusion was correct in 72.7% of the cases evaluated. When performed based on laboratory criteria, the adequacy was 67.2%, and when based on clinical criteria, 76.9% (Table 2). In relation to the clinical reason, sepsis presented adequacy of 60.3%, and pneumonia 63.7%. The other reasons had adequacy over 70%. Adequacy was significantly higher in the group who received transfusions based on clinical criteria, compared to the group based on laboratory indication, with $p<0.001$ (Figure 1).

Transfusions performed with Hb <7 g/dL, 7 to 10 g/dL, and >10 g/dL were correct in 100%, 11.2%, and 0% of cases, respectively (Table 2).

The volume (number of packs) was correct in 45.9% of the transfusions. When one RCC was requested, adequacy was 99%, and when the number was two, it was 27%. All requests for over two RCCs were

**TABLE 1.** GENERAL CHARACTERISTICS OF TRANSFUSIONS PERFORMED

| Variable | | N | % |
|---|---|---|---|
| | | | |
| Gender | Male | 563 | 55.1 |
| (n=1,022) | Female | 459 | 44.9 |
| | | | |
| Age (years) | 14\|---20 | 21 | 2.1 |
| (n=1,022) | 20\|---40 | 123 | 12.0 |
| | 40\|---60 | 323 | 31.6 |
| | 60\|---80 | 428 | 41.9 |
| | 80\|---100 | 127 | 12.4 |
| | | | |
| Clinical condition | Enterorrhagia | 186 | 40.9 |
| (n=455) | Hemodynamic decompensation | 59 | 13.0 |
| | Sepsis | 58 | 12.8 |
| | Lower gastrointestinal bleeding | 44 | 9.7 |
| | Weaknesses | 27 | 5.9 |
| | Sickle cell disease | 16 | 3.5 |
| | Hematuria | 15 | 3.3 |
| | Acute respiratory failure | 12 | 2.6 |
| | Pneumonia | 11 | 2.4 |
| | Others | 27 | 5.9 |
| | | | |
| Reason | Laboratory (asymptomatic) | 567 | 55.5 |
| (n=1,022) | Clinical (symptomatic) | 455 | 44.5 |
| | | | |
| Pretransfusion Hb | <7 g/dL | 708 | 69.3 |
| (n=1,022) | 7 to 10 g/dL | 313 | 30.6 |
| | >10 g/dL | 1 | 0.1 |
| | | | |
| Prescribed volume | 1 CH | 313 | 30.6 |
| (n=1,022) | 2 CH | 588 | 57.6 |
| | 3 CH | 113 | 11.0 |
| | 4 CH | 8 | 0.8 |
| | | | |
| RCC subtype | Filtered | 56 | 30.3 |
| (n=185) | Irradiated | 119 | 64.3 |
| | Washed | 10 | 5.4 |

**TABLE 2.** ADEQUACY OF THE RED CELL CONCENTRATE TRANSFUSION

| Variable | | Total (N) | Correct (N) | Correct (%) |
|---|---|---|---|---|
| | | | | |
| Indicated | Laboratory | 567 | 381 | 67.2 |
| (n=1,022) | Clinic | 455 | 362 | 79.6 |
| | | | | |
| Clinical condition | Enterorrhagia | 186 | 131 | 70.4 |
| (n=455) | Hemodynamic decompensation | 59 | 57 | 96.6 |
| | Sepsis | 58 | 35 | 60.3 |
| | Lower gastrointestinal bleeding | 44 | 31 | 70.5 |
| | Weaknesses | 27 | 27 | 100 |
| | Sickle cell disease | 16 | 15 | 93.8 |
| | Hematuria | 15 | 13 | 86.7 |
| | Acute respiratory failure | 12 | 11 | 91.7 |
| | Pneumonia | 11 | 7 | 63.7 |
| | Others | 27 | 23 | 85.1 |
| | | | | |
| Pretransfusion Hb | <7 g/dL | 708 | 708 | 100 |
| (n=1,022) | 7 to 10 g/dL | 313 | 35 | 11.2 |
| | >10 g/dL | 1 | 0 | 0 |
| | | | | |
| Prescribed volume | 1 CH | 313 | 310 | 99 |
| (n=1,022) | 2 CH | 588 | 159 | 27 |
| | 3 CH | 113 | 0 | 0 |
| | 4 CH | 8 | 0 | 0 |
| | | | | |
| RCC subtype | Filtered | 56 | 10 | 17.9 |
| (n=185) | Irradiated | 119 | 2 | 1.7 |
| | Washed | 10 | 0 | 0 |

incorrect (Table 2). The adequacy in the volume prescription based on laboratory criteria was 31.7%, and based on clinical criteria, 63.5%, with a statistically significant difference (p<0.001) (Figure 1).

In 188 transfusions (18.4%) there was an error in the prescription of RCC subtype (unnecessarily requested or not requested when indicated). In 158 prescriptions, one or more subtypes were requested with no need, totaling 173 subtypes (Table 1). On the other hand, in 30 transfusions the filtered subtype was not prescribed when there was an indication. Irradiated RCC was prescribed in 119 blood transfusions, of which 117 (98.3%) had no need for it. Filtered RCC was prescribed in 56 transfusions and was incorrect in 46 (82.1%) of them. Washed RCC was prescribed ten times, all inappropriately (Table 2). The adequacy of the request for the RCC subtypes in transfusions prescribed based on laboratory and clinical indication was 78.7% and 85.3%, respectively (p 0.006) (Figure 1).

## DISCUSSION

A greater number of blood transfusions were performed in asymptomatic patients, situations in which physicians had time to discuss the clinical case with other colleagues or with the hematologist of the hospital transfusion agency. When patients were symptomatic, the main cause was enterorrhagia.

Almost 70% of transfusions occurred in patients with Hb less than 7 g/dL, a trigger that indeed indicates

the need for transfusion in most clinical situations[15]. Patients in hospitals that follow a restrictive transfusion trigger (perform transfusions in patients with Hb less than 7 g/dL) receive fewer transfusions than those in hospitals that adopt liberal transfusion strategies[17]. Another benefit of the restrictive strategy is the reduction of transfusion reactions in severe patients[18]. All transfusions performed with Hb below 7 g/dL were correct; however, only 11.2% of those performed with Hb from 7 to 10 g/dL were appropriate.

The adequacy in the indication was significantly higher in symptomatic patients. There were more errors in cases of sepsis, for which the current guideline recommends transfusion when Hb levels are below 7 g/dL[16]. Patients with pneumonia without respiratory insufficiency or mechanical ventilation received unnecessary transfusions in almost 40% of cases.

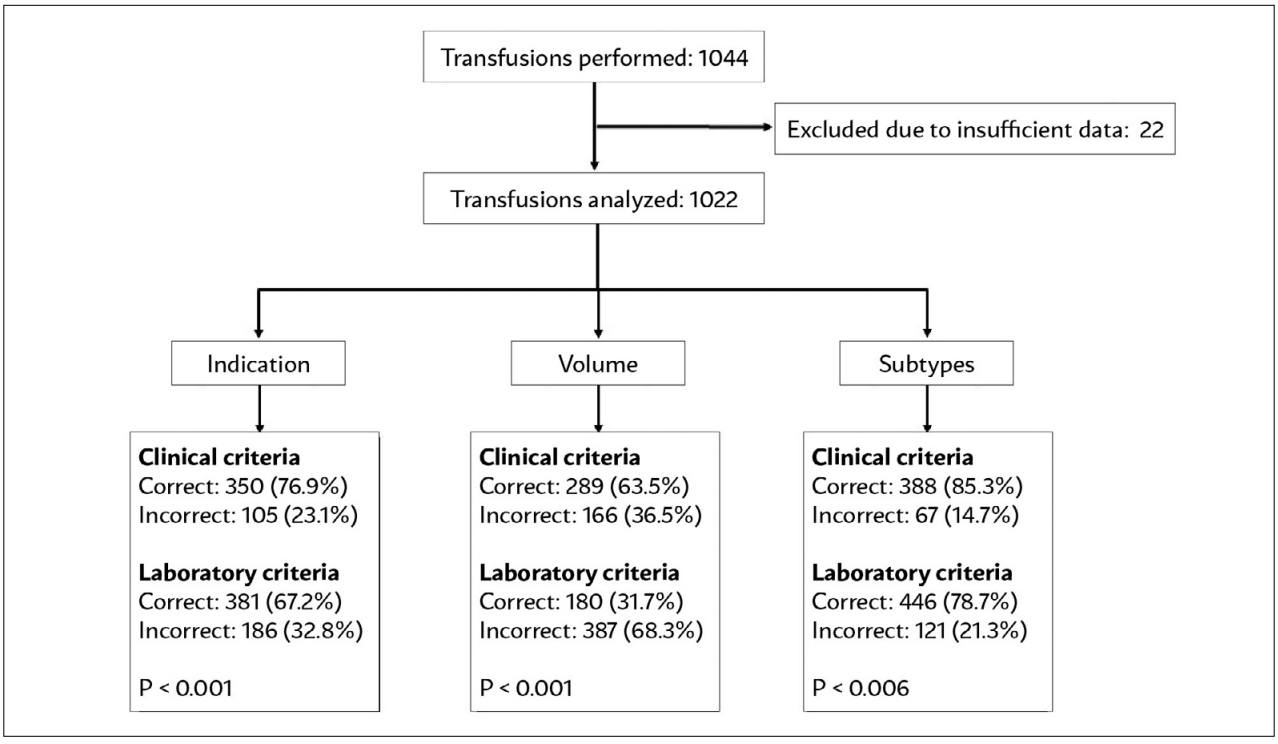
There was excessive volume in 54.1% of prescriptions. All requests for over 2 RCCs were incorrect. The circulatory overload related to a high volume of blood transfusion is one of the most frequent transfusion reactions and presents high mortality[19]. In our study, we found that 54.3% of the patients were over 60 years old, increasing, even more, the risk of transfusion reaction. An American cohort study also observed a greater number of transfusions in elderly patients treated in emergency rooms[20].

Only 6.5% of the specific subtypes prescribed were adequate. It was also observed that in 30 transfusions filtered RCC was indicated but it was not prescribed. All these situations occurred in patients with hemoglobinopathies (27 with sickle cell disease and three with thalassemia major). Filtered RCC is indicated especially in polytransfused patients, such as those with hemoglobinopathies, to prevent febrile non-hemolytic reaction[15]. The prescription of subtypes without need results in increased treatment costs[21]. In some situations, it can increase the wait time for a severe patient due to the preparation time of the subtype[21]. This factor results in an increased risk of death if the transfusion is indicated in emergencies. The washed subtype presents a further complication when unnecessarily requested: it reduces in up to 20% the number of red blood cells, decreasing the transfusion yield[22].

When comparing the group that received transfusions based on clinical criteria (symptomatic) with the group that received it based on laboratory criteria (asymptomatic), we observed that the indication, the calculation for volume, and the choice of subtypes presented higher adequacy in the symptomatic group, with a statistically significant difference in the three analyses.

A hypothesis that justifies the inaccuracies observed is the inadequate medical training on the

**FIGURE 1.** ADEQUACY OF TRANSFUSION COMPARING LABORATORY AND CLINICAL INDICATIONS



subject, both in undergraduate programs and in medical residency. Associated with this, is the lack of continuing education of emergency physicians on transfusion protocols. Since the need to improve the indications for transfusion of red cell concentrate was observed, the hospital transfusion committee received the results of this study with the proposal for measures of continuing education on transfusion hemotherapy. Continuing education is proven to improve the knowledge of the physicians on hemotherapy[23,24]. The lack of knowledge of transfusion protocols increases the risks to patients, making training necessary[25].

The strengths of this study were the number of transfusions evaluated, the analysis of the requests made specifically by emergency physicians of the medical clinic, a small percentage of loss (2.1%), and the availability of an official guide on the indications for transfusion by the Brazilian Ministry of Health, in addition to international guidelines for comparison of the results.

As to the limitations, one can cite the retrospective design of the study and the absence of details on the clinical history in the request form for the hemotherapy procedure.

## CONCLUSION

Transfusions in asymptomatic patients require caution. The protocols for transfusion in sepsis and in patients with respiratory diseases without respiratory failure should be discussed. In relation to the excessive volume of packs prescribed, only in severe cases, such as hemorrhagic hypovolemic shock, a greater number of packs must be requested. The knowledge of subtypes must also be emphasized, because of the lack of prescription when there is an indication increases transfusion risks, while unnecessary prescriptions also present complications. In case of doubt, the issue should be discussed with the hemotherapist of the transfusion agency.


## RESUMO

OBJETIVO: *Avaliar a adequação da prescrição de concentrados de hemácias por médicos emergencistas.*

MÉTODOS: *Estudo transversal por levantamento de fichas de requisição de transfusões preenchidas por médicos emergencistas, no período de maio de 2018 a abril de 2019, em um hospital de emergências. Foram avaliadas as adequações na indicação, volume e subtipo (filtradas, irradiadas e lavadas) de hemácias prescritas. Para comparação dos dados qualitativos, utilizamos o teste de $\chi 2$. O nível de significância adotado foi de 5%.*

RESULTADOS: *Foram avaliadas 1.022 transfusões. A indicação, o volume e os subtipos estavam corretos em 72,7%, 45,9% e 81,6%, respectivamente. A transfusão prescrita em pacientes sintomáticos apresentou adequação superior quando comparada aos assintomáticos, com diferença estatística significativa (indicação: 79,6% vs 67,2% – p<0,001; volume: 63,5% vs 31,7% – p<0,001; subtipo: 85,3% vs 78,7% – p 0,006). Entre as situações clínicas, ocorreram mais erros na sepse (39,7%) e pneumonia (36,3%). Mais da metade das prescrições apresentavam volume excessivo, elevando o risco de sobrecarga circulatória, observando-se que a média da idade foi 60,6 anos. A análise específica dos subtipos prescritos apresentou adequação de 17,9% nas filtradas, 1,7% nas irradiadas e nenhuma das lavadas. Trinta transfusões deveriam ter sido filtradas, porém o prescritor não solicitou o subtipo.*

CONCLUSÃO: *Uma hipótese para as incorreções observadas é a formação médica inadequada sobre o assunto, tanto na graduação como na residência médica, associada à falta de atualização nos protocolos transfusionais. O comitê transfusional recebeu os resultados deste estudo com proposta de medidas de educação permanente sobre hemoterapia transfusional.*


PALAVRAS-CHAVE: *Transfusão de eritrócitos. Transfusão de sangue. Tratamento de emergência. Prescrições. Medicina transfusional.*

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ORIGINAL ARTICLE

# Emergency hormonal contraception in adolescence

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## SUMMARY

OBJECTIVE: *To analyze the degree of knowledge of Brazilian adolescents regarding emergency contraception (EC) such as correct administration, frequency of use, efficacy, mechanism of action, adverse effects, and complications.*

METHODS: *Cross-sectional study. Adolescents aged 11-19 years answered a questionnaire containing questions about sexuality, knowledge, and use of EC.*

RESULTS: *Out of 148 adolescents who were interviewed 8% did not know about the EC. Among the sexually active, 56.7% used EC at least once. The chance of obtaining EC information with friends triples between 15-19 years old [p=0.04; OR=3.18 (1.08-10.53)]. Most used single-dose EC. They said that EC prevents 80% of pregnancy and should be used within 72 hours after unprotected sex. Only 41.2% between 10-14 years old and 82.4% between 15-19 years old know that it prevents fertilization. As reasons for using they cited: rape and unprotected sex in 58.3% of those aged 10-14 years old and 79.6% between 15-19 years old. About side effects, 58.8% of 10-14 years old and 17.6% of those aged ≥15 years old could not answer, but 60.5% between 15-19 years old mentioned nausea and vomiting. A significant portion (17.6-41.2%) believes that EC causes abortion, cancer, infertility, and fetal malformations. Over 80% of the girls agree that it can cause menstrual irregularity.*

CONCLUSION: *Knowledge regarding EC is not satisfactory, especially regarding its risks, regardless of the age and education of the groups evaluated. Improved knowledge may lead to greater adherence to EC and lead to a reduction in unplanned pregnancies.*
*Keywords: Contraception. Contraception, Postcoital. Adolescent.*

## INTRODUCTION

Emergency contraception (EC) is defined by the World Health Organization (WHO) as a contraceptive method to be used after sexual intercourse[1]. It is recommended in cases of failure or incorrect use of contraceptive therapy, rupture or non-use of condoms, and in cases of sexual violence[2].

In Brasil, the EC options available are the progestogen pill, with 1.5 mg of levonorgestrel in a single dose or in two doses of 0.75 mg with a 12-hour interval, the combined pill of estrogen and progestogen in high doses (Yuzpe method), and the copper intrauterine device (IUD). The effectiveness of the levonorgestrel

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pill is 95% when taken within 24 hours, decreasing to 45-79% after this period. It can be effective for at least four days and, potentially, up to five days after sexual intercourse[1-3]. The effectiveness of the Yuzpe method varies between 56% and 86%[1].

The Copper IUD is the most effective emergency contraception method since it provides a pregnancy rate of less than 0.1%. Its advantage is that it is a non-hormonal method that can be used until the fifth day after unprotected sexual intercourse[2,3].

The adolescent population has a high rate of discontinuity and failure in the use of contraception. Sexual and reproductive health education in adolescence can lead to a reduction in the rate of pregnancy and stress the importance of a healthy sex life[2,4].

The objective of this study was to investigate adolescents' level of knowledge on EC, such as its correct use, effectiveness, mechanism of action, frequency of use, adverse effects, and possible complications. The results obtained can be used as a strategy in the design of public health policies, assisting in the prevention of unplanned pregnancy in adolescence.

## METHODS

*Study design:* A cross-sectional descriptive study.

*Study population:* Female adolescents aged between 11 and 19 years were divided into two groups: early adolescence (10 to 14 years) and late adolescence (15 to 19 years).

*Sample:* This research is an arm of an international study conducted in 13 countries of Latin America and the Caribbean. The sample of each region was estimated by taking into account the population of female adolescents in each country participating in the study. With a confidence level of 95% and an alpha error of 5%, the necessary number of participants per country was 77. In the present study, we will describe the results from Brazilian adolescents residing in the southeastern and southern regions.

*Study region and time:* The adolescents were interviewed in schools, outpatient clinics of the Unified Health System (SUS), and private clinics in several cities. The interviews took place between July and December 2016.

*Measuring Instrument:* We used an anonymous questionnaire with 21 questions related to sexuality and the use of EC methods. At the time the participation of adolescents in the study was requested, an informed consent form (ICF) was read and signed by the participant. When the adolescent was not 18 years old yet, the authorization from a tutor was required. Then, the questionnaire was applied for data collection. The teenagers who were unaware of EC were instructed to interrupt the filling out of the questionnaire at question number eight.

*Study variables:* The outcome of the study was the level of knowledge of EC. The variables collected were: age, age at menarche, age of sexual initiation, number and sex of partners, formal education, whether they worked or studied, public or private school, city/region of residence, knowledge on EC, if participants had ever used EC and how was the use was done, the effectiveness of the medication, situations of use, adverse consequences of use, frequency of use, and previous pregnancies.

*Inclusion criteria:* Adolescents who sought medical help, regardless of the reason, both in public and private clinics, able to read and understand the questionnaire.

*Exclusion criteria:* Adolescents who did not want to participate in the research.

*Data Analysis:* The data were described using proportions, means, standard deviations, medians, and their respective confidence intervals of 95% were estimated. The magnitude of the associations was evaluated by calculating the measures of associations (odds ratio) and their respective 95% CI. The entry and statistical analysis processes were carried out using Epi-info 3.5.2.

*Ethical aspects:* The research project was conducted within the standards set forth by the Declaration of Helsinki and Resolution No. 466 of the National Health Council of 12th December 2012. The project was submitted to the Brasil platform and approved by the CAAE decision No 57857316.2.1001.5259 on 31/07/2016.

## RESULTS

We studied 148 adolescents residents of the southeastern and southern regions of Brasil. The mean age was 16.2 ± 2.0 years. Basic formal education was 47.3%, 6% were not studying at the moment, and 13% reported working. Menarche occurred, on average, ate the age of 11.7±1.4. Sexual activity was reported by 40.5% (60) of the group, and its initiation was, on average, at the age of 15.7±1.3. For those in basic education, 30% reported having an active sex life. In secondary education, that number increased to 46.3%; for higher education, it was 81.8%. The number of

partners ranged from 1 to 13 (mean=3.1±2.8). Sexual intercourse was with males in 90% of cases, 3.3% was with girls and 6.7% with both genders (Table 1).

Those unaware of EC stopped filling out of the questionnaire (8.1% -12/148). The subsequent questions were answered by 136 adolescents (17 were 10-14 years old and 119 were 15-19 years).

The adolescents between 10 and 14 years became aware of EC through their parents (35.3%) and teachers (35.3%), followed by friends (29.4%). Those aged 15-19 years obtained information mainly from friends (65.5%), followed by teachers (35.3%), physicians (33.6%), parents (27.6%), and other sources. The odds of obtaining information about EC from friends is three times higher among late teens [p=0.04; OR=3.18 (1.08-10.53)] than early ones (Table 2).

**TABLE 1.** SOCIODEMOGRAPHIC AND SEXUAL CHARACTERISTICS OF THE ADOLESCENTS

| Variable studied | | Freq. | % | CI 95% |
|---|---|---|---|---|
| Age | 10 a 14 | 27/148 | 18.2 | 12.4-25.4 |
| (mean: 16.2±2.0 years) | 15 a 19 | 121/148 | 81.8 | 74.6-87.6 |
| | | | | |
| Formal education | Primary | 70/148 | 47.3 | 39.0-55.7 |
| | Medium | 67/148 | 45.3 | 37.1-53.7 |
| | Top | 11/148 | 7.4 | 3.8-12.9 |
| | | | | |
| Type of School | Private | 88/135 | 65.2 | 56.5-73.2 |
| | Public | 47/135 | 34.8 | 26.8-43.5 |
| | | | | |
| Studies | Yes | 138/147 | 93.9 | 88.7-97.2 |
| | No | 9/147 | 6.1 | 2.8-11.3 |
| | | | | |
| Works | Yes | 19/145 | 13.1 | 8.1-19.7 |
| | No | 126/145 | 86.9 | 80.3-91.9 |
| | | | | |
| Menarche (mean: 11.7±1.4) | 8 a 11 | 64/141 | 45.4 | 37.0-54.0 |
| | 12 a 17 | 77/141 | 54.6 | 46.0-63.0 |
| | | | | |
| Has had sexual intercourse | Yes | 60/148 | 40.5 | 51.1-67.4 |
| | No | 88/148 | 59.5 | 32.6-48.9 |
| | | | | |
| Age of sexual initiation | 13 a 14 | 13/60 | 21.7 | 12.1-34.2 |
| (mean: 15.7±1.3 years) | 15 a 19 | 47/60 | 78.3 | 65.8-87.9 |
| | | | | |
| No. of Partners | 1 to 2 | 31/57 | 54.4 | 40.7-67.6 |
| | 3 a 13 | 26/57 | 45.6 | 32.4-59.3 |
| | | | | |
| Partner sex | Male | 54/60 | 90 | 79.5-96.2 |
| | Female | 2/60 | 3.3 | 0.4-11.5 |
| | Both | 4/60 | 6.7 | 1.8-16.2 |

Freq.: frequency; number of adolescents/total of respondents

Of the total of 60 sexually active adolescents, 56.7% (34) used EC at least once. From the group aged between 10 and 14 years, two reported sexual activity and having already made use of the medication in the form of a single-dose pill. In the group aged between 15-19 years, 58 were sexually active and 56.9% (33) of them had already used EC (p=0.84). Among those aged 15-19 years, 21 had used the single-dose pill, 14 took the pill in two doses, and four used the Yuzpe method, ingesting several combined oral contraceptive pills (ACO). Only one teenager claimed to have been pregnant and reported never having used any EC.

Between the aged 10 to 14 years, 41.2% answered that prevent fertilization and, among adolescents aged from 15 to 19 years, 82.4% responded that EC prevents fertilization. In relation to the method of use, a large part of participants replied that it should be taken up to 72 hours after unprotected sexual intercourse (70.6% aged between 10-14 years, and 84% between 15-19 years).

On the effectiveness of EC, most believe that it prevents pregnancy in 80% of cases and can be used in cases of rape and unprotected sexual intercourse. In both groups, a large number of participants (58.8% aged between 10-14 years, and 79.6% between 15-19 years) said that the EC should be used in both situations and should not replace conventional contraceptives.

On the frequency that EC can be used, 11.8% of adolescents aged 10-14 years and 5% between 15-19 years stated that it should never be used because it is not effective and/or is abortive. On the other hand, 5.9% of patients aged between 10-14 years and 34.5% of the older ones thought it should only be used once a year, and approximately 30% of the two groups responded that it could be used once a month. Almost half of the youngest group (47%) and almost 1/3 of the older group (28.6%) answered the question correctly: whenever necessary. The minority of participants claimed to be unaware of how to use it (5.9% of the younger group and 2.5% of the older group).

In relation to the side effects, 58.8% of the younger participants did not know how to answer, and 60.5% of those aged between 15-19 years mentioned that the major side effects are nausea and vomiting (Table 2).

Table 3 evaluated the knowledge of adolescents about possible complications from the use of EC. On abortion, 6% of adolescents aged 10-14 years and 30.3% of the group aged 15-19 years did not know how to

**TABLE 2.** KNOWLEDGE ON THE USE OF EC

| Variable studied | 10 to 14 years | 15 to 19 years |
|---|---|---|
| How they heard about EC | | |
| Doctor/Nurse | 4 (23.5%) | 39 (33%) |
| Teacher | 6 (35.3%) | 41 (35.3%) |
| Parent | 6 (35.3%) | 32 (27.6%) |
| Friends | 5 (29.4%) | 76 (65.5%) |
| Others (internet, TV) | 2 (11.8%) | 12 (10.3%) |
| How EC works | | |
| Causes abortion | 2/17 (11.8%) | 7/119 (5.9%) |
| Prevents fertilization | 7/17 (41.2%) | 98/119 (82.4%) |
| Both | 1/17 (5.9%) | 6/119 (5.0%) |
| Doesn't know | 7/17 (41.2%) | 8/119 (6.7%) |
| How it is used | | |
| 72h before intercourse | 0 | 7/119 (5.9%) |
| Up to 72h after intercourse | 12/17 (70.6%) | 100/119 (84.0%) |
| Doesn't know | 5/17 (29.4%) | 12/119 (10.1%) |
| The time doesn't matter | 0 | 0 |
| Effectiveness of EC | | |
| Prevents 100% | 1/17 (5.9%) | 18/119 (15.1%) |
| Prevents 80% | 10/17 (58.8%) | 72/119 (60.5%) |
| Prevents 30% | 1/17 (5.9%) | 5/119 (5.0%) |
| Doesn't know | 5/17 (29.4%) | 23/119 (19.3%) |
| When EC should be used | | |
| Rape | 2/17 (11.8%) | 3/117 (2.6%) |
| Unprotected intercourse | 4/17 (23.5%) | 24/117 (20.5%) |
| Both | 10/17 (58.8%) | 90/117 (79.6%) |
| Doesn't know | 1/17 (5.9%) | 0 |
| It is to right to say that | | |
| It can replace other contraceptives | 3/17 (17.6%) | 8/117 (6.8%) |
| It can be used in intercourse with no contraceptives | 12/17 (70.6%) | 99/117 (84.6%) |
| Both are correct | 0 | 8/117 (6.8%) |
| Doesn't know | 2/17 (11.8%) | 2/117 (1.8%) |
| Frequency of use of EC | | |
| 1x/year | 1/17 (5.9%) | 41/119 (34.5%) |
| 1x/month | 5/17 (29.4%) | 35/119 (29.4%) |
| Whenever necessary | 8/17 (47.0%) | 34/119 (28.6%) |
| Doesn't know | 1/17 (5.9%) | 3/119 (2.5%) |
| Never, because it is not effective and/or can be abortive | 2/17 (11.8%) | 6/119 (5.0%) |
| Adverse effects of EC | | |
| Nausea and vomiting | 5/17 (29.4%) | 72/119 (60.5%) |
| Headache and/or convulsions | 1/17 (5.9%) | 20/119 (16.8%) |
| Fever and sweating | 2/17 (11.8%) | 11/119 (9.2%) |
| All the above | 0 | 17/119 (14.3%) |
| None of the above | 10/17 (58.8%) | 21/119 (17.6%) |

Obs.1: The total number is greater than 100% in questions that allowed for more than one answer.

answer. The answer "I don't know" ranged from 3.4 to 9.2% in the other four questions. A significant number of the two groups (ranging from 17.6 to 41.2%) believe that EC causes abortion, cancer, infertility, and fetal malformations. On the other hand, more than 80% agree that it can cause menstrual irregularity. There was no significant difference in any of the questions, which demonstrates that knowledge is not dependent on age (Table 3)

## DISCUSSION

In this study, the age of sexual initiation was in line with that found by another Brazilian study, i.e., ≥15 years in 59.3%[4]. The rate of sexual activity of 30% among adolescents of basic education is in line with that presented by the National Survey on School Health (PeNSE)[5], which pointed out that 28.7% of the students of the ninth year were sexually active. This proportion increased with age, from 13.7% in children up to 13 years to 22.9% in those up to 14 years and to 48.1% by the age of 15 years, something that was also observed in this study.

Upon analyzing the adolescents' knowledge on and frequency of use of EC, over half reported having used it at least once, and only 8.1% were unaware of the method, which is consistent with a study from Nigeria, in which the main predictor for the use of EC is the knowledge on its ease of use and effectiveness[6]. Chofankian et al.[4] assessed patients from the southeast of Brasil and also found that more than half of adolescents use EC, a result higher than those from other studies[7-9].

The adolescents' knowledge is unsatisfactory in several aspects in both groups (how it works, its effectiveness, and frequency of use); however, this does not prevent the use of EC. Chofakian et al.[4] found that adolescents make use of the method even without adequate knowledge.

In the present study, wrong answers or questions among younger participants ranged between 23,4-58,9%, and only one adolescent from this age group had used EC. A study from Ethiopia associated the frequency of EC use with age, showing that the lower the age, the less frequent the use of the medication, a fact that can be explained by more difficult access. These data are consistent with studies conducted in Hawaii, Nicaragua, and Africa[8,10,11]. According to Rafie et al.[12] those under 16 years of age tend to use EC incorrectly, and studies have found that adolescents up to 12 years old have a incorrect understanding of its use[13,14].

Adolescents believe that EC causes many complications, which may be responsible for their

**TABLE 3.** KNOWLEDGE OF THE ADOLESCENTS ABOUT POSSIBLE COMPLICATIONS FROM THE USE OF EC

| What can EC cause | 10 to 14 years | 15 to 19 years | OR (CI 95%) | p-value |
|---|---|---|---|---|
| Causes abortion | | | | |
| Yes | 7 /17 (41.2%) | 29/119 (24.4%) | 1.44 (0.46-4.36) | 0.5 |
| No | 9/17 (52.9%) | 54/119 (45.4%) | | |
| Doesn't know | 1/17 (5.9%) | 36/119 (30.3%) | | |
| Causes cancer | | | | |
| Yes | 3/17 (17.6%) | 35/119 (29.4%) | 0.48 (0.10-1.7) | 0.27 |
| No | 13/17 (76.5%) | 73/119 (61.3%) | | |
| Doesn't know | 1/17 (5.9%) | 11/119 (9.2%) | | |
| Causes infertility | | | | |
| Yes | 5/17 (29.4%) | 43/117 (36.8%) | 0.71 (0.21-2.2) | 0.54 |
| No | 11/17 (64.7%) | 67/117 (57.2%) | | |
| Doesn't know | 1/17 (5.9%) | 7/117 (6.0%) | | |
| Causes menstrual irregularity | | | | |
| Yes | 14/17 (82.3%) | 102/119 (85.7%) | 0.89 (0.19-6.4) | 0.89 |
| No | 2/17 (11.8%) | 13/119 (10.9%) | | |
| Doesn't know | 1/17 (5.9%) | 4/119 (3.4%) | | |
| Causes fetal malformations | | | | |
| Yes | 5/17 (29.4) | 42/119 (35.3) | 0.74 (0.22-2.25) | 0.6 |
| No | 11/17 (64.7) | 68/119 (52.1) | | |
| Doesn't know | 1/17 (5.9) | 9/119 (7.6) | | |

non-adherence to the method. Picavet et al.[15] claim that knowledge about the positive aspects of EC can increase the intention of use, while knowledge of the negative aspects can reduce it. However, the act of using EC is more important than knowledge. Schrager et al.[16] highlighted that knowledge about EC and its correct use were related to a future predisposition for its use, understanding that information about the drug may be relevant to the planned parenthood

Younger adolescents obtained information on EC, in most cases, from teachers or parents. Whereas among older adolescents information came predominantly from friends, which is not as reliable since the degree of the friends' knowledge is unknown.

Chofakian et al.[4] related the use of EC with its ease of access, such as where to find it, information that can be provided by acquaintances who have previously used it, and can also warn about the side effects of the drug. In England, partners and friends are usually responsible for purchasing the medication or accompanying the adolescent during its purchase[17]. In the USA, a recent study found that EC is only accessible to adolescents in 28% of pharmacies in the southwest states[18].

In the present study, most adolescents replied that EC should be taken until 72 hours after unprotected sexual intercourse. However, it can be used up to 120 hours after it[1]; however, the later it is used, the lower its effectiveness. Many adolescents may not seek the method after this period because they do not know it is still effective, information that could benefit more women[19].

In this study, 21% said that EC is 100% effective, unlike in the study by Nappi et al.[20], in which 42% of the women interviewed believed that its effectiveness was 100% when used within 24 hours. With levonorgestrel, pregnancy is avoided in 85% of cases, and with the Yuzpe method, the effectiveness varies between 56-86%[1,21]. Ulipristal acetate is effective if used up to five days after intercourse, but is not available in Brasil[22]. The copper IUD can be indicated as a long-term contraception method, but if inserted within five days of unprotected sexual intercourse, it works as EC. The IUD prevents fertilization, causing chemical changes in the sperm and ovum before they meet. Its advantages are its inexpensive cost and no need to be removed because it can be used for up to 10 years as an effective contraceptive method[1,3,23].

In relation to the adverse effects, 60.5% of those aged between 15-19 years reported that its main effects are nausea and vomiting. The literature supports the use of levonorgestrel as a safe EC. Among the most common adverse effects are nausea (14%) and menstrual irregularity (31%), it can also cause abdominal pain (14%), fatigue (13%), headache (10%), and dizziness

(10%)[24]. Younger adolescents show less knowledge about the adverse effects than the older ones. In the present study, 35.8% of the adolescents believed that EC causes infertility, and 6% did not know how to answer the question. Nappi et al.[20] found that 46% of interviewees did not know whether the use of EC causes infertility.

The belief that it caused abortion was the same among adolescents aged between 10-14 years and older ones (p=0.5). A study from Spain showed that 30% of women had already used EC and over half of the interviewees stated that it an abortive drug[25], while a third interviewed by Nappi et al.[20] also shared the same belief.

## CONCLUSION

The study concluded that among the adolescents interviewed, 8% were unaware of EC, and over half of them reported having used it at least once. Many adolescents believe that EC should not be used because it causes miscarriage or significant consequences, such as cancer, infertility, and fetal malformations, which reveals an important degree of ignorance and low adherence to the use of EC.

Adequate knowledge was not associated with age or schooling. The improvement of knowledge can provide greater adherence to EC, which, in turn, could become an important tool to reduce unplanned pregnancy in adolescence

Ethical aspects

The research project was conducted within the standards set forth by the Declaration of Helsinki and Resolution No. 466 of the National Health Council of 12th December 2012. The project was submitted to the Brasil platform and approved by the CAAE decision No 57857316.2.1001.5259 on 31/07/2016.

### Conflict of interest

No competing financial interests exist

### Authors' contributions

DLMM and LDH developed the design and method of the study. DLMM, MFVRP, LDH, and RA assessed the data and participated in the elaboration of the results. DLMM, MFVRP, LDH, RA, and RMR drafted the manuscript. DLMM, LDH, and RMR edited the manuscript. All authors read and approved the final version of the manuscript.


## RESUMO

OBJETIVO: *Analisar o grau de conhecimento das adolescentes brasileiras em relação à contracepção de emergência (CE) como administração correta, frequência de uso, eficácia, mecanismo de ação, efeitos adversos e complicações.*

MÉTODO: *Estudo transversal. Adolescentes de 11 a 19 anos responderam questionário contendo questões sobre sexualidade, conhecimento e uso de CE.*

RESULTADOS: *Das 148 adolescentes entrevistadas, 8% desconheciam a CE. Entre as sexualmente ativas, 56,7% utilizaram a CE pelo menos uma vez. A chance de obter informação sobre CE com amigos triplica entre 15-19 anos [p=0,04; OR=3,18(1,08-10,53)]. A maioria usou a CE em dose única, afirmou que evita gravidez em 80% e que deve ser usada até 72 horas após relação sexual desprotegida. Somente 41,2% entre 10-14 anos e 82,4% entre 15-19 anos sabem que evita a fecundação. Uso em casos de estupro e relação sexual desprotegida foi citado por 58,3% nas com 10-14 anos e 79,6% entre 15-19 anos. Quanto aos efeitos colaterais, 58,8% de 10-14 e 17,6% das com ≥15 anos não souberam responder, mas 60,5% entre 15-19 anos citaram náuseas e vômitos. Importante parcela (17,6-41,2%) acredita que a CE causa aborto, câncer, infertilidade e malformações fetais. Mais de 80% concorda que pode causar irregularidade menstrual.*

CONCLUSÃO: *O conhecimento em relação à CE não é satisfatório, principalmente quanto aos seus riscos, independente da idade e escolaridade dos grupos avaliados. A melhora do conhecimento pode proporcionar maior adesão à CE e acarretar redução da gravidez não planejada.*


PALAVRAS-CHAVE: *Anticoncepção. Anticoncepção pós-coito. Adolescente.*

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ORIGINAL ARTICLE

# Association between atherogenic dyslipidemia and fournier's gangrene

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## SUMMARY

OBJECTIVE: *We aimed to determine whether atherogenic dyslipidemia is associated with the disease and morbidity in our patients treated for Fournier's gangrene (FG).*

METHODS: *Sixty-two patients who were treated with the diagnosis of FG at our center between 2012 and 2017 were retrospectively screened.*

RESULTS: *The triglyceride values of the patients who required reconstructive surgery were statistically significantly higher than those of the patients for whom wound debridement and primary suturing was sufficient (p:0.001). A total of 65.7% of the patients had normal triglyceride values in the group in which wound debridement and primary suturing was sufficient, while this rate was 22.2% in the group of patients who needed reconstructive surgery; the difference was statistically significant (p: 0.002). The UFGSI score of those with triglyceride values higher than the normal range was statistically significantly higher (p:0.006). The cut-off point for the triglyceride value for which Fournier's gangrene was more morbid and the probability of reconstructive surgery need was significantly higher, i.e., >233mg.*

CONCLUSION: *Our study has demonstrated that atherogenic dyslipidemia, especially hypertriglyceridemia, is an important factor affecting morbidity and associated with high patient care costs after hospitalization and discharge in FG.*

KEYWORDS: *Fasciitis. Hypertriglyceridemia. Genitalia. Fournier gangrene. Genital diseases, male.*

## INTRODUCTION

Fournier's gangrene (FG) is a polymicrobial infection of the perineal and scrotal regions and manifests itself as a rapidly progressing necrotizing fasciitis. Predisposing factors include diabetes due to macroangiopathy and polyneuropathy, alcoholism, and immune-defects[1].

Despite radical surgical debridement and treatment with broad-spectrum antibiotics, it has a high mortality and morbidity rate, and the course of the disease is unpredictable. It is essential to understand the pathophysiology and predisposing factors for early diagnosis and treatment. The Fournier's Gangrene Severity Index (FGSI) and Uludag Fournier's Gangrene Severity Index (UFSGI) are used to evaluate prognosis and stratify risks in these patients[2].

In recent years, hypertriglyceridemia has been shown to be closely associated with atherosclerosis, endothelial dysfunction, and micro-angiopathy[3]. Atherogenic dyslipidemia (AtheroD) is a problem characterized by high triglyceride levels, especially when

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cholesterol levels are normal or low, and features very high atherogenicity[4]. In this study, we attempted to determine whether atherogenic dyslipidemias are associated with disease and morbidity in our patients treated for FG.

## METHODS

After Institutional review board (IRB) approval was acquired from our university's ethics committee with the IRB number of "HNH EAH KAEK 2018/11", all patients who were treated with a diagnosis of FG at our center between 2012 and 2017 were retrospectively screened. Age, comorbidities, regularly used medications, laboratory analyses between admission and hospitalization, the UFGSI scores, wound cultures, medical treatments performed, surgical procedures performed, and hospitalization times of the patients were retrospectively recorded. Patients on medication affecting blood fat levels (antipsychotics, beta-blockers, bile acid binders, estrogen, corticosteroids, immunosuppressant, isoretinone, protease inhibitors, tamoxifen, thiazides) and patients with HgA1c ≥10% were excluded from the study. Also, the laboratory analyses and UFGSI scores of the remaining 62 patients were compared with several morbidity factors such as duration of hospitalization, antibiotic revisions, and need for reconstructive surgery.

In laboratory analysis, hemoglobin A1c (HbA1c), C-reactive protein (CRP), and hemogram parameters such as leucocyte (WBC), neutrophil (NEU), lymphocyte (LYM), and thrombocyte (PLT) counts were evaluated. In the evaluation of standard lipid profile, total cholesterol (TC), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), and triglyceride (TG) levels were measured. TC, HDL-C, and TG levels were measured directly, while LDL-C values were calculated indirectly by the Friedewald formula. LDL-C levels were directly measured in those who had a TG level higher than 400 mg/dL. Laboratory analyzes of all patients were performed on a full stomach within the first 24 hours of the patients' admission to our hospital.

All of our patients were hospitalized after being evaluated in the emergency clinic and empirically treated with ceftriaxone 2 * 1gr / 24h + metronidazole 2 * 0.5gr / 24h. All patients underwent extensive debridement by our urology department within the first 24 hours under antibiotic treatment. A culture sample was sent from debrided tissue and wound and the antibiogram was studied. Clinical inflammatory response and antibiogram results were evaluated by the infectious disease specialist within the first 72 hours. Based on that, it was decided if antibiotic therapy should be continued or revised. Primary wound suturing was performed in patients who had a clinical inflammatory response and no new tissue necrosis after extensive debridement and antibiotic treatment. Reconstructive secondary surgery was performed in patients with inadequate inflammatory control or new tissue necrosis. The patients who underwent vacuum-assisted closure (VAC) therapy and stoma treatment were followed up by the general surgery clinic, so they were excluded from the study.

## STATISTICAL ANALYSIS

When evaluating the findings obtained in this study, IBM SPSS Statistics 22 for statistical analysis (SPSS IBM, Turkey) programs were used. The fit of the parameters to normal distribution was evaluated by the Shapiro Wilks test. In the evaluation of the data, descriptive statistical methods (mean, standard deviation, frequency), as well as the comparison of the quantitative data and Student's t-test were used for the comparison of the parameters which were normally distributed, and the Mann-Whitney U test was used for the comparison of the parameters that did not show normal distribution. Continuity (Yates) Correction was used to compare qualitative data. Logistic regression analysis was performed for multivariate analysis. The cut-off point was chosen based on the ROC curve analysis. Significance was evaluated as $p < 0.05$.

## RESULTS

The study was carried out with 62 patients aged between 37 and 86 years old. The mean age of the patients was 60.52 ± 11.55. The body mass index (BMI) values ranged from 22 to 40 with a mean value of 30.92 ± 4.06.

In 61.3% of our patients, antibiotic treatment was revised based on the reproduction in the wound culture and clinical course in consultation with the infectious diseases department. Escherichia coli, bacteriodes fragilis, corynebacterium, peptostreptococ, actinomyces turicensis, methicillin-resistant staphylococcus aureus, staphylococcus epidermidis, lactobacillus casei, staphylococcus lugdunencis, and candida

albicans reproductions were observed in the wound cultures of our patients. The hospitalization period of the group with revised antibiotic treatment was statistically significantly longer (p: 0.001). The rate of reconstructive surgery need was 60.5% in the group in which antibiotic treatment was revised, whereas it was 16.7% in the group in which empirical treatment was sufficient. The UFGSI scores of the group in which antibiotic treatment was revised were higher but not statistically significant (p: 0.071). The rate of hypertriglyceridemic patients in the group of patients requiring antibiotic revision was higher than in the group of patients who did not require revision (60.5% vs 41.7%, respectively) (Table 1).

In 56.5% of our patients, adequate control was achieved through primary debridement and suturing, whereas 43.5% required reconstructive secondary surgery due to tissue necrosis. The TG values of those who required reconstructive surgery were significantly higher than those of the patients for whom primary debridement was sufficient (p: 0.001). While 65.7% of the cases had normal TG values in the group for whom primary debridement was sufficient, this rate was 22.2% in the group requiring reconstructive surgery, and the difference was statistically significant (p:0.002). Again, the UFGSI scores of those who required reconstructive surgery were statistically significantly higher (p=0.000) (Table 2).

The TG values of our patients ranged from 84 mg to 596 mg with a mean of 238.74 mg ± 121.8. According to the 2001 NCEP ATP III and 2012 Endocrine Society Guidelines, 53.2% of our patients were hypertriglyceridemic[5,6]. The UFGSI score of those with triglyceride values higher than the normal range was statistically significantly higher (p:0.006). A ROC curve was drawn for the TG value to predict the need for reconstructive surgery. The area under the curve was 0.787, and the standard error was 0.06. The area under the ROC curve was significantly higher than 0.5 (p: 0.001). The cut-off point determined for the TG value which predicts the need for reconstructive surgery was calculated as >233 mg/dL. The sensitivity of this value was found as 74.1%, specificity as 82.8%, positive predictive value as 76.9%, and negative predictive value as 80.6% [Figure 1].

**TABLE 1.** EVALUATION OF AGE, BMI, DURATION OF HOSPITALIZATION, HBA1C, CRP, HEMOGRAM, BLOOD LIPIDS, UFGSI AND SURGICAL PARAMETERS IN THE GROUP REQUIRING ANTIBIOTIC THERAPY REVISION.

| | Antibiotic treatment revision | | p |
|---|---|---|---|
| | Yes | No | |
| | Mean±SD | Mean±SD | |
| Age | 60,71±10,5 | 60,21±13,28 | [1]0,869 |
| BMI | 31,32±4,31 | 30,29±3,63 | [1]0,338 |
| Duration of hospitalization (days) | 19,29±8,19 | 12,46±6,51 | [1]0,001* |
| HbA1c | 9,28±3,15 | 7,95±2,04 | [1]0,049* |
| CRP | 12,83±9,45 | 8,19±5,93 | [1]0,036* |
| WBC | 14,79±5 | 13,21±5,24 | [1]0,240 |
| NEU | 11,92±5,23 | 10,36±5,21 | [1]0,256 |
| LYM | 1,62±1,06 | 1,74±0,94 | [1]0,659 |
| PLT | 285,76±79,6 | 290,42±91,21 | [1]0,833 |
| LDL-C | 132,15±29,49 | 129,91±30,51 | [1]0,785 |
| HDL-C | 34,47±7,5 | 36,38±7,92 | [1]0,345 |
| TC | 201,13±39,68 | 200,13±54,13 | [1]0,933 |
| TG | 255,53±118,62 | 213,71±124,99 | [1]0,190 |
| TG group n(%) | | | |
| Normal | 15 (%39,5) | 14 (%58,3) | [2]0,235 |
| Hypertriglyceridemic | 23 (%60,5) | 10 (%41,7) | |
| UFGSI (median) | 3,24±1,76 (3) | 2,63±1,61 (2) | [3]0,071* |
| Surgery n (%) | | | |
| Reconstructive surgery | 23 (%60,5) | 4 (%16,7) | [2]0,002* |
| Primary Debridement | 15 (%39,5) | 20 (%83,3) | |

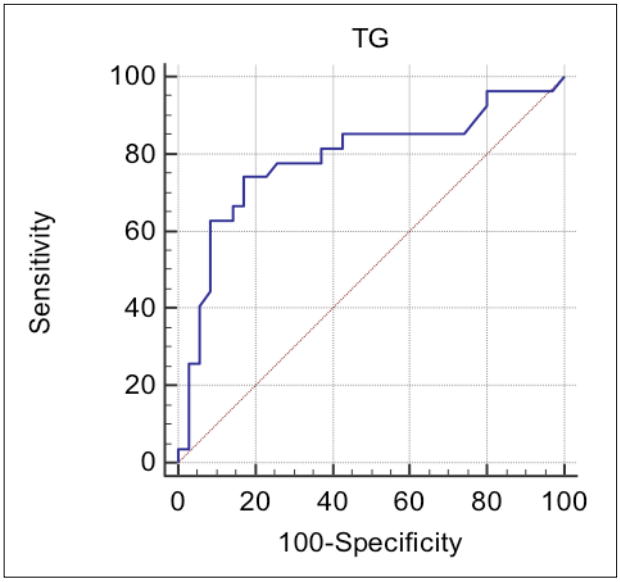
**1** Student t Test. **2** Continuity (Yates) Correction. **3** Mann Whitney U test. *p<0.05. Hemoglobin A1c (HbA1c), C-reactive protein (CRP), leucocyte (WBC), neutrophil (NEU), lymphocyte (LYM), thrombocyte (PLT), low density lipoprotein (LDL-C), high density lipoprotein (HDL-C), total cholesterol (TC) and triglyceride (TG)

**TABLE 2.** EVALUATION OF AGE, BMI, DURATION OF HOSPITALIZATION, HBA1C, CRP, HEMOGRAM, BLOOD LIPIDS, UFGSI IN PATIENTS HAD A TRIGLYCERIDE VALUES BELOW AND ABOVE THE CUTOFF VALUE (233 MG).

| | Triglyceride values | | p |
|---|---|---|---|
| | ≤233 mg | >233 mg | |
| | Mean±SD | Mean±SD | |
| Age | 62,67±11,03 | 57,54±11,81 | [1]0,085 |
| BMI | 29,5±3,18 | 32,88±4,38 | [1]0,002* |
| Duration of hospitalization (days) | 15,61±8,77 | 18,08±7,38 | [1]0,248 |
| HbA1c | 8,24±2,71 | 9,5±2,88 | [1]0,083 |
| CRP | 8,74±7,24 | 14,2±9,27 | [1]0,012* |
| WBC | 13,92±5,79 | 14,54±4,07 | [1]0,641 |
| NEU | 11,33±5,92 | 11,3±4,23 | [1]0,982 |
| LYM | 1,57±0,96 | 1,81±1,08 | [1]0,348 |
| PLT | 268,83±67,96 | 313,5±96,82 | [1]0,037* |
| LDL-C | 129,67±33 | 134,15±22,86 | [1]0,553 |
| HDL-C | 35,64±7,31 | 34,62±8,23 | [1]0,608 |
| TC | 193,89±47,07 | 210,23±41,99 | [1]0,164 |
| UFGSI (median) | 4,06±1,09 (4) | 6,35±3,32 (5) | [2]0,002* |

**1** Student t Test. **2** Mann Whitney U. *p<0.05. Body mass index (BMI), Hemoglobin A1c (HbA1c), C-reactive protein (CRP), leucocyte (WBC), neutrophil (NEU), lymphocyte (LYM), thrombocyte (PLT), low density lipoprotein (LDL-C), high density lipoprotein (HDL-C), total cholesterol (TC) and UFGSI (Uludag Fournier's Gangrene Severity Index)

**FIGURE 1.** ROC CURVE FOR TG IN THE DETERMINATION OF RECONSTRUCTIVE SURGERY.




## DISCUSSION

Fournier's Gangrene-associated mortality rates can reach up to 40% in the literature[7]. Although hyperbaric oxygen therapy has been popular in the last decade among the treatment methods, urgent radical surgical debridement and broad-spectrum antibiotic therapy are still considered the first-line treatment in FG[8]. Very long hospitalizations, too many surgical procedures (especially genital/perinea debridement, orchiectomy, cystostomy, colostomy), mechanical ventilation, and other supportive care lead to considerably higher treatment costs. Early diagnosis, aggressive surgical interventions, and intensive postoperative care have undoubtedly controlled mortality rates. It is imperative to understand the pathophysiology and predisposing factors for early diagnosis and treatment.

Hypertriglyceridemia is frequently detected in routine laboratory screenings and accompanied by other dyslipidemias. Primary hypertriglyceridemia is associated with familial/hereditary causes whereas secondary hypertriglyceridemia is associated with nutrition, obesity, insulin resistance, endocrinological diseases, and alcohol consumption[9]. Hypertriglyceridemia may be adversely affected by endothelial dysfunction and lead to chronic low-grade inflammation, foam cell formation on the arterial wall, oxidative stress, and fibrinolysis/coagulation anomalies[3]. AtheroD usually refers to conditions where LDL-C levels are normal or low while atherogenicity is high[4]. The main clinical features in AtheroD are increased levels of TG and reduced levels of HDL-C[4]. When we look at the group represented by AtheroD, the risk of cardiovascular disease is higher than the general population. The data from the PROVE IT-TIMI 22, ACCORD-Lipid, IDEAL, and TNT studies have shown that elevated TG levels are associated with an increased incidence of death and major cardiovascular events[4,10].

In a cross-sectional study, Schilling et al.[11] evaluated cerebral vascular diseases by magnetic resonance imaging and found that they were statistically significantly associated with elevated plasma TG levels as opposed to other lipid fractions. Again in 2015, in a study by Shin et al.[12], a significantly high correlation was found between serum TG levels and acute lacunar infarction in patients with DM. In another study, in the 6.5-year follow-up of 2207 adult patients without hypertension and prehypertension, the development of hypertension was predicted by waist circumference, CRP levels, and fasting TG along with diabetes in women in a multivariable logistic regression analysis[13]. This observation supports the fact that the inflammatory process contributes significantly to the development of hypertension through significant TG elevation. Also in our study, in patients with higher FG morbidity levels (those with high UFSGI, prolonged hospitalization, antibiotherapy change, and

those who need additional reconstructive surgery), TG levels were significantly higher and HDL-C levels were lower but not significantly correlated with LDL-C or TC. The above study and our study support the evaluation of inflammation as a key mediator in microvascular infarction caused by TG.

Although many risk factors for FG have been reported in the literature, increased BMI is not among them. In a study in which patients were divided into two groups according to their survival status, no statistically significant difference was found between the BMIs of the two groups[14]. In our study, although the BMIs were higher in the group of patients who needed antibiotic revision and reconstructive surgery, this difference was not statistically significant. The findings of our study revealed that the BMI of patients was significantly higher in the hypertriglyceridemic group, which was also predicted to have higher morbidity, with a sensitivity of 74.1% and a specificity of 82.8%.

In our study, the hospitalization durations and requirement for reconstructive surgery were statistically significantly higher, as expected, in the group in which antibiotic treatment was revised. TG values of those who required reconstructive surgery were statistically significantly higher than the TG values of the patients for whom primary debridement was sufficient. The UFGSI scores of those with triglyceride values higher than the normal range were statistically significantly higher. This data suggests that atherogenic dyslipidemia, especially TG elevation, may provide preliminary information about the course and morbidity of the disease in patients with FG. The need for antibiotic treatment revision and requirement for reconstructive surgery were significantly higher in patients with triglyceride values higher than the normal range. It can be predicted that FG patients with hypertriglyceridemia will have higher hospital stay and post-discharge care costs. In randomized controlled studies in which TG lowering treatments were applied, reductions in coronary events were reported[15,16]. These agents can be used in the follow-up and treatment of FG patients with hypertriglyceridemia.

There are some limitations to our study. Firstly, since clinical data were obtained retrospectively, selection and information biases may be possible. Secondly, nutritional status can affect TG levels significantly; however, our study did not collect data about the individuals' history of the most recent nutritional activity.

## CONCLUSION

Despite today's advanced technology and treatment alternatives, FG is still a high-cost disease with high mortality and morbidity rates. While further studies are needed to demonstrate the pathophysiological mechanism of necrotizing fasciitis, we believe that atherogenic dyslipidemia, especially TG elevation, is significantly and consistently associated with disease progression, morbidity, and higher patient care costs.

### Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### Informed consent

Informed consent was obtained from all individual participants included in the study.

### Conflict of interest

The authors declare they have no conflict of interest.

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### Author's contributions

All authors contributed equally to this study.

## RESUMO

OBJETIVO: *Nosso objetivo foi determinar se as dislipidemias aterogênicas estão associadas à doença e à morbidade em nossos pacientes tratados para a gangrena de Fournier (GF).*

MÉTODOS: *Sessenta e dois pacientes tratados com o diagnóstico de GF em nosso centro entre 2012 e 2017 foram selecionados retrospectivamente.*

RESULTADOS: *Os valores de triglicérides dos pacientes que necessitaram de cirurgia reconstrutiva foram estatisticamente significativamente maiores em comparação com aqueles dos pacientes nos quais o desbridamento da ferida e a sutura primária foram suficientes*

*(p:0,001); 65,7% dos pacientes apresentaram valores normais de triglicérides no grupo em que desbridamento da ferida e sutura primária foram suficientes, enquanto que essa taxa foi de 22,2% no grupo de pacientes que necessitaram de cirurgia reconstrutiva, e a diferença foi estatisticamente significativa (p:0,002). O escore UFGSI daqueles com valores de triglicerídeos acima da faixa normal foi estatisticamente significativamente maior (p:0,006). O ponto de corte para o valor de triglicérides pelo qual a gangrena de Fournier era mais mórbida e a probabilidade de necessidade de cirurgia reconstrutiva era significativamente maior foi >233 mg.*

CONCLUSÃO: *Nosso estudo demonstrou que a dislipidemia aterogênica, especialmente a hipertrigliceridemia, é um fator importante que afeta a morbidade e os altos custos associados ao cuidado do paciente após hospitalização e alta na GF.*

PALAVRAS-CHAVE: *Fasciite. Hipertrigliceridemia. Genitália. Gangrena de Fournier. Doenças dos genitais masculinos.*

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ORIGINAL ARTICLE

# Family planning among female medical students: are their plans comparable to other professionals?

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## SUMMARY

INTRODUCTION: *Late pregnancy is a problem among physicians, especially surgeons. This paper studies family planning among Medical Students (MS) and Law students (LS).*

METHODS: *A questionnaire was sent to all female MS and LS attending the two last years of University in the first semester of 2019. Data on age, family income, marital status, and family planning (age, planning for future pregnancies, timing, professional relationship or other issues, the ideal moment for a pregnancy, attitude towards eventual pregnancies, or maternity leave) were researched.*

RESULTS: *MS were significantly older than LS. A minority of women did not plan future pregnancies (10.6% of MS and 16.4% of LS), for markedly different reasons: 40% of the MS mentioned career plans, while for 70% of LS motherhood was not a personal project. The ages chosen for pregnancy also differed: MS tended to choose older ages. The most important priorities were financial planning and professional career for both groups, but specialization/post-graduation were only cited among MS. Both groups considered that the ideal moment for pregnancy was after professional consolidation in the job market. There were differences between MS that chose a surgical specialty and other MS.*

DISCUSSION: *MS tend to go through pregnancy late, especially students planning a surgical career. Professional issues are more influential over MS than LS. Medical educators and health managers must recognize there is a need to reconcile the medical career and motherhood as females represent > 50% of MS in Brasil.*

KEYWORDS: *Family planning. Reproductive health. Students, Medical. Women.*

## INTRODUCTION

Late pregnancy is a serious problem among physicians, especially surgeons. Obstetric problems, lower fertility, and frequent usage of in vitro fertilization are more frequent in this group[1-4]. This problem is getting more serious as the proportion of female students grows in Medical schools.

This paper aims to describe family planning among Medical Students (MS), as compared to Law students (LS). We hypothesize that MS enter Medical School at an older age than university students of other professions and postpone pregnancy till the completion of specialization/residency, due to the

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length, degree of commitment and ethos in Medical School and Residency.

## METHODS

A list of female students meeting the research criteria was obtained from the concerning offices of the Medical and Law schools of the Federal Fluminense University, a Public University in Rio de Janeiro, Brasil. A questionnaire was sent by e-mail to all female interns of the Medical School and all female students attending the last two years of Law School at the Federal Fluminense University, in the first semester of 2019, using a free web-based platform (Google Forms) to collect data, with immediate anonymization of the responses.

We opted for a quantitative research using a questionnaire planned for this specific purpose. The multiple choice, closed-ended questions involved epidemiological information (age, family income, marital status) and family planning (age, future planning of pregnancies, timing, professional relationship or other issues, ideal moment for pregnancy, attitude towards eventual pregnancies or maternity leave).

The questionnaires were sent by email three times, with a one-month interval, to each interviewee after the researchers presented the research project in face-to-face group encounters during meetings inserted into routine academic activities. There were no financial incentives. Each interviewee signed an informed consent concerning their participation in the research.

The chi-square test with Yates correction was used to analyze categorical data, considering p values < 0.05 as statistically valid. There was no funding for this research. The authors report no conflicts of interest. All authors reviewed the manuscript. SB and JA applied the questionnaire and compiled the data. LEJ analyzed data and wrote the manuscript.

## RESULTS

52.45% (96/183) of MS and 34.97% (64/183) of LS responded our questionnaire. Five questionnaires were excluded due to inadequate filling (2 MS, 3 LS), leading to a final cohort of 94 MS and 61 LS.

MS were significantly older than LS (Table 1 and Figure 1). A total of 52.1% of MS were ≤ 25 years-old, compared to 90.2% of LS (p=0.006). Family income was similar among the two groups. Most students belong to Medium/Higher income brackets in Brasil (78.7% and 67.2% with family income > 4 Brazilian minimum wages - approximately 1000 dollars - among MS and LS, respectively, p=0.158, Table 1). Being in a stable relationship or not was also comparable: 53 MS (56.4%) were not and 41% were in stable relationships, as compared to 39 (63.9%) and 21 (34.4%) LS (p=0.371). One LS did not declare her status (1.6%).

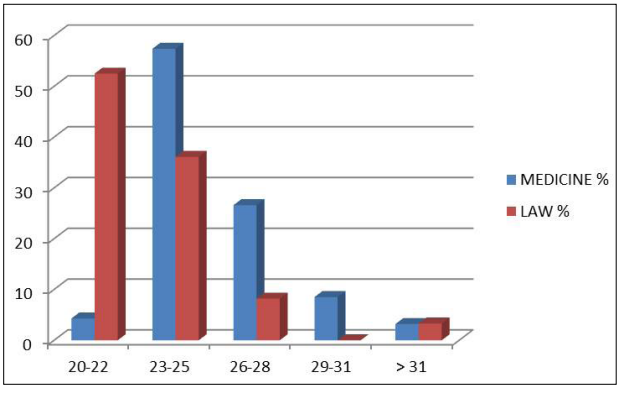
Most students (82 MS - 87.2% - and 51 LS - 83.6%) planned to have children in the future. Two MS were already mothers (2.2%). One of them graduated first in another profession and studied Medicine as a second graduation, and the other had a son after an unplanned pregnancy during MS. One of them planned future pregnancies and the other did not (allegedly for professional reasons).

A similar minority of women who did not have children did not plan future pregnancies (10.6% of MS and 16.4% of LS, p=0.455), but the reasons for their

**TABLE 1.** AGE DISTRIBUTION AND FAMILY INCOME OF MS AND LS (MS: MINIMUM SALARY IN BRASIL, APPROXIMATELY 250 DOLLARS IN THE FIRST SEMESTER OF 2019)

| AGES | MS | % | LS | % |
|---|---|---|---|---|
| 20-22 years-old | 4 | 64,3 | 32 | 52,5 |
| 23-25 years-old | 54 | 57,4 | 22 | 36,1 |
| 26-28 years-old | 25 | 26,6 | 5 | 8,2 |
| 19-31 years-old | 8 | 8,5 | 0 | 0 |
| >31 years-old | 3 | 3,2 | 2 | 3,3 |
| **Family income** | **MS** | **%** | **LS** | **%** |
| 1-2 MS | 5 | 15,3 | 10 | 16,4 |
| 3-4 MS | 15 | 16 | 10 | 16,4 |
| 5-6 MS | 19 | 20,2 | 10 | 16,4 |
| >6 MS | 55 | 58,5 | 31 | 50,8 |

**FIGURE 1.** AGES OF MEDICAL AND LAW STUDENTS INTERVIEWED



options were markedly different: while 40% of MS (n=4) related their abdication to the career, 70% of LS declared that maternity was not a personal project (Table 2). The ideal ages to become a mother also differed among the two groups: MS tended to prefer older ages (Table 2). A total of 26.9% of LS believed the best age for having the first child would be < 30 years-old, as compared to 9.5% of the MS (p=0.015).

We also studied the most important prominent factors for family planning. Some differences were notable (Figure 2). For both groups, the priorities were financial planning and professional career, but specialization/post-graduation were cited only among MS (16 citations). Family structure was mentioned as an important issue, as well as maternal age/maternal health (cited by approximately a third and half of the cohorts, respectively). Both groups considered that the ideal time for pregnancy was after consolidation as a professional in the job market (69.1% of MS and 75.4% of LS). Only 1 MS would choose to start a family after graduation and before residency, while 11.5% (n=6) of the LS would choose this moment as ideal (p=0.031). Most students in both groups declared that familiar planning did not influence their professional choices (75.5% and 83.6% of MS and LS, respectively, p=0.393), and most would not consider postponing their academic career for a pregnancy (69.1% and 82% of MS and LS, respectively, p=0.236).

There were notable differences in a comparison between MS that would choose a surgical specialty (NSMS – 73 students, 77.8%) and other MS (SMS – 21 students – 22.3%). Ages, frequency of stable relationships, and family income were similar between the two groups, despite a tendency of SMS for a bimodal distribution of household incomes.

The proportion of SMS and NSMS desiring future pregnancies was similar (90.3% and 85%, respectively), but only NSMS (11%, n=8) would choose to have children when aged < 30 years-old. Concerning the reasons influencing familiar planning, there were notable differences among NSMS and SMS (Figure 2). Career and specialization were much more cited as important by SMS (p=0.053 and p=0.001, respectively). Surprisingly, both cohorts denied family planning would affect professional choices in similar proportions (p=0.831). Family structure, in contrast, was much more important for NSMS.

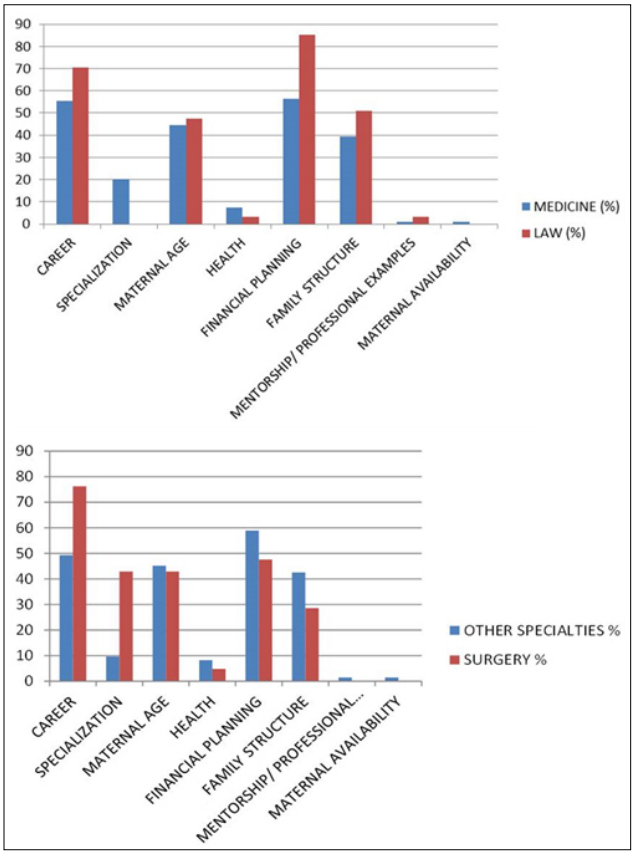
**TABLE 2.** REASONS TO ABDICATE FROM A FUTURE MATERNITY PROJECT AND IDEAL AGE FOR PREGNANCY

| REASONS TO ABDICATE FROM FUTURE MATERNITY | | | | |
|---|---|---|---|---|
| REASON | MS | % | LS | % |
| CAREER | 4 | 40 | 2 | 20 |
| NOT A PERSONAL PROJECT/WISH | 4 | 40 | 7 | 70 |
| DID NOT ANSWER | 2 | 20 | 1 | 10 |
| TOTAL | 10 | 100 | 10 | 100 |
| **IDEAL AGE FOR PREGNANCY** | | | | |
| AGES | MS | % | LS | % |
| 20-24 years-old | 0 | 0 | 1 | 1,6 |
| 25-29 years-old | 8 | 8,5 | 13 | 21,3 |
| 30-34 years-old | 65 | 69,1 | 31 | 50,8 |
| >34 years-old | 11 | 11,7 | 7 | 11,5 |
| Did not respond | 10 | 10,6 | 9 | 14,8 |
| TOTAL | 94 | 100 | 61 | 100 |

## DISCUSSION

Our paper suffers from the usual limitations of research based on mailed questionnaires. Survey fatigue and lack of direct involvement/personal interest with the research may justify the lower ratio of responses from LS. Notably, electronic questionnaires have been extensively used to explore opinions of

**FIGURE 2.** FACTORS INFLUENCING FAMILY PLANNING AMONG MEDICAL AND LAW STUDENTS



medical professionals or students in many fields, particularly concerning quality of life and professional choices, including most of the references cited in our research. The usage of a non-validated questionnaire is also a limitation, but we were unable to find a similar research project for comparison. Our questionnaire was exhaustively discussed and modified by our team before being considered satisfactory for our purposes. Standardization and anonymity were guaranteed. Face to face exposition of our research project was done previously to the delivery of the questionnaire to clarify any doubts/interpretation problems and to present the project.

This research project was proposed by MS in mentorship meetings with a female Professor, in the context of discussing their worries about family planning and difficulties in accepting maternity and maternity leave in the ethos of Medicine, which frequently lead female MS to find there was a contradiction between pregnancy and motherhood and a career in medicine. We hypothesized that those dilemmas, however common among females in contemporaneous societies, are worse for Physicians, as compared to other professions. We were unable to find published data about Brazilian physicians/MS, but our hypotheses were confirmed in foreign studies. For 77.6 of American MS their career choice was a definitive influence over family planning: ¼ postponed pregnancies and 7.5% opted against parenthood exclusively because they were MS[5]. Another research among emergency doctors (56% women), also in the USA, confirmed that institutional policies concerning parenthood were unsatisfactory for 1/3 of female professionals, who desired clearer policies, longer parental leave, better financial security, better planned work shifts for substitutes during parental leave and breastfeeding support[6]. In another paper, 6 and 16% of female and male thoracic surgeons, respectively, admitted that a pregnancy would be interpreted as something negative in the professional environment[3]. This was confirmed by another research, demonstrating that even other female residents considered a colleague's pregnancy disruptive[7], both confirming that medical ethos can be a negative factor towards pregnant female professionals. The low priority of family planning in medicine was demonstrated in a recent research involving 127 medical schools in the USA: only 34% have protocols covering pregnancy, and 2/3 offer only 6-8 weeks of parental leave[8,9].

An important issue, confirmed in the literature, is the option for later pregnancies that predominates among MS: more than 90% intended to get pregnant in their 4th decade of life and > 10% after 34 years of age. Late pregnancy planning was prominent amonsgt SMS as compared to NSMS, and is possibly related to greater demands for residency/specialization in surgical specialties and the professional environment and competition in Surgical specialties. The influence of Residency over family plans is confirmed by other researchers: 70% of MS judged that the best moment for a pregnancy was after Residency[9].

Late pregnancy has negative consequences on fertility and obstetric health. Female surgeons, urologists, and orthopedists generally postponed pregnancies with higher frequencies of obstetric complications, infertility, and use of in vitro fertilization methods[1-3]. Among female urologists, pregnancies occurred 7-8 years later and the need for in vitro fertilization was 10 times more common, as compared to the general population[4].

LS were chosen as a comparative cohort to guarantee reasonable similarity: both cohorts would graduate in the following year and both groups come from similar social strata in Brazilian society (predominance of high/medium class), which was confirmed in our research.

LS were younger than MS. This is probably due to late admission in Medical School and signals a difference between professions. In Brasil, yearly admission exams to Public University Courses are mandatory and extremely competitive to acess Medical School (89.41 candidates/spot in 2018, compared to 21.67 candadates/spot in Law School)[10]. Students frequently need to pass multiple exams to access Medical Schools. Also, graduation in Medicine is longer than in Law (6 and 4 years, respectively). We did not detect differences between the two groups that seemed to be attributed to age differences, including being or not in a stable relationship.

A small proportion of women did not plan a future pregnancy in both cohorts (12.8% among MS and 16.4% among LS). This ratio is similar to the general population of females that opt not to become mothers in Brasil (14%, according to the Brazilian Institute of Geography and Statistics – IBGE)[11]. However, it is possible that the proportion of LS opting against motherhood changes in time, due to their younger age. A novel finding in our research is that LS opted against future pregnancies for personal reasons, as Brazilian women in general, but professional reasons were disproportionately high amongst MS (40%), especially SMS.

Financial planning and professional career were the most important factors relating to family planning for both groups, reflecting the reality of medium and high social class in Brasil. However, for MS, Residency and specialization assumed a prominent position, while amongst LS post-graduation was not influential. Maternal age/maternal health worries, cited by half of the students in both groups, was an important consideration, probably related to late pregnancy plans.

Surprisingly, both cohorts, including SMS, denied family planning to affect professional choices in similar proportions. Family structure, in contrast, was much more important for NSMS and LS than for SMS. We could not explain this finding; it may be directly related to the "type A" personality commonly attributed to female surgeons.

Most students would not consider postponing their academic career for a pregnancy, suggesting that this option, cited in the literature as a possible strategy to avoid late pregnancies among female doctors would not be well accepted in Brasil. This has also been demonstrated in the USA, where 13/18 students after pregnancy or parenthood (15% of medical students) would extend parental leave, but only if it did not imply to postpone graduation[12].

Gender inequality is a fact in Medicine, although more than half of the students that graduate nowadays from medical school are female in most countries[13]. The unavailability of female mentors, despite being considered an important problem for medical educators, has been denied as influential or important by female medical students in many research papers[13]. This was also seen in our research: the absence of female professional examples, including their life experience with pregnancy was not cited as influential over future familial planning.

A recent paper about career satisfaction among Surgical Residents in USA that had children (mean age 30.5 years-old) showed that they considered leaving career or revisiting their career choices because of difficulties in reconciling pregnancy and motherhood with surgical training and because of their perception of stigma during pregnancy. Many would advise female students against surgery as a career for women[14,15]. Other attest that 2/3 of the female surgeons opted for pregnancy during training, but 85.6%, while concerned that their work schedule would adversely affect their pregnancy, maintained their work schedules throughout pregnancy. Most resented the absence of institutional support for pregnancy, maternity leave, and lactation[15]. Differences between male and female Surgical Residents and Surgeons have been demonstrated: while 64% and 95% of the males had children, only 15 and 40% of the females did so, during and after residency. Most women considered that part-time work would be a solution to reconcile parenting and the surgical practice[16].

## CONCLUSION

MS choices concerning family planning are directly related to late pregnancy, specially among students who plan a surgical career, and give rise to obstetric and fetal health concerns, spontaneous infertility, and need for in vitro fertilization. Professional issues are more influential over career planning among MS than among LS. Medical educators and health managers must recognize there is a need to reconcile the Medical career and motherhood, especially among surgical professionals, as the proportion of females among MS and physicians is over 50% in most countries, including in Brasil.

### Author's contribution

Sthan Bacelar ORCID – Lisieux Eyer de Jesus - Planing of the study, development of the original concept;

Juliana Araújo - Design of the questionnaire;

Sthan Bacelar - Data aquisition, and tabulation;

Juliana Araújo – Lisieux Eyer de Jesus - Interpretation of the data and statistical evaluation;

Juliana Araújo – Sthan Bacelar – Lisieux Eyer de Jesus - Manuscript drafting;

Juliana Araújo – Sthan Bacelar – Lisieux Eyer de Jesus - Final review of the manuscript.

## SUMMARY

INTRODUÇÃO: *A gravidez tardia é um problema entre médicas, principalmente entre cirurgiãs. Este trabalho analisou o planeamento familiar de estudantes de medicina (MS) e estudantes de Direito (LS).*

METODOLOGIA: *Um questionário foi enviado para todas as estudantes de medicina e direito cursando os dois últimos anos do curso universitário no primeiro semestre de 2019. Idade, renda familiar, estado civil e planejamento familiar (idade, planejamento de futuras gestações, relacionamento profissional ou com outras questões, momento ideal para uma gestação, atitude em relação a uma eventual gravidez ou licença maternidade) foram investigados.*

RESULTADOS: *As MS eram significativamente mais velhas que as LS. Uma minoria das mulheres não planeja futuras gestações (10,6% das MS e 16,4% das LS), por razões distintas: 40% das MS mencionaram planos profissionais, enquanto para 70% das LS a maternidade não era um projeto pessoal. As idades escolhidas para a gravidez também foram diferentes: MS, em geral, optaram por idades mais avançadas. As prioridades mais mencionadas foram o planeamento financeiro e a carreira em ambos os grupos, mas especialização/pós-graduação só foram citadas entre as MS. Ambos os grupos consideraram que o momento ideal para uma gestação seria após a consolidação profissional no mercado de trabalho. Houve diferenças entre as MS que escolheram uma especialidade cirúrgica e outras MS.*

DISCUSSÃO: *MS tem uma tendência a gestações tardias, especialmente as que planejam uma carreira cirúrgica. Questões profissionais têm mais influência entre as MS do que entre as LS. Educadores e gestores da área médica devem reconhecer de que há uma necessidade de conciliar a carreira médica e a maternidade, já que as mulheres representam > 50% dos estudantes de medicina no Brasil.*


PALAVRAS-CHAVE: *Planejamento familiar. Saúde reprodutiva. Estudantes de Medicina. Mulheres.*

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ORIGINAL ARTICLE

# Physiotherapy services in the face of a pandemic

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Research in Education and Community Intervention (RECI)

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## SUMMARY

BACKGROUND: *Physiotherapy services are necessary for hospitalized patients of COVID-19 as well as chronic patients. Thus, physiotherapists present an increased risk of exposure to coronavirus. This study aimed to determine the number of physiotherapists who interrupted their services because of the COVID-19 pandemic and to verify the procedures adopted by the ones who are still working.*

METHODS: *The sample comprised 619 physiotherapists who worked in Portugal, 154 (24.9%) male and 465 (75.1%) female, aged between 22 and 67 years (34.47±8.70). The measurement instrument was an on-line questionnaire applied in late March 2020 through contacts and social networks.*

RESULTS: *453 (73.2%) physiotherapists interrupted their work activities in person because of the pandemic and 166 (26.8%) continue to work in person. The main measures adopted by physical therapists who continue to work in person included: hand washing (21.5%), mask use (20.3%), material disinfection (19.3%) and, glove use (19.3%). Of the physiotherapists who are not working in person (n = 453), 267 (58.9%) continue to monitor their patients at a distance, and 186 (41.1%) are not monitoring the patients. The main measures used by physiotherapists to monitor their patients at a distance included: written treatment prescription (38%), making explanatory videos (26.7%), and synchronous video conference treatment (23.5%).*

CONCLUSIONS: *Our data revealed that most of the physiotherapists interrupted their face-to-face practices because of the COVID-19 pandemic, however, once they do not follow up their patients' treatment in person, most of them adapted to monitor their patients from a distance.*

KEYWORDS: *COVID-19, physical therapists, adopted measures, pandemic, health professionals*

## INTRODUCTION

Coronaviruses are a group of viruses belonging to the family of Coronaviridae, enveloped, positive single-stranded large RNA viruses with "human-to-human" transmission through respiratory secretions.[1,2]

The first case of coronavirus disease 2019 (COVID-19) was reported in Wuhan, Hubei Province of China, on 31 December 2019,[1,3] and the cumulative COVID-19 case number increased quickly. Currently (April 6,

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2020), COVID-19 was classified, by the World Health Organization (WHO), as a pandemic detected in 203 countries, with 348 867 positive cases and which caused 16,351 deaths.[3]

The clinical manifestations of COVID-19 comprise fever, cough, nasal congestion, fatigue, and other signs of upper respiratory tract infections including dyspnoea and severe chest symptoms corresponding to pneumonia,[1,4-6] and, to date, no specific therapeutic drug has been found.

WHO recommendations include frequent hand washing, social isolation, avoid touching the eyes, nose, and mouth, practice respiratory hygiene (to cover the nose and mouth with a flexed elbow or disposable tissue when coughing and sneezing), in case of fever, cough and difficulty breathing, seek medical attention early.[5,7]

Health care professionals are at the front line of providing care to patients with COVID-19, so they have an increased risk of occupational exposure to coronavirus. In this way, health professionals have to comply with a series of prevention and infection control recommendations to minimize the risk of infection.[5]

In Portugal, as well as in other countries, the number of cases of COVID-19 has increased every day, with 2 positive cases being detected on March 2 and, today (April 6, 2020), the number of infected people is 11,730 with 311 dead. The Portuguese Directorate-General for Health decided on several measures to be followed by health professionals, including hand hygiene, the use of a surgical mask (or the appropriate PPE for clinical activity), daily self-monitoring to identify early suggestive symptoms of COVID-19.[8]

Physiotherapy is the 3rd largest profession in the area of healthcare and is the most representative profession in the area of Rehabilitation in Portugal. Physiotherapy services provide the development, maintenance, and recovery of people's movement and functional ability, improving their quality of life.[9] In this way, many hospitalized patients in the acute phase of COVID-19, as well as chronic patients, need physical therapy services. The World Confederation for Physical Therapy (WCPT) has prepared a document that describes the recommendations for physical therapy management for COVID-19 in a hospital setting for acute cases.[10]

The purpose of this study was to determine the number of physiotherapists who interrupted their services because of the COVID-19 pandemic and to verify the procedures adopted by the physiotherapists who are still working.

## METHODS

This is a cross-sectional study developed to obtain data about the employment situation of physiotherapists working in Portugal.

This research has been approved by the Research in Education and Community Intervention (RECI) research center. All participants were informed of the objectives of the study and that the anonymity of the responses would be ensured, having given their consent to participate in this study.

### Population

This studied population consisted of physiotherapists of all sexes and ages.

The research inclusion criteria defined physiotherapists who worked in Portugal, who were working in clinical practice, and who freely agreed to participate in this research.

According to data from the Portuguese Association of Physiotherapists, the number of physiotherapists in Portugal is 13,000 (population). The sample size was determined using an estimated mean injury prevalence of 50%, and assuming an error margin of 5% with a 95% confidence interval (CI). Using these assumptions, the minimum sample size contained 374 physiotherapists.[11]

### Measurement instrument

The measurement instrument was an on-line questionnaire. Data collection took place between 26 and 30 March 2020. The questionnaires were disseminated through telephone contacts via WhatsApp, emails, social networks, and on institutional pages.

Since questionnaires on this topic are unknown, this measurement instrument was developed by the authors and, subsequently, had its content validity subjected to critical analysis (by Ph.D. Physiotherapist Professors) based on an objective approach to the analysis of statements used to measure a concept. Then, this questionnaire was submitted to a pre-test, having been sent to 3 physical therapists.

This questionnaire included questions about gender, age, years of professional practice, the region of practice, the subgroup of physiotherapy usually practiced on (could pick more than one), self-employed or employed, if they kept a person-to-person clinical practice and, if so, which prevention measures are being taken. The physiotherapists that were not working on a person-to-person clinical practice should say why, whether they started monitoring their patients

from distance and, if so, indicate how, if the number of sessions per week was being kept, and if the amount charged was the same.

## DATA ANALYSIS

Statistical analysis was performed with Statistical Package for Social Sciences (SPSS), version 26.0, and descriptive statistics were performed. Chi-square was used to test for a significant association between categorical variables. Statistical significance was set at 0.05.

## RESULTS

Of the 630 questionnaires delivered, 2 were excluded because they had errors in filling out and 9 were excluded because the physiotherapists were not working in Portugal. Thus, the sample consisted of 619 physiotherapists, with 154 (24.9%) males and 465 (75.1%) females, aged between 22 and 67 years (34.47±8.70 years old). The sample was 65% higher than expected for the population's representativeness.

Years of practice in the profession ranged from 4 months to 43 years (11.42±8.69 years).

Regarding the area of intervention, the physiotherapist was given the option to choose more than one area, with the majority working in the musculoskeletal area (28%), followed by trauma-orthopedics (15.9%), 13.7% neurology, 12.9% geriatrics, continuous and palliative care, 10.6% general practice, 9.1% cardiorespiratory, 8.4% pediatrics, 0.7% urogynecology, 0.4% dermatofunctional, and 0.3% in other areas of intervention.

A total of 390 (63%) physiotherapists were employed and 229 (37%) were self-employed.

Currently, 453 (73.2%) physiotherapists interrupted their work activities in person due to the pandemic, and 166 (26.8%) continue to work in person.

Of the physical therapists who continue to work in person, 27 (16.3%) were self-employed and 139 (83.7%) were employed. Of the physical therapists who interrupted their physical activities, 202 (44.6%) were self-employed and 251 (55.4%) were employed ($p \leq 0.001$).

Table 1 shows the association between the interruption of the profession and the area of Portugal in which the physical therapist practices.

The measures adopted by physiotherapists who are still working are shown in figure 1.

Of the physiotherapists who are not working in person (n=453), 49% (257 responses) answered that they stopped their work activity at their own will and 51% (268 responses) due to the imposition of the workplace.

Still considering physiotherapists who are not working in person, 267 (58.9%) continue to monitor their patients at a distance, and 186 (41.1%) are not monitoring patients. Figure 2 shows the measures used by physiotherapists to monitor their patients from a distance.

Of the physiotherapists who continue to monitor their patients remotely (n = 267), 36 (13.5%) maintained the frequency of their weekly sessions, and 231 (86.5%) changed the frequency of treatment. Only 22 (8.2%) physiotherapists maintained the same amount charged per remote treatment session and the majority (245; 91.8%) changed the price for this new type of distance treatment.

## DISCUSSION

Data of this study revealed that most physiotherapists interrupted their in-person practices because of the COVID-19 pandemic, and many of them (47%) were self-employed, which means they had to adjust their financial situation due to this interruption.

To minimize the impact of this public health crisis due to the new coronavirus, the Portuguese government has extended the deadline of State contribution payments for self-employed workers, exceptional financial support has also been created for workers who have to stay at home; for those staying home

**TABLE 1.** PRACTICE OF THE PROFESSION IN PERSON DISTRIBUTED OVER THE AREAS OF PORTUGAL

| Portugal areas | Practice of the profession in person | | Total |
|---|---|---|---|
| | Still practicing | Interruption of practice | |
| Azores archipelago | 0 | 9 (2%) | 9 (1.5%) |
| Autonomous Region of Madeira | 3 (1.8%) | 8 (1.8%) | 11 (1.8%) |
| North region | 37 (22.3%) | 134 (29.6%) | 171 (27.6%) |
| Center region | 20 (12%) | 64 (14.1%) | 84 (13.6%) |
| Lisbon and Vale do Tejo | 61 (36.7%) | 154 (34%) | 215 (34.7%) |
| Alentejo | 7 (4.2%) | 18 (4%) | 25 (4%) |
| Algarve (South region) | 37 (22.3%) | 62 (13.7%) | 99 (16%) |
| Did not mention | 1 (0.6%) | 4 (0.9%) | 5 (0.8%) |
| Total | 166 | 453 | 619 (100%) |

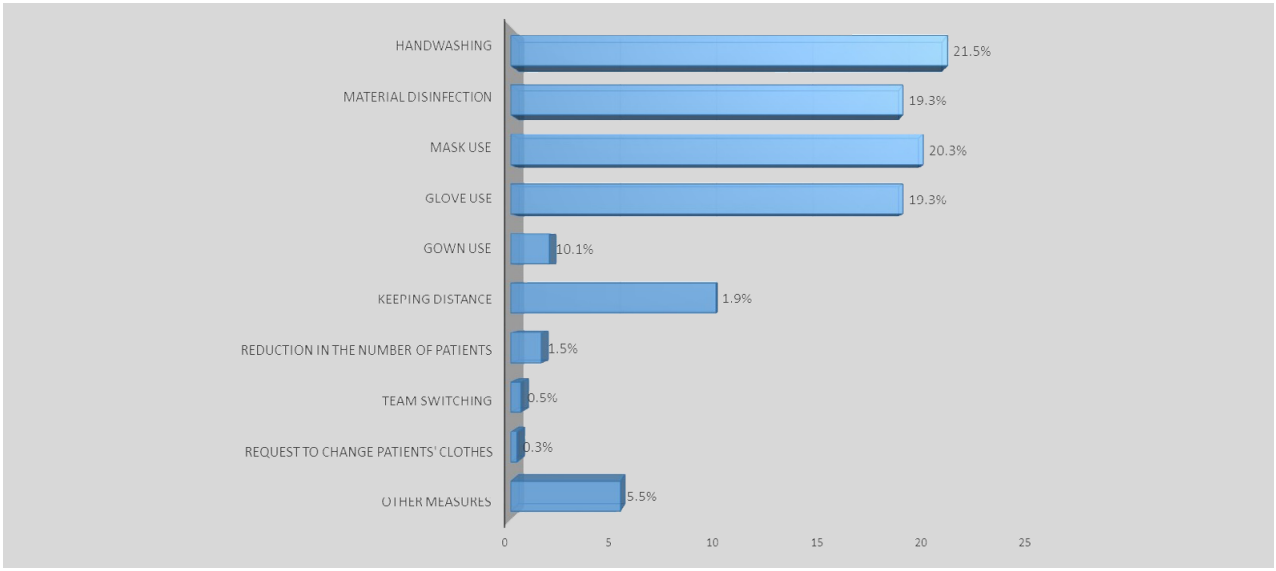


**FIGURE 1.** PREVENTIVE MEASURES ADOPTED BY PHYSIOTHERAPISTS

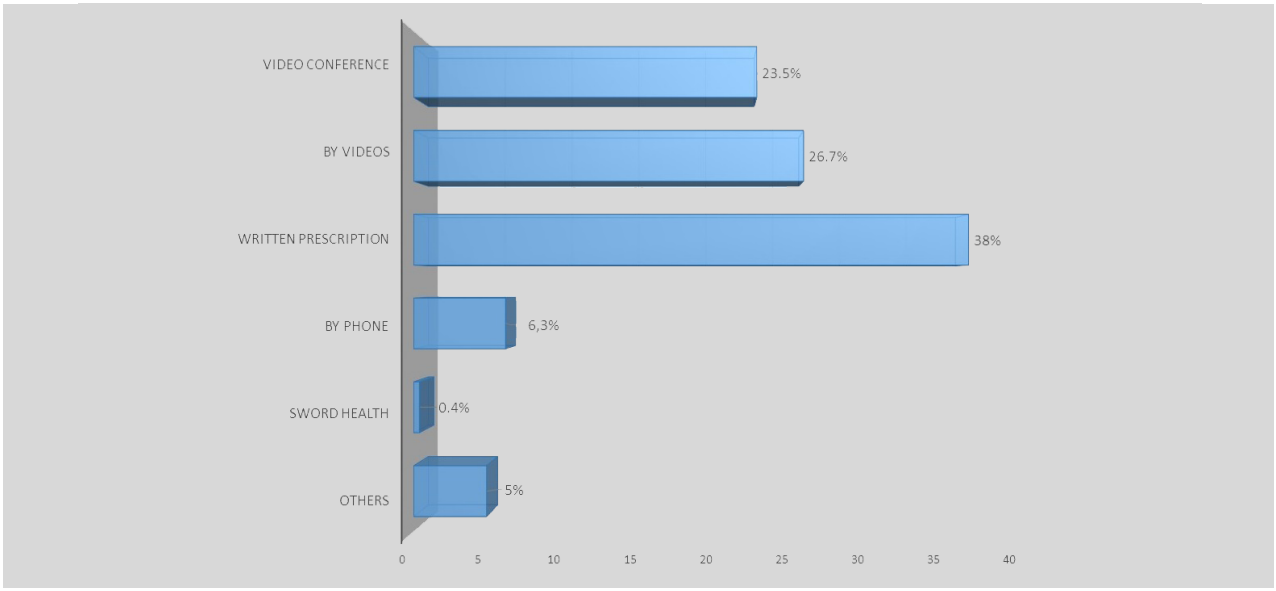


**FIGURE 2.** WAYS OF MONITORING PATIENTS REMOTELY

with children up to 12 years of age, assistance is equivalent to 1/3 of the average salary. As for employees, the Government created exceptional financial support for those who must stay at home to accompany their children up to 12 years of age, with 66% of the basic salary being paid to them, 33% paid by the employer and 33% paid by the State.

The government took measures to reduce the impact of work interruption for physiotherapists but many patients who need their care are without the main tool of the profession: manual contact. To minimize these problems, most physiotherapists who interrupted their face-to-face practice have followed-up their patients remotely.

The form of monitoring patients most used by physical therapists has been the prescription of treatment in writing. We believe that this measure is related to the difficulty of accessing and using a computer and the internet. Many physiotherapists have also produced videos showing all the exercises to be performed and some use video-conference resources as a way to make live-streamed sessions happen.

A tool not much used and even unknown by many is Sword Health, an application that allows patients to perform physiotherapy sessions at home, monitored in real-time and remotely by a team of physiotherapists and doctors, who prescribe, evaluate, and supervise the entire process. This pandemic forced

physiotherapists to adapt to the new digital tools in order to keep exercising their profession, just as patients, who also had to adapt to the digital age.

Some adaptations to the physiotherapy session characteristics had to be made since most patients may not have the necessary equipment/materials for its practice at home, space may not be adequate, and there is no face-to-face monitoring by a professional. Probably, changes in the number of sessions per week, as well as changes in the amount charged for it, can be explained by these factors mentioned above. Few physiotherapists maintained the same amount charged per session. However, in some places, such as state health centers, patients do not pay for the sessions, and, in these cases, the values would not be changed.

The objective of this study was not to analyze the ways used by physiotherapists to accompany their patients, in terms of structure, dynamization of sessions, duration, equipment used, among others. In the same way, future studies are suggested to evaluate the effectiveness of conducting sessions at a distance and compare its results with those obtained from face-to-face sessions.

The data in this study also reveals that the physiotherapists who are still working have generally respected the preventive measures applied by the General Directorate of Health of Portugal[7] and by the World Physiotherapy Confederation,[10] the most adopted measures being hand washing, the use of protective equipment, and disinfection of materials used.

According to the World Health Organization (WHO)[12] "physiotherapists assess, plan and implement rehabilitative programs that improve or restore human motor functions, maximize movement ability, relieve pain syndromes, and treat or prevent physical challenges associated with injuries, diseases, and other impairments". Thus, physiotherapy services are necessary not only for chronic patients but also in health promotion and disease prevention and, currently, due to the pathological complications promoted by COVID-19, it is essential to provide physiotherapy services in intensive health care units.

Physiotherapists are professionals who are involved in the monitoring of patients with respiratory conditions in acute, subacute, and chronic contexts, either with spontaneous ventilation or in invasive and non-invasive mechanical ventilation.13 Given this current pandemic situation, the Portuguese Association of Physiotherapists, together with its Cardiorespiratory Physiotherapy Interest Group, prepared a position paper with the objective of disseminating the physiotherapist's competences in intensive care, especially in patients infected with COVID -19, and make available, voluntarily, physiotherapists with experience in intensive care to collaborate in this care,14 since the number of physiotherapists working in this area is still reduced and the number of infected individuals with a high number of morbidities increases every single day.

Some preventive measures to prevent transmission of communicable diseases like COVID-19 include: minimize surface contact, use of a respirator (like N95 respirator) instead of facemask during aerosol-generating procedures (non-invasive ventilation, high flow oxygen therapy, intubation/extubation, nebulization, open suctioning of airway secretions, bronchoscopy, induction of sputum, bag and mask ventilation, cardiopulmonary resuscitation, others), hand hygiene and personal protective equipment, respecting the proper sequence to dress (HH—gown—mask—goggles—gloves) and undress (gloves—goggles—gown—mask—HH), disposing of disposable materials when their function is complete, reusable/non-disposable materials must be carefully disinfected according to the manufacturer's recommendations, promote surface cleaning and disinfection frequently.[15,16] However, Ng et al.[17] suggest that the use of surgical masks, hand hygiene, and other standard procedures would be enough to protect health professionals from infection risk, indicating that N95 masks are not superior to surgical masks to prevent influenza infection; though the use of the N95 mask or equivalent equipment while performing an aerosol generation procedure is recommended.

Health professions preventing and controlling Coronavirus Disease 2019 are prone to skin and mucous membrane injury, which may cause acute and chronic dermatitis, secondary infection, and aggravation of underlying skin diseases. This is a consensus of Chinese experts on protective measures and advice on hand- cleaning- and medical-glove-related hand protection, mask- and goggles-related face protection, UV-related protection, eye protection, nasal and oral mucosa protection, outer ear, and hair protection. It is necessary to strictly follow standards of protective equipment and specifications for sterilizing and cleaning. Insufficient and excessive protection will have adverse effects on the skin and mucous membrane barrier. At the same time, using moisturizing products is highly recommended to achieve better protection.

The use of protective equipment (mask, goggles, gloves) can lead to skin and mucous membrane injury in health professionals. Thus, the use of moisturizing creams is essential to prevent these injuries. Another preventive method can be the use of an adhesive bandage on the skin.[15,18]

All the data for this study were collected between March 26th and April 3rd of 2020. The General Directorate of Health of Portugal published a list of guidelines with measures to all the physiotherapists that work in rehabilitation units and provide respiratory care at home. [19] Some of those measures are already in place, as it can be observed in the answers given by the professionals that are still delivering their services.

Given that, it becomes necessary to create online courses to promote skill improvement for physiotherapists who work in all areas to prevent the risk of infection. It is believed that a training program, for 1 to 2 weeks, on COVID-19 and public health surveillance could provide essential skills and knowledge, particularly if associated with continuous training and supervision.[20]

It is necessary to emphasize that these professionals can work for long hours under significant pressure, with resources often inadequate, while accepting the dangers inherent to close interaction with sick patients.[21] Besides that, most health professionals working in isolation units and hospitals do not receive any training for providing mental health care, which includes fear and anxiety.[22]

## CONCLUSIONS

This study showed that most physiotherapists had to interrupt their practice because of COVID-19. However, since they cannot follow up with their patients' treatment in person, most physiotherapists adapted to monitor their patients from a distance using digital tools that are new to their professional activity. This was a necessary strategic measure to prevent the further spread of this pandemic.

### Conflict of interest

None

### Contribution of each author

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## SUMMARY

INTRODUÇÃO: *Os serviços de fisioterapia são necessários para o tratamento de pacientes hospitalizados com COVID-19 e também para pacientes crônicos. Assim, os fisioterapeutas apresentam um maior risco de exposição ao coronavírus. O objetivo deste estudo foi determinar o número de fisioterapeutas que interromperam seus serviços devido à pandemia do COVID-19 e verificar os procedimentos adotados pelos fisioterapeutas que continuam trabalhando.*

METODOLOGIA: *A amostra foi constituída por 619 fisioterapeutas, que trabalhavam em Portugal, sendo 154 (24,9%) do sexo masculino e 465 (75,1%) do sexo feminino, com idades compreendidas entre os 22 e 67 anos (34,47 ± 8,70 anos). O instrumento de medida utilizado consistiu num questionário* online, *tendo sido aplicado em finais de março de 2020, através de contatos e redes sociais.*

RESULTADOS: *453 (73.2%) fisioterapeutas interromperam as suas atividades laborais de forma presencial por causa da pandemia e 166 (26.8%) continuam a trabalhar presencialmente. As principais medidas adotadas pelos fisioterapeutas que continuam a trabalhar presencialmente incluíram: lavagem das mãos (21.5%), uso de máscaras (20.3%), desinfecção do material (19.3%) e uso de luvas (19.3%). Dos fisioterapeutas que não estão a trabalhar presencialmente (n=453), 267 (58.9%) continuam a acompanhar os seus pacientes à distância e 186 (41.1%) não estão a acompanhar os pacientes. As principais medidas utilizadas pelos fisioterapeutas para acompanhar os seus pacientes à distância incluíram: prescrição do tratamento por escrito (38%), realização de vídeos explicativos (26.7%) e tratamento por videoconferência de forma síncrona (23.5%).*

CONCLUSÕES: *Os dados do presente estudo revelaram que a maioria dos fisioterapeutas interromperam as suas práticas presenciais em virtude da pandemia COVID-19, no entanto, apesar de não estarem a acompanhar os seus pacientes pessoalmente, a maioria deles elaborou ferramentas para monitorar seus pacientes à distância.*

PALAVRAS-CHAVES: *COVID-19, fisioterapeutas, medidas adotadas, pandemia, profissionais de saúde*

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ORIGINAL ARTICLE

# Coronavirus disease 2019 (COVID-19) in Brasil: information to physical therapists

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**SUMMARY**

*The emergence of the Coronavirus Disease 2019 (COVID-19) pandemic shows a rapid increase in cases and deaths. The World Health Organization (WHO) has shown that more than 200.000 confirmed cases have been identified in more than 166 countries/territories. Public health authorities in Brasil have reported 532 confirmed cases by March 19. Approximately 5% of the patients will require intensive care unit treatment with oxygen therapy and mechanical ventilation. Limited data are available about rehabilitation protocols for severe illness and intensive care treatment of COVID-19 increase. Thus, we aim to show current information about COVID-19, describing symptoms and the respiratory management for critical patients and preventive care. Physical therapists and all health care professionals need to recognize the challenges they will face in the coming months.*

KEYWORDS: *Coronavirus infections. Respiratory distress syndrome, adult. Respiratory therapy.*

## INTRODUCTION

The coronavirus (COVID-19 or 2019-CoV) infection became a critical illness and is considered a pandemic infectious disease with high transmissibility[1]. In December 2019, a series of pneumonia cases of unknown cause emerged in Wuhan. In less than 4 months, several countries, including Brasil, identified the pathogen of COVID-19[2]. Confirmed cases in Brasil are increasing and the COVID-19 outbreak challenges both healthcare personnel and the medical supply system. Physical therapists are directly involved in the treatment of suspect and confirmed cases with an important role in Intensive Care Units (ICU). At the moment, no specific consensus or guidelines have been published regarding ICU protocols, and only a few articles reporting several cases from China and other Asian countries have supported the management of infected patients with respiratory disorders.

Thus, we have described key information according to clinical features pandemic infectious disease for physical therapists describing the main symptoms and respiratory treatments for patients with COVID-19.

## CLINICAL CHARACTERISTICS

To differentiate COVID-19 from other circulating respiratory viruses is extremely important to epidemiologic studies and clinical management[3]. Confirmed cases of COVID-19 result in clinical priority and lead to the implementation of efficient infection control practices. Initial data estimate that 50–70% of cases

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are asymptomatic at the time of diagnosis[4]. It has been estimated that 86% of all infections were undocumented and these individuals may have infected up to 79% of documented cases[4]. The current estimated mean incubation period is 6.4 days, ranging from 2.1 days to 11.1 days and even asymptomatic patients can transmit COVID-19[5].

The most common symptoms at illness onset are fever and cough[5]. Other common symptoms include shortness of breath (dyspnea), myalgia or fatigue, sputum production, chest tightness, headache, hemoptysis, and diarrhea[5]. Disease onset may result in pneumonia, progressive respiratory failure due to alveolar damage, hyperthermia, decreased lymphocytes and white blood cells count, and new pulmonary infiltrates[6]. Clinical symptoms of COVID-19 according to disease severity are shown in figure 1. Studies performed in China with severe cases of COVID-19 suggest that the mean number of days from the appearance of the first symptom to death was 14 days[5].

## GENERAL CARE FOR COVID-19 INFECTION

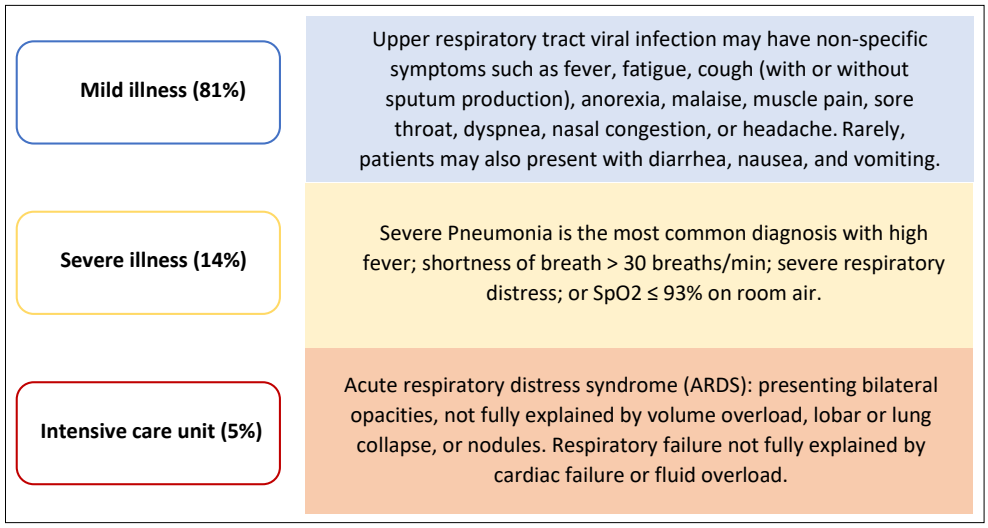
Most people with COVID-19 develop mild or uncomplicated illness (81%); however, 14% develop severe symptoms that require hospitalization and oxygen support, and 5% will require ICU treatment (figure 1)[5].

Patients with mild disease may not require hospital interventions unless there is concern about rapid deterioration; however, home isolation is necessary to avoid transmission[2]. All health professionals, including respiratory therapists, must consider the suitability for home care. Moreover, the patient and other household members must have access to appropriate minimum personal protective equipment (gloves and facemasks) and be capable of adhering to recommended precautions (respiratory hygiene and cough etiquette, as well as adequate hand hygiene)[5]. Such patients must also be advised about the signs and symptoms of disease complications.

High Flow Nasal Oxygen (HFNO) and Non-Invasive Ventilation (NIV) are part of the clinical practice of respiratory therapists and may be used in case of limited access to mechanical ventilation and in selected patients prior to the development of severe hypoxemic respiratory failure[3]. It is important to highlight that systems with good interface fitting do not create widespread dispersion of exhaled air, and their use can be considered at low risk of airborne transmission[3]. Although there is no consensus regarding the use of NIV in patients with COVID-19, limited data suggest a high failure rate in other viral infections such as MERS-CoV[3]. Evidence-based guidelines on HFNO do not exist, and reports on HFNO in patients infected with other coronaviruses are limited[7]. Respiratory therapists must also consider, along with other health professionals, that all hospitalized patients in use of HFNO or NIV need regular monitoring of vital signs and clinical deterioration as supportive care interventions may be necessary[7].

Until now, no consensus or guidelines have been previously published about ICU protocols for mechanical ventilation in patients with COVID-19. Some recommendations are frequently based on the clinical characteristics presented by patients of other

**FIGURE 1.** CLINICAL SYMPTOMS ASSOCIATED WITH COVID-19.[5]



countries who have been exposed to the virus for a longer time[5]. Approximately 5% will require intensive care unit treatment, and respiratory failure is the main reason for early endotracheal intubation[5]. The aim of invasive ventilation support is to reverse the severe hypoxemia installed[8]. Lung protection ventilation is the main strategy, with volume-controlled or pressure support ventilation models, tidal volume around 4-8 ml/Kg of Predicted Body Weight (PBW) and lower inspiratory pressures (plateau pressure < 30 cmH2O), aiming at a driving pressure of 10 cm H2O, or the lowest possible[8]. It is possible that targeting driving pressure may improve safety strategies[9].

This recommendation is very similar to Acute Respiratory Distress Syndrome (ARDS), (PaO2/FiO2 ≤ 100 mmHg with PEEP ≥ 10 cmH2O, or non-ventilated) which recommends supplemental oxygen therapy delivered via a face mask with reservoir bag (flow rates of 10–15 L/min) immediately to patients with respiratory distress, hypoxemia or shock, targeting SpO2 > 94%. However, some cases have presented little or no changes in lung compliance[5]. Prone positioning has proved to be a primary strategy, and it is recommended for 12–16 hours per day[10]. Prone position significantly reduces mortality in patients with moderate to severe ARDS when used early and for over 16 hours per day in patients receiving protective lung ventilation[10]. Additionally, extracorporeal membrane oxygenation may be considered, although there are no reports of its benefits[3].

## PREVENTIVE CARE, INTENSIVE SURVEILLANCE AND EPIDEMIOLOGICAL INVESTIGATIONS

Physical therapists have been inserted in the Primary Care of the Brazilian Unified Health System aiming to expand the roles of professionals from Primary Care. Among the strategies that physical therapists develop in this context, preventive and educational actions stand out[11]. It is important to highlight the role of physical therapists as agents of prevention and health promotion who can act directly in helping to control virus dispersion in our country. Physical therapists' performance through health education services with the community, risk factors surveillance, and matrix support favor the containment and early treatment of possible cases in the community[11].

With regard to health education, physical therapists who have direct contact with the population in spaces such as hospital waiting rooms, health clinics, schools, and other community environments can provide information and guidance on ways to prevent the virus spread, in addition to preparing materials such as informative folders, videos, booklets, and posters to expand the dissemination of information[11]. Therefore, the relevance of physical therapists' work in the Brazilian Unified Health System is highlighted to fight COVID-19, especially in terms of population awareness, surveillance of risk factors, and involvement in collective planning strategies to protect the health of the Brazilian population.

## CONCLUSION

Possibly, Brasil will show an epidemiological trend similar to that of European and Asian countries. All health professionals must be up-to-date and committed to the prevention and treatment of patients with COVID-19. This is an ongoing disease, and little is known about the standard treatment parameters, but it is possible to treat and rehabilitate patients with severe symptoms from COVID-19.

### Authors' contributions

RP: study design, wrote the manuscript, and revised final version.

ESF: wrote the manuscript.

INDFL: wrote the manuscript.

LG: wrote the manuscript.

### Declarations of interest

None.

## RESUMO

*O surgimento da pandemia do Coronavírus 2019 (COVID-19) tem demonstrado rápido aumento dos casos e das mortes. A Organização Mundial da Saúde (OMS) apontou que mais de 200.000 casos confirmados foram identificados em mais de 166 países/territórios. As autoridades de saúde pública no Brasil relataram 532 casos confirmados até 19 de março. Aproximadamente 5% dos pacientes necessitarão de tratamento em unidade de terapia intensiva com oxigenoterapia e ventilação mecânica. Temos disponíveis dados limitados sobre protocolos de reabilitação para doenças graves e tratamento em unidade de terapia intensiva de pacientes com COVID-19. Assim, nosso objetivo é mostrar informações atuais sobre o COVID-19, descrevendo sintomas e controle respiratório de pacientes críticos e cuidados preventivos. Fisioterapeutas e todos os profissionais de saúde precisam reconhecer os desafios que enfrentaremos nos próximos meses.*


PALAVRAS CHAVE: *Infecções por Coronavirus. Síndrome do desconforto respiratório do adulto. Terapia respiratória.*

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ORIGINAL ARTICLE

# Study of angiopoietin and plasminogen genes in hereditary angioedema

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## SUMMARY

OBJECTIVE: *To investigate the presence of the Angiopoietin 1 (ANGPT1) and Plasminogen (PLG) mutations in patients with Hereditary Angioedema (HAE) and normal C1 esterase inhibitor (C1-INH) levels, who do not harbor the F12 gene mutation.*

METHODS: *Patients clinically diagnosed with HAE but without C1-INH deficiency or dysfunction and F12 gene mutation were evaluated. DNA extraction, quantification, and dilution were performed at a concentration of 100 ng/µL, followed by a DNA amplification (PCR) for molecular evaluation of exon 2 of the ANGPT1 gene and exon 9 of the PLG gene for identification of mutations c.807G>T / p.A119S and c.988A>G / p.K330E, respectively. The PCR product was evaluated in 1% agarose gel electrophoresis. Sequencing was performed using the Sanger method. The electropherograms were analyzed using the FASTA® program.*

RESULTS: *DNA samples from 15 women were sequenced. Their ages ranged from 10 to 60 years and the normal C1 esterase and C4 inhibitor serum levels ranged from 22 to 39 mg/dL and from 10 to 40 mg/dL, respectively. No mutations were detected in the analyzed exons of ANGPT1 and PLG. However, a single-nucleotide polymorphism (SNP) was detected in two homozygotic and five heterozygotic patients.*

CONCLUSION: *Further studies are needed to evaluate these SNPs and scrutinize their potential for use as molecular markers of HAE and as novel therapeutic targets.*

KEYWORDS: *Bradykinin, Mutation, Angiopoietin-1, Plasminogen.*

## INTRODUCTION

Hereditary Angioedema (HAE) is a rare and severe genetic disease of the kallikrein-kinin system caused by a deficiency of the C1-esterase inhibitor (C1-INH), which is inherited in an autosomal dominant manner. It affects approximately 1 in 60,000 inhabitants (ranging from 1:10,000 to 1:160,000) belonging to different

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ethnic groups. Although it is an autosomal dominant disease, it is detected more frequently and severely in women.[1-5]

Family history with similar clinical manifestations reinforces the HAE diagnosis. About 75-80% of HAE cases occur in the same family while 20-25% of cases are due to novel spontaneous mutations.[1-3]

HAE can be classified into three phenotypes: (1) quantitative C1-INH deficiency due to mutations, located throughout the *SERPING1* gene, that affect the structure of the protein and impair its secretion; (2) C1-INH dysfunction due to a mutation in exon 8 of the *SERPING1 gene* that results in the secretion of a non-functional protein; and (3) normal C1-INH that may be associated with mutations in the *F12*, *ANGPT1*, *PLG,* and Kininogen 1 (*KNG1*) genes, mainly found in female patients with normal C1-INH protein levels and activity.[1-14]

A variant of the *ANGPT1* gene was reported to interfere with the interaction between the angiopoietin protein and its natural receptor, endothelial tunica of the kinase cell– (TIE2), in endothelial cells leading to increased vascular permeability and edema. [12,15,16]

A mutation in the *PLG* gene has also been reported to increase fibrinolysis, which in turn causes plasmin formation and increased levels of bradykinin, leading to edema (*PLG*). [11,13,14]

The presence of genetic alterations in different genes emphasizes the importance of molecular genetic analysis in Brazilian patients to expand our knowledge on HAE and identify new strategies for the treatment of this disease.[11,12]

The objective of this study was to investigate the presence of mutations in the *ANGPT1* and *PLG genes* of HAE patients without C1-INH deficiency or dysfunction and *F12* gene mutations.

## METHODS

A 5 mL blood sample was collected from each patient via venous puncture, followed by genomic DNA extraction using the Wizard Genomic DNA Purification® kit (Promega). DNA was quantified in a spectrophotometer and, when necessary, diluted to a concentration of 100 ng/µL for sequencing. After extraction, the DNA was used to amplify exon 2 of the *ANGPT1* gene and exon 9 of the *PLG* gene by polymerase chain reaction (PCR). The PCR products were resolved by 1% agarose gel electrophoresis and subjected to Sanger sequencing for detecting the mutations c.807 G>T / p.A119S and c.988 A>G / p.K330E in exon 2 of the *ANGPT1* gene and exon 9 of the *PLG* gene, respectively.

The forward primer of the *ANGPT1* gene was 5'GTTGACAACTGGATTCCTGTG3', and that of the *PLG* was 5'CTTAGTTTAGTACTGGAACGCAGG3', and reverse primer of the *ANGPT1* gene was 5'CGCATAGCATGTCAGGCAGTC3', and that of the *PLG* was 5'CAGGCTTTCTGACCACAATAGC3'. The sequencing reaction was performed using the Big Dye Terminator® v.3.1 kit (Thermo Fischer Scientific, Waltham, MA, USA).

Samples of purified sequencing reaction products were heated at 80°C for 15 minutes to inactivate the ExoSAP enzyme and subsequently, the products were precipitated.

After the precipitation of the DNA in the plates, it was resuspended in a specific buffer and DNA sequencing was performed by the Sanger method.

The electropherograms were analyzed by FASTA®, a software package for the alignment of DNA and protein sequences.[17]

## STATISTICS

The data were inserted in an Excel® spreadsheet. The allele frequencies were combined on alleles I and II. Then the frequencies of the mutations in both alleles were added and compared with the relative frequencies reported in the specific literature using the Chi-square test with a result of $p < 0.05$ was not considered as significant.

## RESULTS

A total of 69 patients with HAE, including both genders, were treated at the Allergy and Immunology Clinic of the Hospital de Clínicas Complex, Federal University of Paraná - Curitiba (CHC-UFPR). Of these, 27 patients diagnosed with normal C1-INH HAE were evaluated; as all of them were women, this study focused on female patients.

Patients with C1-INH deficiency or dysfunction, patients with mutations involving the *SERPIN*G1 gene and other forms of non-hereditary angioedema were also excluded.

The clinical features were recorded using a questionnaire form. The 27 patients were evaluated for *F12 gene* mutations and 12 of them were excluded

**TABLE 1.** CHARACTERISTICS OF PATIENTS STUDIED

| FAMILY | PATIENT | RELATIONSHIP | GENDER | BIRTHDATE | AGE SYMPTONS STARTED | FAMILY HISTORY | TREATMENT |
|---|---|---|---|---|---|---|---|
| 1 | HAE001<br>HAE003 | SISTER (HAE003)<br>SISTER (HAE001) | F<br>F | 06/19/1979<br>12/27/1961 | 36 YEARS OLD<br>52 YEARS OLD | YES<br>YES | NO<br>NO |
| 2 | HAE005 | XXXXX | F | 11/16/1981 | 18 YEARS OLD | YES | NO |
| 3 | HAE006 | XXXXX | F | 07/13/2009 | 6 YEARS OLD | YES | NO |
| 4 | HAE007 | XXXXX | F | 02/12/1979 | 15 YEARS OLD | YES | NO |
| 5 | HAE008 | XXXXX | F | 02/02/1987 | 17 YEARS OLD | YES | NO |
| 6 | HAE009 | XXXXX | F | 06/22/1986 | 25 YEARS OLD | YES | NO |
| 7 | HAE011 | XXXXX | F | 11/12/1982 | 20 YEARS OLD | YES | NO |
| 8 | HAE012 | XXXXX | F | 03/24/1980 | 16 YEARS OLD | YES | NO |
| 9 | HAE013 | XXXXX | F | 01/10/1981 | 04 YEARS OLD | YES | NO |
| 10 | HAE014 | XXXXX | F | 06/22/1969 | 30 YEARS OLD | YES | NO |
| 11 | HAE015<br>HAE016 | SISTER (HAE016)<br>SISTER (HAE015) | F<br>F | 08/12/1983<br>05/03/1988 | 15 YEARS OLD<br>05 YEARS OLD | YES<br>YES | NO<br>NO |
| 12 | HAE019 | XXXXX | F | 11/13/1975 | 39 YEARS OLD | YES | NO |
| 13 | HAE021 | XXXXX | F | 10/08/1985 | 22 YEARS OLD | YES | NO |

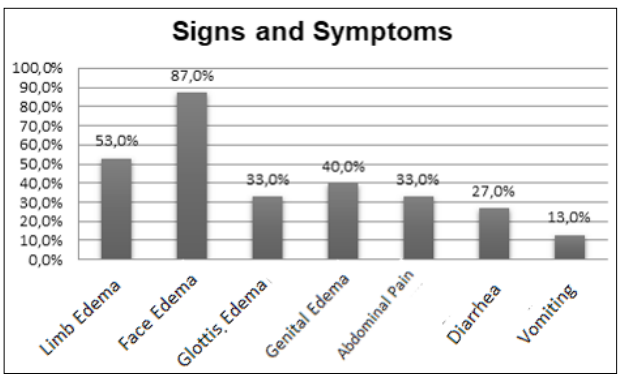
from the study because they presented positive results. Therefore, 15 patients without *F12* gene mutations were examined for the presence of mutations in exon 9 of the *ANGPT1 gene* and exon 2 of the *PLG gene*.

Biochemical tests revealed normal C1-INH and C4 serum levels ranging from 22 to 39 mg/dL and 10 to 40 mg/dL, respectively in the patients with HAE, who were aged between 10 and 60 years, and had 1 to 4 flares lasting for 3 days on an average per month. All patients reported a family history of angioedema (TABLE 1).

The patients reported flare symptoms in during emotional stress and menstrual cycle, leading to emotional problems and depression in some cases as well as financial burden. Chart 1 shows the most common signs and symptoms of HAE.

DNA sequence analysis did not detect the mutation c.807G>T / p.Ala119Ser in the *ANGPT1* gene and the mutation c.988 A>G / p. lys330Glu in the *PLG* gene.

**GRAPH 1.** MOST FREQUENT SIGNS AND SYMPTOMS



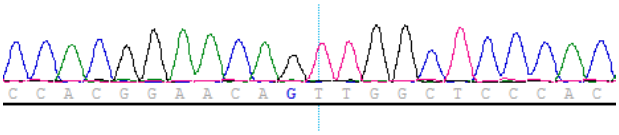

However, a single-nucleotide polymorphism (SNP) in the *PLG* gene was identified.

The electropherograms were evaluated by FASTA[17] and are shown below:

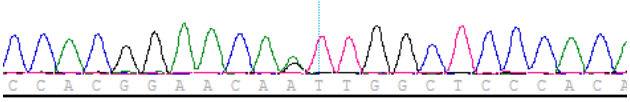
NORMAL SEQUENCE:
CAATCCTGACGGAAAAGGGCCATGGTG

MUTATED SEQUENCE:
GCAATCCTGACGGARAAAGCCATGGTG

HOMOZYGOUS SEQUENCE:
CCACGGAACAGTTGGCTCCCAC




HETEROZYGOUS SEQUENCE
CCACGGAACAA/GTTGGCTCCCAC




SNP silent c.1083A>G p.Gln 361= (CAA CAG→)

## DISCUSSION

Bork and Binkley have described a type of HAE with normal C1 inhibitor, in which the functional activity of C1-INH and C4 levels remained normal, suggesting that HAE diagnosis would be more accurate through genetic analysis.[18,19]

HAE with normal C1-INH levels is the rarest among

the HAE phenotypes described in literature, occurring in about 30% of patients.[11] *F12* gene mutation was present in 44% of the 27 patients included in this study, although this prevalence is higher than that cited in other studies and may be related to ethnic differences among the populations studied.

Initially, the symptoms of HAEs with normal C1-INH were shown to affect predominantly women and to be associated with estrogen usage; however, because it is an autosomal dominant disease, men are also affected but are often asymptomatic.[9] The 15 patients who participated in this study reported clinical features that corroborate the literature such as limb, face and genital edema, abdominal pain, diarrhea, and vomiting. Of these, 87% reported face edema as the most common symptom of HAE with normal C1-INH. [1,3,9,11]

Of the two mutations that were evaluated in the 15 patients, the c.807G>T/ p.Ala119Ser in exon 2 of the *ANGPT1* gene has been described in an Italian family;[12] however, in this study, this mutation has been detected in a Brazilian family of non-Italian origin.[16] The c.988 A>G / p. lys330Glu mutation in exon 9 of the *PLG* gene has been described in 13 families in Europe,[11] including 3 in France and 2 families in Japan. [14,15] Considering the colonization and the population brazilian composition of 47.5% of European descendants according to IBGE[23], this research in Brazilian patients is justified.

The mutations described were not identified in the patients. However, a silent homozygous SNP c.1083A>G / p. Gln 361= (CAA CAG→) in the *PLG* gene was detected in two unrelated patients, where the presence of base G occurred on both alleles. Furthermore, five patients were heterozygous for this SNP . This SNP is identified as silent since it does not alter the protein sequence and has no clear effect on the gene function or the phenotype of the individual carrying the mutation. [20-22]

According to the literature,[24] the incidence of the SNP rs13231 flanking the *PLG* gene mutation c.1083A>G p.Gln 361= CAA CAG→ is 0.78% and 0.21 (or 21%) for alleles A and G, respectively. According to the ABRAOM[25] database, the incidence of this SNP in the Brazilian population was reported for the A allele 0.74% and for the G allele 0.26%.. In the sample studied, the frequency of the SNP was 30% (9/30), higher than that described for Brazilian and European populations; however, this is not a statistically significant difference (p>0.05).

All patients who participated in the study were clinically evaluated and diagnosed with Hereditary Angioedema of unknown cause (HAE-U), according to the criteria established by the Brazilian Guidelines for the diagnosis and treatment of hereditary angioedema.[1]

These Brazilian Guidelines were published in 2017 and therefore, cite only the *F12* gene mutations. After that, three more mutations have been identified as related to HAE with normal C1-inhibitor, including the two mutations analyzed in this study.[9,10]

This study has some limitations, particularly the small sample size. Nevertheless, the incidence of HAE in the Brazilian population is 1/160,000 and of these, only 30% have HAE with normal C1-INH.[1-3]

## CONCLUSION

No mutations were detected in the evaluated exons in the 15 patients studied; however, 7 patients had a silent SNP, c.1083A>G / p.Gln 361= (CAA CAG→).

Further studies on SNPs are needed to clarify whether they can be used as molecular markers of HAE and as therapeutic targets for new treatments.


## RESUMO

OBJETIVO: *Investigar a presença das mutações no gene Angiopoietina (ANGPT1) e gene Plasminogênio (PLG) em pacientes com Angioedema Hereditário (AEH) com inibidor C1 esterase (C1-INH) normal e negativos para mutação do gene F12.*

MÉTODOS: *Foram avaliados pacientes com diagnóstico clínico de AEH sem deficiência ou disfunção de C1-INH e negativos para mutação do gene F12. Realizou-se extração, quantificação e diluição do DNA a uma concentração de 100 ng/uL, em seguida amplificação do DNA (PCR) para avaliação molecular do exon 2 do gene ANGPT1 e do exon 9 do gene PLG para identificação das mutações c.807G>T.p.A119S e c.988A>G p.K330E, respectivamente. O produto da PCR foi avaliado em eletroforese em gel de agarose 1%. Foi realizado o sequenciamento pelo método de Sanger. As análises dos eletroferogramas foram realizadas pelo programa FASTA®.*

RESULTADOS: *Foram sequenciadas amostras de 15 mulheres, idade entre 10 e 60 anos, com níveis séricos de inibidor de C1 esterase e C4 normais variando de 22 a 39mg/dL e 10 a 40mg/dL, respectivamente. Não foram identificadas mutações nos éxons analisados dos genes ANGPT1 e PLG. Entretanto no gene PLG foram encontrados polimorfismo de nucleotídeo único (SNP), em duas pacientes homozigotas e cinco heterozigotas.*

CONCLUSÃO: *Mais estudos sobre SNP são necessários para esclarecer estes achados pois eles podem ser utilizados como marcadores moleculares do AEH e alvo para novos tratamentos.*

PALAVRA CHAVE: *Bradicinina, Mutação, Angiopoietina-1, Plasminogênio.*

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REVIEW ARTICLE

# Retro-odontoid pseudotumor: a poorly recognized alteration of the craniocervical junction

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## SUMMARY

INTRODUCTION: *Retro-odontoid pseudotumor (ROP) is a rare disease that affects the atlantoaxial joint and, in general, is associated with local biomechanical alterations that may or may not cause instability.*

METHODS: *Descriptive study of the literature available in databases MEDLINE/PubMed, LILACS, and Scopus. The research was conducted in April 2019.*

DISCUSSION: *ROP is, possibly, a syndromic designation that encompasses a significant variety of diseases of the atlantoaxial joint. There are different pathophysiological mechanisms implicated in its genesis. The patients, almost in their entirety, present with severe myelopathy, and most of them are treated surgically, with the posterior decompression being the most commonly used method, with or without arthrodesis. Evolution is usually favorable.*

CONCLUSION: *The ROP is still poorly recognized as a differential diagnosis between the diseases of the cranial-cervical junction. The information available in the literature analyzed was based mainly on the study of reports or case series; therefore, it is insufficient to define conducts with a high level of scientific evidence.*

KEYWORDS: *Odontoid process/pathology. Atlanto-axial joint/pathology. Review.*

## INTRODUCTION

Retro-odontoid pseudotumors (ROP) are an infrequent disorder that involves the atlantoaxial joint. As a result of population aging (with the consequent appearance of degenerative changes in the cervical spine) and the use of imaging examinations on a larger scale - particularly of magnetic resonance -, the number of cases identified has increased[1,2].

When present, expansive retro-odontoid lesions should draw attention to the possibility of coexisting rheumatopathies involving the atlantoaxial joint,

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particularly the subluxation observed in rheumatoid arthritis. Cases of ROP without subluxation or C1-C2 instability are rare[3,4].

Over the past decade, there was an increased understanding of the physiopathology of ROP, thus, patients started to be better grouped in order to determine the most appropriate treatment for each case. However, the data currently available in the literature are not sufficiently uniform to ensure the development of strong evidence. From this analysis, we understand that it is fundamental to have an organized presentation and discussion about the disease, its differential diagnoses, and therapeutic modalities to contribute to the clinical practice, particularly of neurosurgeons, orthopedists, and rheumatologists.

## METHODS

A descriptive study of the literature available in the Medline/PubMed, Lilacs, and Scopus databases. The search was carried out using the terms "retro-odontoid pseudotumor", "retro-odontoid mass", and "cervical *Pannus*". Other variants and expressions found in articles from the search were included in order to sensitize the method. Works that were duplicated and whose content was not within the context studied were excluded. The search was carried out in April 2019.

## DISCUSSION

One of the first descriptions using the therm "pseudotumor" in order to refer to a mass in the craniocervical junction was made by Sze et al.[5] in 1986. This author reported the cases of three patients with expansive lesions of atypical presentation in that area.

However, the lesions involving this segment of cervical spine are classicaly described as *pannus*, in patients with rheumatoid arthritis. By definition, *pannus* is an inflammatory tissue that causes erosion of the subchondral bone and cartilage in the synovial joints. However, similar lesions in individuals without systemic inflammatory diseases has led to the discovery of a pathological entity characterized by the presence of a non-inflammatory mass composed predominantly of fibrocartilaginous tissue. Joint cysts of degenerative nature are described between pseudotumoral lesions in this region[6].

Most studies found in the literature consists of case reports or case series. Thus, it is not possible to properly determine the prevalence and incidence of ROP in the population.

It is known, however, that patients with rheumatoid arthritis comprise the subgroup of higher risk for the disease. They may have their cervical spine affected as a consequence of the disease activity in more than 40% of the cases, and anterior atlantoaxial subluxation is the most common form of involvement[7]. On the other hand, most of these patients do not develop ROP[8]. Thus, the disease is unusual[1,8], especially if not associated with atlantoaxial instability[9].

In addition to inflammatory rheumatopathies, other conditions that may be related include long-term hemodialysis, mucoid degeneration of the transverse ligament of the atlas[10], trauma, *os odontoideum*[11], deposition of crystals, and disc herniation[12].

There is no clear physiopathological mechanism for ROP. In rheumatoid arthritis, the formation of the *pannus* is usually attributed to the release of proteases, which destroys the extracellular matrix of the cartilage, and the proliferation of fibroblast-like cells. It is possible that the genesis of tissue deposition in the retro-odontoid space in ROP - especially in the topography of the cruciate ligament band[13] - holds some similarity to these phenomena.

Classically, the element that triggers the process is chronic instability in the atlantoaxial joint. Goel[9] suggests that the origin of the lesion is related to an instability that begins in the facets and that involves excessive arching of the posterior longitudinal ligament (which predisposes its detachment), with a consequent periosteal reaction and formation of osteophytes.

On the other hand, cases of ROP without demonstrated atlantoaxial instability have been described[3]. A prospective study with 201 rheumatoid arthritis patients found an inverse relationship between the size of the mass and the atlantodental interval (which expresses the integrity of the transverse ligament and, therefore, the stability of the joint)[8].

One theory suggests that the change in the amplitude of movement between the occipital condyles and C3 interferes in the process. Chikuda et al.[1] argued that the biomechanical change that occurs, for example, in the calcification of the anterior and posterior longitudinal ligaments and in ankylosis, can determine increased stress on the atlantoaxial complex due to the reduction of movement amplitude below that level. As a consequence, a process of damage and repair is initiated, resulting in the deposition of fibrocartilaginous

material with ligament hypertrophy, involving mainly the transverse ligament. This theory explains the occurrence of ROP on subaxial spondylosis. In this process, the formation of a pseudotumor and the emergence of atlantoaxial instability can be simultaneous or not. Therefore, the hypothesis that patients with an expansive retro-odontoid lesion become symptomatic due to medullary compression before there are radiological signs of residual subluxation in C1-C2 is plausible.

Acknowledging the existence of distinct physiopathologies, Tanaka et al.[14] classified ROP into three types, differentiating them primarily by etiology and findings on magnetic resonance imaging, and type 1 (secondary to atlantoaxial subluxation) is the most prevalent. Table 1 summarizes the author's classification, whose analysis allows us to discuss the theoretical limitations in its construction. In it, for example, are not included cases such as crowned dens syndrome, which cannot be objectively categorized using the basic mechanisms singled out by Tanaka et al.[14].

The clinical presentation is variable, and the most common form is compressive cervical myelopathy, present in up to 100% of the cases of a series[15]. In the patients with ROP without atlantoaxial instability evaluated in a systematic review, 95% evolved with progressive myelopathy[16]. There can also be mechanical neck pain, bulbar symptoms, and radiculopathy.

Among the differential diagnoses are neoplastic lesions and crowned dens syndrome. The latter is characterized by the presence of a significant inflammatory reaction (usually with increased acute-phase proteins), followed by the calcification of the ligaments around the odontoid process thanks to the deposition of hydroxyapatite or calcium pyrophosphate dihydrate. It usually responds to treatment with anti-inflammatory steroidal and non-steroidal drugs[17]. Some authors include crowned dens syndrome as one of the presentations of ROP[16].

Clinical suspicion must be raised primarily for patients with inflammatory reumatopathy and signs of involvement of the cervical spine. Nevertheless, it should also be considered as a differential diagnosis for cervical myelopathy among the elderly.

The diagnosis is aided by imaging methods. Magnetic resonance imaging (MRI) is the main examination method because it provides more detailed information about the lesion (the radiological characteristics of ROP in MRI are described in Table 1 and shown in Figure 1), as well as the degree of involvement of adjacent structures, in particular, the spinal cord.

Computed tomography can contribute to a in-depth study of osseous components and is very useful for identifying calcifications in crowned dens syndrome.

Dynamic radiographs of the cervical spine are relevant because they determine the presence or absence of atlantoaxial instability through measures such as the atlantodental interval (ADI) and changes in the range of motion.

In cases in which there is still doubt as to the nature of the retro-odontoid lesion, a biopsy can be carried out to conduct an anatomopathological study. Upon analysis, ROP is composed of predominantly necrotic degenerated fibrocartilaginous tissue[18], which may contain a focal proliferation of blood vessels[4].

Regarding treatment, in general, the surgical approach is used, consisting of the direct excision of the lesion or spinal cord decompression with or without arthrodesis[19]. Direct resection can be done via the transoral route or by posterior laminectomy (epidural or transdural).

Based on the pathophysiological aspects of ROP, it has been established that treatment with decompression and fixation (C1-C2 or occipital-cervical) is associated with better clinical and radiological evolution,

**TABLE 1.** CLASSIFICATION OF RETRO-ODONTOID PSEUDOTUMOR ACCORDING TO TANAKA

| | Type 1 | Type 2 | Type 3 |
|---|---|---|---|
| Incidence | Frequent* | Rare | Rare |
| Etiology | Atlantoaxial subluxation | Spondylosis<br>Ankylosis<br>OALL | Disc herniation |
| Finding in MRI | T1: hypo- or isointense<br>T2: heterogeneous (hyper- and hypointense areas) | Same as in type 1 | T1: hypo- or isointense<br>T2: Hypointense<br>Herniated C2-C3 disc, contiguous with retro-odontoid space |

OALL: ossification of the anterior longitudinal ligament ; MRI: magnetic resonance imaging. *Among the cases diagnosed. Adapted from "Tanaka S, Nakada M, Hayashi Y, Mohri M, Uchiyama N, Hamada J. Retro-odontoid pseudotumor without atlantoaxial subluxation. J Clin Neurosci. 2010 May;17(5):651".

particularly in cases where there is already documented pre-operative atlantoaxial instability. Some authors advocate simple decompression, without arthrodesis, for treating patients with ROP without atlantoaxial subluxation.

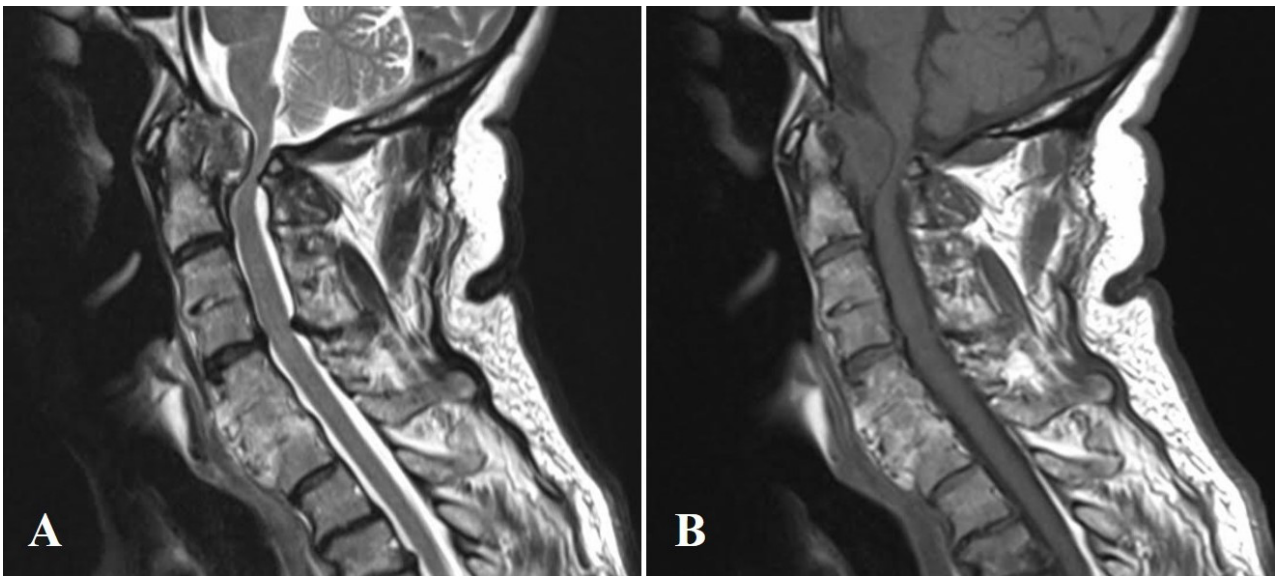
In our search, we found no well-controlled randomized clinical trials evaluating the effectiveness of one technique over the other. Kobayashi et al.[20] compared, in a series of cases, two groups of patients treated by the posterior route (with and without fusion), and no statistical difference was found between them in relation to functional recovery measured by the JOA (Japanese Orthopaedic Association) score[21]. On the other hand, the groups were statistically different regarding the regression of the lesion on magnetic resonance imaging; it was greater among patients treated with arthrodesis. Other three series of cases comparing fusion and no fusion did not have the same results[1,22,23].

A systematic review performed by Robles & Mundis[16] summarized a strategy for defining the treatment method for these cases from their physiopathological mechanism, establishing surgery (with or without stabilization) as the standard treatment. However, oligosymptomatic cases and those without focal neurological deficits were not discussed. Special attention should be paid to the fact that about one-third of the patients previously described presented subaxial spondylosis[14]. Based on this, the reduction of excessive mechanical demand and of the range of motion of the atlantoaxial joint may contribute, at least partially, to the local progression of ROP. Thus, and taking into account that elderly patients have higher surgical risk, in patients with no documented instability and milder clinical presentations, without signs of compressive myelopathy, a cervical collar can be used. There are reports of the use of this strategy even for patients with atlantoaxial instability[24], with a consequent reduction of ROP observed during follow-up by imaging exams. It is important to emphasize that the conservative approach needs to be followed-up periodically and re-discussed in case of changes in the course of the disease.

## CONCLUSION

ROP is a rare disease usually associated with atlantoaxial subluxation, but its pathophysiological mechanisms are not yet fully understood. Its diagnosis is based on clinical, epidemiological, and imaging exams. In general, the treatment is surgical, which is the choice when there is C1-C2 instability. Currently, there is no evidence that the surgical treatment for ROP cases without instability in oligosymptomatic patients presents a greater benefit than the clinical follow-up. Well-controlled prospective, randomized studies can provide new data and conclusions in this regard, in order to guide the best approach for the management of these patients.

**FIGURE 1.** MAGNETIC RESONANCE SAGITTAL SECTIONS OF THE CERVICAL SPINE SHOWING EXPANSIVE LESION LOCATED POSTERIOR TO THE ODONTOID PROCESS, CHARACTERIZED BY THE PRESENCE OF HETEROGENEOUS SIGNAL IN T2 WEIGHTED IMAGE (A) AND ISO/ HYPOSIGNAL IN T1 (B). IN THIS CASE, SUBAXIAL SPONDYLOSIS IS NOTED, PREDOMINANTLY AFFECTING THE C5-C6-C7 SEGMENT, A FINDING THAT IS OBSERVED IN THE TANAKA TYPE 2 ROP. SOURCE: PERSONAL COLLECTION.



## Author's contributions

1. Conception and design of the methodology: Andrew Vinícius de Souza Batista, Guilherme Brasileiro de Aguiar, José Carlos Esteves Veiga. 2. Literature search and selection of articles for review: Andrew Vinícius de Souza Batista, Guilherme Brasileiro de Aguiar, Jefferson Walter Daniel. 3. Analysis and interpretation of the selected articles: Andrew Vinícius de Souza Batista, Guilherme Brasileiro de Aguiar, Jefferson Walter Daniel. 4. Writing of the manuscript and standardization according to the requirements of the periodical: Andrew Vinícius de Souza Batista, Guilherme Brasileiro de Aguiar. 5. Critical review of the text: Jefferson Walter Daniel, José Carlos Esteves Veiga


## RESUMO

INTRODUÇÃO: *O pseudotumor retro-odontoide (PRO) é uma patologia rara que acomete a articulação atlantoaxial e, em geral, está associada a alterações biomecânicas locais que podem ou não causar instabilidade.*

METODOLOGIA: *Estudo descritivo da literatura disponível nas bases de dados Medline/PubMed, Lilacs e Scopus. A pesquisa foi realizada em abril de 2019.*

DISCUSSÃO: *O PRO é, possivelmente, uma designação sindrômica que abrange uma variedade significativa de doenças da articulação atlantoaxial. Existem diferentes mecanismos fisiopatológicos implicados em sua gênese. Os pacientes, quase em sua totalidade, apresentam quadro de mielopatia grave e a maioria deles é tratada cirurgicamente, sendo a descompressão posterior o método mais utilizado, com ou sem artrodese. A evolução costuma ser favorável.*

CONCLUSÃO: *O PRO ainda é pouco reconhecido como diagnóstico diferencial entre as doenças da junção crânio-cervical. As informações disponíveis na literatura analisada foram baseadas principalmente no estudo de relatos ou séries de casos, sendo, portanto, insuficientes para definir condutas com alto nível de evidência científica.*


PALAVRAS-CHAVE: *Processo odontoide/patologia. Articulação atlantoaxial/patologia. Revisão.*

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REVIEW ARTICLE

# Structural Volume of Hippocampus and Alzheimer's Disease

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KEYWORDS: *Hippocampus. Magnetic resonance spectroscopy. Titrimetry. Alzheimer disease.*

## INTRODUCTION

Alzheimer's disease (AD) is a common and important disorder in which hippocampal atrophy is reported. It is the main neurodegenerative disease from aging, affecting about 5.2 million patients in the US with its prevalence expected to triple by the year 2050. While the importance of hippocampal atrophy and Alzheimer's disease are unquestionably related, there is little knowledge on their predictive clinical progression.

Studies on the changes of hippocampal structures attest to changes in neuronal plasticity, myelination, and interneuronal connectivity, being an important disease. In the present scenario, in addition to symptoms suggestive of the disease, there are few quantitative data on macroscopic reference showing how the composition of the structure is affected. Currently, the primary basis of neuroimaging is the temporal medial atrophy score (MTA) or Scheltens Scale (Figure 1)[2], prepared in 1995, which is obtained by visual analysis using MRI and coronal sections of the hippocampus T1 at the level of the anterior bridge, in which scores 0-4 indicate none to significant atrophy of the structure hippocampal and, in patients aged 75 or more, a score above 3 is considered abnormal[3].

There are few studies that directly compare the predictive value of the measurements of the hippocampus and whole brain, most of which have inconsistent results. The majority of them compare hippocampal atrophy rates with measurements of total brain volume and baseline hippocampal volume in the same sample. There is not, to date, a paper documenting the average volume for the human species, a fact that encouraged the early search for determining a true value. Then, it would be possible to correlate and establish it as a development predictor of disease

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based on the hippocampal volume of each individual, compared to the average human and possible margins of anatomical variations of a normal hippocampus.

The importance of the study of the direct hippocampal volume follows the order in which brain regions are affected, according to the pathological and histological progression of Alzheimer's disease. Few studies have established the relationship between macroscopy and the hippocampus in Alzheimer's disease literature[4,5], probably due to technical difficulties involved in this study area and in the absence of an established average volume structure found in humans.

## OBJECTIVES

This study aimed to carry out a systematic review of international specialized literature, addressing the AD characteristics and confirming the existence of standard volume size of the hippocampus structure in humans and, thereby, establish the relationship between volumetry and values below average in healthy individuals who do not present cognitive decline. This would indicate a higher risk of developing Alzheimer's disease, thus determining another risk factor to be explored by science.

## METHODS

The review was based on data found on Medline, PubMed, Scielo, Lilacs, periodicals portal of Higher Education Personnel Improvement Coordination - CAPES and in Google Scholar national and international scientific articles published from 2000 to 2019 using as descriptors: Alzheimer's disease, Hippocampus, Volumetry Hippocampus, Hippocampal Volumetry.

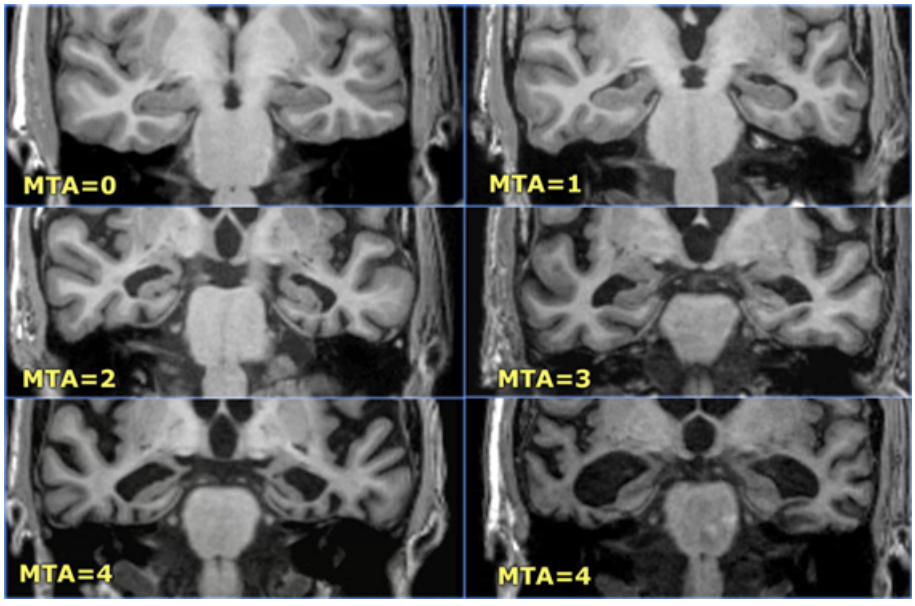
Only English literature was selected. The eligibility criteria were studies that presented data relating to the disease disorders, gross brain lesions detected with MRI in software and segmentation, along with their control groups. We also included studies in which there was only the volumetric measurement of the hippocampus to determine the values that could establish a correlation of smaller hippocampal structure and risk of developing the disease.

## RESULTS

During one year, Arlt et al.[6] investigated the relationship between automated volumetric measurements and performance on neuropsychological tests in 50 patients with mild cognitive impairment (MCI), AD, and control. They examined the relationship between the volume of different brain regions with the results of tests and found a strong correlation between the decrease in hippocampal volume and cognitive disorders.

A meta-analysis from 14 studies[4], including a total of 365 patients with MCI and 382 controls, analyzed the extent of differentiated hippocampal atrophy in AD and MCI and evaluated the pattern of hippocampal volume asymmetry in control groups. The findings showed a bilateral loss of hippocampal volume in CCL

**FIGURE 1**



and a lower extent of atrophy than in AD. When comparing the volume of the left and right hippocampus, a pattern of consistent asymmetry, lower than the average was found, but with different levels of control between studies.

Martini et al.[7] proposed a relationship between the volumes of the hippocampus and genetic influences in 170 healthy volunteers aged 46-77 years and revealed, in a lateralized analysis of the hippocampus, that the right hippocampus is, on average, slightly higher than the left in all age groups, and that hippocampal volume is slightly higher for women than men. In such an analysis, the mean volume was established based solely on the sample obtained.

The study by Yavuz et al.[8] used manually measured volumes as the method of choice to assess the structures of 26 patients with AD, 22 with MCI, and 15 with a healthy cognitive state. The hippocampal volume was normalized by the total brain volume and corrected by the size of the head. This study demonstrated the existence of a correlation between hippocampal atrophy, mild cognitive decline, and AD.

Recently, the Working Group EADC-ADNI on the Harmonized Protocol for the Hippocampus Manual segmentation and for Neuroimaging Initiative Alzheimer's Disease reported an average volume of 3.244 cm3 as normal in the healthy population with a mean age of 24 to 42 years old (40 patients)[9].

Boccardi et al.[10] reported an average volume of the hippocampus (normalized to the intracranial volume) of 2.436 cm 3 in normal aging, education average of 16 years, mean age 76 years; 1.804 cm 3 in patients with AD, education average of 15 years, mean age 76 years.

## DISCUSSION

It is clear that scientific production based on hippocampal macroscopy, although existent for a long time, is still scarce. O'Brien[11] has suggested, since 1995, that MRI of the temporal lobe has a sensitivity and specificity of 85% to 90% in the separation of clinically diagnosed ADs controls matched for age and seriously depressed patients.

Several publications based on the examination of structural neuroimaging typically assess brain structures compared to those of control groups, and there is no evaluation directed to healthy individuals (without mild cognitive impairment), using imaging as an intrinsic risk factor for disease development. It is certain that the temporal lobe volume assessed by RM imaging allows separating patients with mild AD from healthy controls, as occurred in the analysis of the above works. A total of 1070 individuals studied converged on the idea that hippocampal atrophy is already present in the CCL.

## CONCLUSIONS

We may conclude that besides the great importance of clinical and epidemiological studies, any possibility of developing another predictive factor of development in previously healthy individuals is critical. Therefore it is proposed to carry out a prospective study in the general population on their hippocampal volumes to determine the hypothesis that a healthy person presents a smaller structure than the average human volumes and, thus, may have a higher chance of developing the disease in old age.

**TABLE 1**

| Authors | Measurement method and study N | Findings |
|---|---|---|
| Shi et al.[4], 2009 | Meta-analysis of 14 studies, (n = 365 patients with DCL and 382 controls). Variable Measurement Methods | Bilateral loss of hippocampal volume in DCL and that the extent of atrophy is less than in AD. |
| Arlt et al.[6], 2013 | Automatic Volumetry (n = 50, age: 45-95 years) | Strong correlations between decreased hippocampal volume and cognitive changes during one year of follow-up. |
| Martini et al.[7], 2013 | Automatic Volumetry (n = 170) | The right hippocampus is slightly larger than the left (all age groups). However, the mean volume was established based only on the sample obtained. |
| Yavuz et al.[8], 2007 | Volumetry Manual | Correlation between hippocampal atrophy with DCL and AD. |
| Pruessner et al.[9], 2000 | Volumetry Manual (n = 40) | Average volumes of 3,244 cm 3 as normal in a healthy population with a mean age of 24 to 42 years. |
| Boccardi et al.[10], 2015 | Volumetry Manual | Develop a measurement standard; They reported average volumes of the hippocampus: 2,436 $cm^3$ in subjects with normal aging; 1,804 cm 3 in patients with AD. From 12 protocols, reduced to 4 segmentation units to perform Volumetry. |

## Declaration of conflict of interest

The authors declare no conflict of interest.

## Financial support of the project

There was no financial support.

## Author's Contribution

João Vitor Lois Balestrieri: dissertation, interpretation, and data analysis; Mahara Barbosa Nonato: dissertation, interpretation, and data analysis; Larissa Gheler: dissertation, interpretation, and data analysis; Mirto Nelso Prandini: guidance, and finalization

**RESUMO**

*Pesquisas recentes demonstram que o hipocampo apresenta uma redução de volume no final da idade adulta, mantendo uma estreita relação com o declínio cognitivo. A aquisição da imagem por diversos métodos de medição de volume nos leva a encontrar na ressonância magnética o método de destaque, pois permite quantificar o volume de determinadas estruturas cerebrais utilizando a reconstrução computadorizada tridimensional das imagens obtidas.*

OBJETIVOS: *Confirmar a existência de diferenças entre o volume hipocampal e o declínio cognitivo leve, doença de Alzheimer e cognição normal.*

MÉTODOS: *Levantamento bibliográfico de estudos que apresentassem dados referentes aos distúrbios da doença de Alzheimer, alterações macroscópicas cerebrais detectadas com softwares na ressonância magnética e segmentação. Foram adicionados estudos apenas da medição volumétrica do hipocampo, objetivando-se chegar a valores que possam estabelecer uma correlação do menor valor estrutural hipocampal e risco de desenvolvimento da doença.*

RESULTADOS: *Um total de 1.070 indivíduos foi analisado em seis estudos clínicos, demonstrando a relação da diminuição do hipocampo na neuroimagem, correlacionado com o comprometimento cognitivo leve e doença de Alzheimer.*

CONCLUSÕES: *O desenvolvimento de um valor padrão para esse fim seria bastante útil na coleta de dados, permitindo melhor compreensão de algumas alterações que podem ocorrer na cognição, determinar valores prognósticos e até, em um futuro próximo, fator de risco imagiológico para a doença.*

PALAVRAS-CHAVE: *Hipocampo. Espectroscopia de ressonância magnética. Titulometria. Doença de Alzheimer.*

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REVIEW ARTICLE

# Basic principles of risk score formulation in medicine

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**SUMMARY**

*Risk models play a vital role in monitoring health care performance. Despite extensive research and the widespread use of risk models in medicine, there are methodologic problems. We reviewed the methodology used for risk models in medicine. The findings suggest that many risk models are developed in an ad hoc manner. Important aspects such as the selection of risk factors, handling of missing values, and size of the data sample used for model development are not dealt with adequately. Methodologic details presented in publications are often sparse and unclear. Model development and validation processes are not always linked to the clinical aim of the model, which may affect their clinical validity. We make some suggestions in this review for improving methodology and reporting.*

KEYWORDS: *Logistic models. Risk assessment. Methodology. Medicine.*

## INTRODUCTION

Risk models play a vital role in the monitoring of healthcare performance and in health care policies. For a risk model to be used routinely in practice, the modeling methodology should be correct and robust. Furthermore, the proposed model must be straightforward to implement and clinically relevant[1].

Some authors provide sparse details about their methods, thus making it difficult to ascertain what was really done. Moreover, different conclusions may be reached depending on the risk model used. Therefore, it is important to ensure that risk modeling is carried out in a correct and systematic manner and that robust and accurate models are developed. Since some deficiencies may exist in the earlier processes, thus making the clinical application questionable, the objective of the risk model should be clear to prevent it from being used in the same way as other clinical situations previously studied. The performance of a model should be evaluated in light of the specified goals[2,3].

The objective of this study is to review the methodology used for risk modeling in medicine, suggesting a correct methodological sequence for avoiding common errors in the development of this type of research.

## STEPS

### Objectives of the risk score

The first step is the formulation of clear objectives, as these will have effects on the choice of variables

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to be studied and be directly involved in the clinical application of the model[4]. (figure 1 and 2)

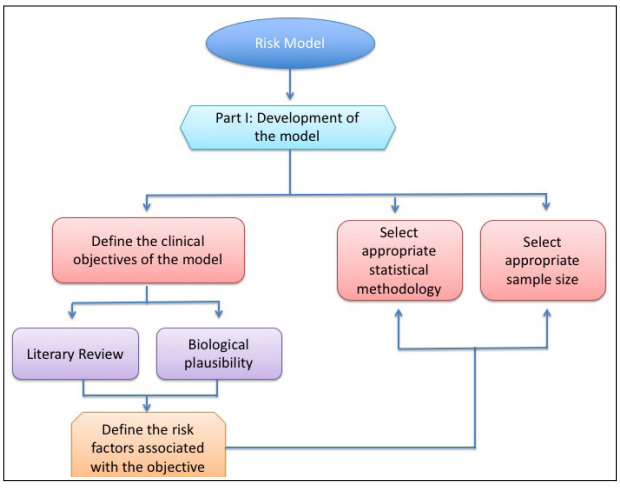
### Choice of variables to be studied

The choice of variables usually follows a hierarchical model based on biological plausibility and external information (ie., literature) regarding the strength of the associations (along with the occurrences) related to the study outcome; associations are of fundamental importance[3,5]. The choices of the variables are in accordance with the clinical objectives specified for the model in question. Likewise, they demonstrate a balance between the complexity required and what can be collected in clinical practice. Highly complex risk models can satisfy the most diverse clinical objectives, but may be impractical and even despised in clinical practice[4]. Parsonnet et al.[6] suggests testing the evaluated variables that have a prevalence greater than 2% in the sample to avoid possible bias.

In choosing the variables, we tried to minimize bias in this detailed situation. The value of the regression coefficient was calculated (see below) to be as accurate as the average effect of X, but the result would be misleading if X has different effects in different zones. The implication may be particularly misleading if the average value of X does not occur in any of the zones. For example, the impact of left ventricular ejection fraction on mortality is not linear: A decrease of 10%, from 30% to 20%, carries greater risk than a decrease from 50% to 40%[7].

An important detail at the end of the score is that all the risk factors surveyed were generated in the final model are presented[4].

**FIGURE 1**




### Definition of derivation cohort or development group and their size

The first analysis usually occurs with a specific sample of patients. This is called a derivation cohort or developmental group, which is basically the primary objective in the development of the prediction score[3].

The number of events per variable analyzed by logistic regression should be greater than or equal to 10, minimizing possible statistical errors[8]. In general, the results of models with less than 10 outcome events per independent variable are thought to have questionable accuracy, and the usual tests of statistical significance may be invalid. Large confidence intervals associated with individual risk estimates may indicate an over-fitted model under these circumstances[7].

### Application of logistic regression analysis and preliminary score

After the variables in the sample were studied, multiple logistic regression was applied. The predictor score was then calculated. This was derived by utilizing the variables that are true and independent factors, generally in keeping with the score of all the variables with a level of significance of $p < 0.05$[3-5]. Generally, the variable selection strategy employed by the score developers to produce their final score used variable selection methods such as backward elimination, forward selection, and stepwise approaches[9].

Typically, a risk score produces coefficients for each risk factor in the final score representing their weights in predicting studied outcome. If not chosen this way, there are methods available to translate coefficients into integer scores with minimal loss of precision[10]. One of the more commonly used forms is a risk-weighted score based on the magnitude of the coefficients b of the logistic equation. When they were transformed (exp [b]) into odds ratios (odds ratios), the values were rounded to make up the initial predictor score[11].

### Score Predictor calibration test

Ideally, the prediction score should be subjected to calibration and discrimination tests. Calibration evaluates the accuracy to predict risk in a group of patients. More succinctly, if the score proposes that the clinical event in 1,000 patients would be 5% and the observed clinical event is 5% or close to that value, it would be prudent to conclude that the model is well-calibrated. The strength of the calibration can be assessed by testing the quality of the fit using the Hosmer-Lemeshow

test[12,13]. A p value> 0.05 indicates that the score fits the data and predicts the outcome adequately.

### Score Predictor discrimination test

Discrimination measures the ability of the score to distinguish between low-risk and high-risk patients. In other words, if most clinical events occur in patients identified as high risk, we will say that the model has good discrimination. On the contrary, if most clinical events occur in patients identified as low risk by the model, we will say that the model has poor discrimination[14].

Discrimination is measured using the statistical technique called area below the ROC curve. It is typically used for the evaluation of prognostic models in cardiology and represents the likelihood of a predictive model. In the case of a risk score, it is used to assign a higher probability of an event occurring in those who will actually present the event. The area under the ROC curve is a summary of the accuracy of the score and is represented by the C (concordance) statistic for binary outcomes. C is equal to 0.5 when the ROC curve corresponds to the probability, represented by the diagonal line in the curve, and results in 1.0 when the accuracy is maximum in discriminating between those with and without the outcome under study. For example, a ROC area of 0.75 means the model correctly ranks 75% of the patient pairs according to their predicted probability. Risk score with statistic C classified as excellent discrimination refers to values above 0.97; very good discrimination is in the range of 0.93 to 0.96; good discrimination between 0.75 and 0.92; below 0.75 corresponds to models deficient in the ability to discriminate. In practice, models rarely exceed 0.85[5,13,15,16].

### Internal validation of the Score Predictor in a validation cohort

Like all prediction scores, the initial score needs to be validated (figure 3). The evaluation of the performance of the prediction model in data not belonging to the derivation cohort is the most important. This can be achieved using internal validation, which is the submission of the model to a new population of the same center and evaluating its predictive performance in the second group, the so-called validation cohort[3].

Depending on the aims, the validation process should consider the total picture; the ability of a model to predict the outcome of the risk score accurately; the range of predictions (whether these are clinically useful or not); and the ability to discriminate between high, intermediate, and low-risk patients[4].

The validation dataset should be large enough to enable precise comparison between the outcomes observed and predicted and to enhance statistical methods such as the H-L test with sufficient power. For the H-L test to be valid, the predicted number of events in each risk group used in the test should always be greater than 1, and for most risk groups it should be at least 5[12]. It has been suggested as a general principle that adequate model evaluation requires at least 100 outcomes in the validation sample[9].

### Logistical Model

In addition to the final score, the resulting logistic model can be presented (see formula below), in which it is possible to obtain direct estimates of the probability of occurrence of an outcome. This process, using the mathematical model directly, is understood and regarded by some authors as the most appropriate in obtaining event estimates, although it presents a

**FIGURE 2**

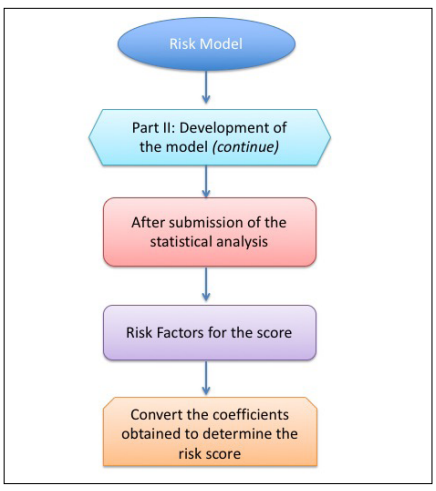
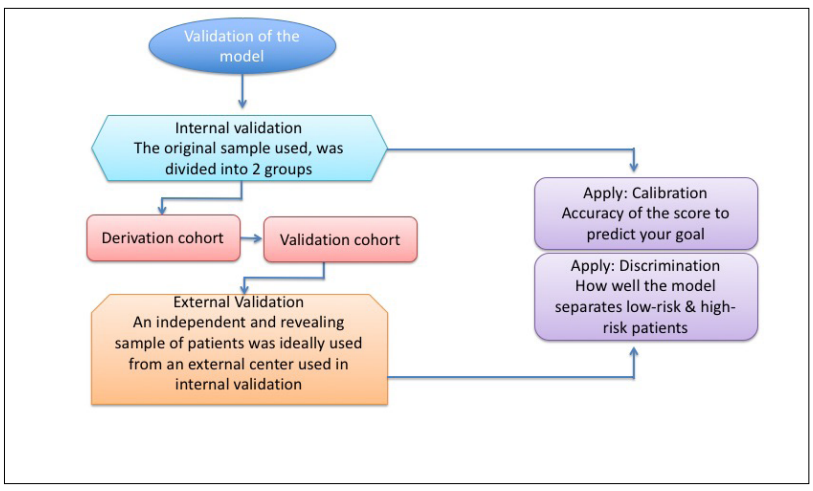



**FIGURE 3**



certain degree of mathematical complexity for its use in daily medical practice. The application of the logistic model is more adequate for the prognosis of individual risk, especially in patients with very high risk in the additive model[17].

$$P(event) = 1 / 1 + \exp(- (\beta 0 + \beta 1x1 + \ldots + \beta kxk))$$

## LIMITATIONS OF ANALYSIS OF RISK SCORES

The analysis of the performance of a risk model based only on its discriminatory capacity (C-statistics) and calibration has limitations. One of the main limitations to be highlighted is the observation that once the area under the ROC curve reaches a certain level, large sizes of new variable effects are required to achieve small increases in the area under the ROC curve. Due to these limitations, new methods of quantifying performance improvement have been developed, such as risk reclassification, Net Reclassification Improvement (NRI), and Integrated Discrimination Improvement (IDI)[18].

Several studies suggest that the scores are less effective when applied to patients outside the scope of the target group intended for the study. Therefore, external validation is fundamental to increase its clinical acceptance, especially for centers outside the site of the creation of the score[3,4]. As with any risk stratification score, it should always be evaluated and re-evaluated in the long term, considering existing variables. Risk score methodologies should also be designed to accommodate and incorporate the presentation of new variables.

## CONCLUSION

Risk models play an important role in health care policy. For a risk model to be used routinely in practice, the modeling methodology should be correct and robust. The proposed model must be straightforward to implement and clinically relevant. It is important that researchers implement a structured and transparent model-building process linked to the stated clinical objective. Furthermore, it is imperative they evaluate the model's performance in the context for which it had been developed. Researchers should also develop guidelines before starting a modeling process, describing how each step will be handled, and strictly adhere to these protocols. Clearer descriptions of each step of the process are required in published papers and reports.

### Authors contribuition

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**RESUMO**

*Os modelos de risco desempenham um papel fundamental no monitoramento dos desempenhos dos serviços de saúde. Apesar de extensa pesquisa e do amplo uso dos modelos de risco na Medicina, existem problemas metodológicos. Revisamos a metodologia utilizada nestes modelos na Medicina. Os achados sugerem que muitos modelos de risco são desenvolvidos de maneira ad-hoc. Aspectos importantes, como a seleção de fatores de risco, a forma utilizada de dados perdidos e o tamanho da amostra empregada não são detalhados adequadamente. Detalhes metodológicos presentes em publicações são frequentemente esparsos e incertos. Os modelos de desenvolvimento e de validação nem sempre estão associados com o objetivo clínico do modelo, o que pode afetar sua validade clínica. Nós produzimos algumas sugestões nesta revisão para otimizar a metodologia e as publicações.*

PALAVRAS-CHAVE: *Modelos logísticos. Medição de risco. Metodologia. Medicina.*

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REVIEW ARTICLE

# Beyond ventilatory support: challenges in general practice and in the treatment of critically Ill children and adolescents with SARS-CoV-2 infection

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**SUMMARY**

*Severe acute respiratory syndrome coronavirus 2 (Sars-CoV-2 infection) is a new challenge for all countries, and children are predisposed to acquire this disease. Some studies have demonstrated more severe diseases in adults, but critically ill pediatric patients have been described in all ages. Pulmonary involvement is the major feature, and ventilatory support is common in critical cases. Nevertheless, other very important therapeutic approaches must be considered. In this article, we reviewed extensively all recent medical literature to point out the main clinical attitudes to support these pediatric patients during their period in respiratory support. Radiologic findings, fluid therapy, hemodynamic support, use of inotropic/vasopressors, nutritional therapy, antiviral therapy, corticosteroids, antithrombotic therapy, and immunoglobulins are analyzed to guide all professionals during hospitalization. We emphasize the importance of a multi-professional approach for adequate recovery.*

KEYWORDS: *Child. Coronavirus. Sars-CoV-2. COVID-19.*

## INTRODUCTION

A pneumonia case of unknown cause detected in Wuhan, China, was first reported to the WHO Country Office in China on 31 December 2019, but current case data in China reveal that children < 18 years of age accounted for only 2.4% of all reported cases (WHO data, 2020). However, there have been multiple reports, to date, of children with asymptomatic Sars-CoV-2 infection (Severe acute respiratory syndrome coronavirus 2). The main sources of the infection are patients infected by novel coronavirus disease (COVID-19) with or without clinical symptoms. In addition, patients in the incubation period may also b able to transmit the virus based on case evidence[1]. Since then, however, more regions around the world

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have launched pathogen detection campaigns and, since younger children cannot wear masks and no other special preventive and control measures have been taken, the number of child infection cases has increased significantly. Therefore, higher attention to this part of the population should be given. At the same time, children with other diseases (such as congenital heart, lung, and airway diseases, malnutrition, renal dysfunction, liver dysfunction, immunodeficiency, tumors, etc.) are vulnerable to infections by Sars-CoV-2 and, more specifically, predisposed to a severe clinical condition[1,2].

Sars-CoV-2 originated from bats and is confirmed to be similar to Sars-CoV (Severe acute respiratory syndrome caused by Coronavirus in 2003), entering cells by binding to the angiotensin-converting enzyme 2 (ACE-2) cell receptor. According to the current data, the main routes of transmission are respiratory droplet transmission and contact transmission. It has also been reported that Sars-CoV-2 can be transmitted through aerosols, the fecal-oral route, and suspected mother-to-infant transmission, but some pediatric cases may progress to lower respiratory tract infection. Severe COVID-19 in children is rare. To date, the largest review of children with COVID-19 included 2143 children in China. Only 112 (5·6%) of 2143 children had severe disease (defined as hypoxemia), and 13 (0·6%) developed respiratory or multiorgan failure or pediatric acute respiratory distress syndrome (PARDS)[1,3].

In adults, certain findings are associated with severe illness, such as high serum ferritin and bilateral abnormalities on chest CT. It is very difficult to determine common clinical characteristics in children with severe disease, and it is unclear whether there is a common biomarker due to the small number of cases[1,4].

## Radiologic Findings

The chest x-ray may be normal in early or mild disease. Of all adult patients with COVID-19 requiring hospitalization, 69% had an abnormal chest radiograph at admission, and 80% had radiographic abnormalities sometime during hospitalization. Findings are more significant around 10-12 days after symptom onset. The most frequent findings are airspace opacities, whether described as consolidation or, less commonly, ground-glass opacification (GGO). The distribution is most often bilateral, peripheral, and lower-zone predominant, and pleural effusion is rare (3%)[5,6].

Growing evidence shows the usefulness of lung ultrasound in patients with COVID-19 and pneumonia from diagnosis, to monitoring, and follow-up. In the setting of COVID-19, wireless probe and tablets represent the most appropriate ultrasound equipment. The following patterns have been observed, with a tendency to bilateral and posterobasal predominance: multiple B-lines (ranging from focal to diffuse with spared areas, representing thickened subpleural interlobular septa); irregular, thickened pleural line with scattered discontinuities; subpleural consolidations, alveolar consolidation, restitution of aeration during recovery (reappearance of bilateral A-lines)[5-7].

Unlike adult patients, only a small number of pediatric patients had multilobes affected, so we assume that children and adolescents generally have milder CT findings than adults. In adults, the findings in CT scan can be very diverse depending on high or low compliance[8]: most appeared as pure GGO, GGO with consolidation, interlobular septal thickening, bronchiolar wall thickening, and asymmetric paving pattern, whereas rare manifestations included halo sign, pleural effusion, pericardial effusion, and lymphadenopathy. In a pediatric study that analyzed 6 patients, only GGO and consolidative GGO were found[5,6,9].

## Fluid Therapy

For the acute resuscitation of children and adolescents with COVID-19 and shock, we suggest using a conservative over a liberal fluid strategy. Buffered/balanced crystalloids over unbalanced crystalloids can be useful with adequate metabolic and electrolyte monitoring. For the acute resuscitation of children and adolescents with COVID-19 and shock, we recommend using crystalloids over colloids. All colloids are more costly than crystalloids, and the availability of colloids is limited in some settings (e.g. some low- and middle-income countries)[10-12].

One study performed by Maitland et al demonstrated that fluid boluses significantly increased 48-hour mortality in critically ill children with impaired perfusion in resource-limited settings in Africa. The results of this study challenge the importance of bolus resuscitation as a lifesaving intervention in resource-limited settings for children with shock who do not have hypotension and raise questions regarding fluid-resuscitation guidelines in other settings as well. Another study conducted the Surviving Sepsis Campaign Guidelines and did not demonstrate

any advantages in more aggressive fluid therapy treatment in children with septic shock[10-15].

One dynamic analysis during fluid therapy seems to be related to a better evolution.

## Hemodynamic Monitoring and Inotropic/Vasopressor Support

Shock can be a presentation in children with COVID-19, but the prevalence is low even in patients with severe respiratory dysfunction. Cardiac injury may correlate with the prevalence of shock and impact in the prognosis. In a study of 150 adult patients from 2 hospitals in Wuhan, China, shock was a major reason for death in 40% of the cases, which may, at least in part, be due to fulminant myocarditis. Monitoring some clinical hemodynamic non-invasive and invasive parameters is very important: skin temperature, capillary refilling time, cardiac rate, invasive arterial pressure, oximetry, capnography, pulse pressure variation, mental status, diuresis, sequential central venous pressure, central venous oxygen saturation, lactate, and cardiac index[10,11,15].

Accumulating clinical data, in addition to the common clinical presentation of respiratory failure caused by COVID-19, the cardiovascular manifestations induced by this viral infection have generated considerable concern. In adults, for example, NT-proBNP elevation and arrhythmias were significantly more common in patients with elevated troponin levels, and NT-proBNP was significantly correlated with troponin levels. Special attention is necessary for patients with congenital cardiac malformation because viral illness can further damage myocardial cells through several mechanisms including direct damage by the virus and systemic inflammatory response[14-16].

For children and adolescents with COVID-19 and shock, we prefer epinephrine or norepinephrine (depending on the manifestation of hypo- or hyperdynamic shock), instead of dopamine. In the case of COVID-19 and shock with strong evidence of cardiac dysfunction and persistent hypoperfusion despite fluid resuscitation and epinephrine or norepinephrine, we suggest adding dobutamine or another inotropic agent[15,16].

## Nutritional Therapy

It's very important to avoid overfeeding patients with SARS-CoV-2 due to the risk of hypercapnia. In adults, 50.5% of patients reported a digestive symptom, including: lack of appetite (81 [78.6%] cases), diarrhea (35 [34%] cases), vomiting (4 [3.9%] cases), and abdominal pain (2 [1.9%] cases). Altered digestive process and malabsorption can occur, and special diets (oligomeric without lactose) may be necessary. We also need to bear in mind that viruses can persist in feces long after they are absent from nasopharyngeal secretions. It has been found that ACE2 is not only expressed in lung Alveolar type 2 progenitor cells (AT2 cells), but also in upper esophageal and stratified epithelial cells, as well as intestinal epithelial cells in the ileum and colon. Therefore, intestinal symptoms of SARS-CoV-2 may be associated with the invasion of intestinal epithelial cells. Another study in adult patients with SARS-CoV-2 infection who were transferred to the intensive care unit found a higher frequency of abdominal pain in these patients than in those with SARS-CoV-2 infection who did not require intensive care, and 10% of patients with COVID-19 experienced diarrhea and nausea symptoms[17,18].

In critically ill patients with SARS-CoV-2 infection and severe pulmonary injury, avoiding gastroesophageal reflux in consequence of excessive gastric distention is a major attitude. The gastric administration of the diet is preferred to optimize digestive activity but in the case of failure, we suggest the postpyloric via (jejunal preferably)[17,18].

Nutritional treatment recommendations to date are based on observations, rather than evidence from clinical trials.

## Drug Therapy

Since the COVID-19 outbreak in December 2019, doctors around the world have faced several challenges in the management of COVID-19 patients. One of them is the choice of adequate therapy[1,19-21]. A wide range of medications is being studied for the management of these patients; however, none of them has been established as the gold standard yet. Supportive therapy, like the ones cited previously in this article, are still the mainstay in the management of COVID-19 patients[1,20]. Since there are no specific antiviral agents against Sars-CoV-2, multiple pharmacologic agents are being tested, some of them such as anti-viral agents, antimalarial drugs, corticosteroids, intravenous immunoglobulin, and selective cytokine blockers, such as anakinra or tocilizumab[1,22-25]. Among these options, one available choice is using a broad-spectrum antiviral drug like nucleoside analogs and HIV-protease inhibitors that could attenuate virus infection[26]. Besides antiviral agents, antimalarial

drugs have also been tested with apparently positive results[27]. In children, until now, no antiviral therapeutic agent is recommended and the only treatment recommendation described suggests the use of nebulized interferon-alpha-2b[20,28].

Given the multiple treatment options, we chose to unravel the drugs that seem more promising and the various studies that have been conducted. Most of these studies have been carried out in adult populations since children seem to have a milder clinical course, with multiple, but still unknown, possible reasons[1,20,29-32]. One suggested reason is that children may be less susceptible to the infection as a result of possible differences in the expression of the angiotensin-converting enzyme 2 (ACE2)[24,25,32]. Despite that, the importance of children in virus transmission remains uncertain. If bacterial coinfection is suspected, antibiotic therapy must be timely initiated[1,20].

Antimalarial agents, such as chloroquine and its derivative, hydroxychloroquine, potential antiviral drugs, have shown positive results during in vitro testing against SARS-CoV-2 and in some clinical studies with COVID 19 adult patients[27,33,34]. Chloroquine blocks viral entry to endosomes by increasing their pH, inhibiting the replication and spread of SARS-CoV-2[33,34]. The immunomodulant effect of chloroquine may enhance the antiviral effect in vivo[23,26,27,33]. The low cost and safety profile of chloroquine are major benefits for its use in the healthcare system; however, this is still a topic for debate.

The use of lopinavir and ritonavir, both antiviral drugs, is being discussed as a treatment option against Sars-CoV-2[26,33,35]. One study conducted in Hong Kong showed benefits in SARS patients treated with lopinavir/ritonavir and ribavirin when compared with only ribavirin[36,37]. However, a recent open-label trial with 199 patients conducted in China found no benefits in the lopinavir/ritonavir group and had more adverse events with the use of the medication[38]. Another retrospective study did not observe the shortening of viral shedding duration after lopinavir/ritonavir treatment[39]. Further studies are necessary to establish the real role of this medication in the Sars-CoV-2 treatment, especially in the pediatric population.

## Corticosteroids

Infection by Sars-CoV-2 can induce an important inflammatory response and provoke the release of cytokines, therefore corticosteroid use for the treatment of patients with severe illness was an option since they can reduce the inflammatory-induced lung injury[23]. Despite that, posterior evidence suggested that corticosteroids did not affect mortality. Instead of this desired result, corticosteroids delayed viral clearance. So, in the meantime, the use of corticosteroids should not be routine[40].

Notwithstanding the evidence against the use of corticosteroid, in some clinical situations, they are beneficial, such as PARDS, encephalitis, hemophagocytic syndrome, or septic shock and asthma patients[1,10,22,32].

## Coagulopathy and Antithrombotic Therapy

To date, there is no literature regarding anticoagulation in COVID-19 patients in the pediatric population. All information comes from adult studies[41-43].

In adult patients with COVID-19, two recent retrospective studies have shown that the existence of disseminated intravascular coagulation is common in nonsurvivors, with abnormal coagulation results, in particular elevated D-dimer and fibrin degradation product[42,44,45]. This information may help guide therapy and evaluate prognosis. Besides these results, a recent article reported that occlusion and microthrombosis formation in pulmonary small vessels occurred in one critical patient with COVID-19 after lung organ dissection[46]. A recently published study demonstrated that anticoagulant therapy seems to be associated with better prognosis in severe COVID-19 patients, especially those with markedly elevated D-dimer[47].

Considering the risk for venous thromboembolism in patients with severe COVID-19, expert consensus in China and by the International Society of Thrombosis and Haemostasis recommend a prophylactic dose of low molecular weight heparin to all COVID-19 patients who require hospital admission, in the absence of any contraindications[47-49]. It is also recommended the therapeutic administration of heparin in cases of pro-thrombotic conditions. Unfortunately, until the time of this publication, there are no data that support its use in children.

## Plasma / Immunoglobulins

No specific treatment has been proven to be effective for Sars-CoV-2, and specific drugs have been researched. Convalescent plasma or immunoglobulins have been used as an empirical treatment during the Ebola virus outbreak in 2014 and in the Middle East respiratory syndrome coronavirus in 2015. In patients with pandemic 2009 influenza A H1N1 virus infection (H1N1pmd09), there was a reduction in the relative

risk of mortality and no adverse events were observed. Therefore, the use of convalescent plasma transfusion could be beneficial in patients with SARS-CoV-2. The plasma is donated from recovered SARS-CoV-2 patients that may have a high level of antibodies[47-50]. Recently, Shen et al.[47] described a case series of 5 patients with severe disease, rapid progression, and refractory hypoxemia. They were treated with plasma and their clinical condition improved, as did their body temperature, PaO2/FiO2 ratio, and chest imaging[51]. A study performed by Zhang et al.[50] showed no serious adverse reactions associated with the transfusion of convalescent plasma in four critically ill patients infected with SARS-CoV-2. The risks of convalescent plasma administration are associated with the transfer of blood substances, which include infections and immunological reactions to serum constituents. The Surviving Sepsis Campaign guideline of COVID-19 suggests against the routine use of standard intravenous immunoglobulin (IVIG) and the routine use of convalescent plasma because poor efficacy data are available and more evidence is necessary[10]. The FDA (US Food and Drug Administration) has approved the use of plasma from recovered patients to treat people who are critically ill with COVID-19[51]. Therefore, therapy with convalescent plasma may be considered within the context of a well-designed clinical trial.

## Physiotherapy during COVID-19

It's very important to have adequate management of the physiotherapy team considering the following aspects: avoid or minimize movement of professionals during work shifts; encourage psychological assistance programs to the entire team in consequence of

**TABLE 1.** INTERVENTIONS INVOLVING THE PARTICIPATION OF A PHYSICAL THERAPIST

| INTERVENTIONS INVOLVING THE PARTICIPATION OF A PHYSICAL THERAPIST | MODERATE INFECTION | SEVERE INFECTION | CRITICAL INFECTION |
|---|---|---|---|
| Removal of airway secretion (upper and/or lower) | If secretion present in airway | YES | YES |
| Pulmonary Reexpansion | If atelectasis | If atelectasis | YES |
| Prone Position | Not applicable | YES | YES |
| Early mobilization | If comorbidities and/or immobilization syndrome | YES | NO |
| Mobilization/Exercises (passive and/or active-assisted) | If comorbidities and/or immobilization syndrome | YES | YES |
| Low flow oxigen (uo to 6 L/min) | YES | NO | Not applicable |
| High Flow Nasal Oxegen therapy (HFNO) | If in negative pressure ward (or ventilated isolation ward) + indicated PPEs | NO | Not applicable |
| Non-Invasive Ventilation (NIV) | If in negative pressure ward (or ventilated isolation ward) + indicated PPEs | If in negative pressure ward (or ventilated isolation ward) + indicated PPEs | Not applicable |
| Cuff-pressure monitoring | YES, if patitent with tracheostomy | YES, if tracheostomy or intubated patient | YES |
| Bag-mask ventilation | NO | NO | YES, if bacterial filter use in a bag and/or acrylic box |
| Manual Hiperinsuflation | NO | NO | YES, if bacterial filter use in a bag and/or acrylic box |
| Respiratory mechanic monitoring | If in NIV or chronic ventilated patient | YES | YES |
| Inhaled nitric oxide (Noi) | Not applicable | NO | YES |
| HFOV / HFV | Not applicable | Not applicable | Not applicable |
| Endotracheal intubation | NO | May be necessary | YES |
| Extubation | NO | May be necessary | YES, when clinically stable |
| Unplanned extubation | Not applicable | May occur | May occur |
| Airway aspiration | May be necessary | YES | YES |

OBS: in asymptomatic cases or cases with mild COVID-19 infection there is no need for a physical therapist in the hospital environment; it is understood as "not applicable" when there is no scientific evidence and/or clinical report of the benefits of the conduct; it is understood as YES when the conduct can be applied in pediatrics and includes the performance of a Physiotherapist; it is understood as NO when the conduct is not applied in pediatrics and/or does not require the participation of a Physiotherapist. LEGEND: NIV = non-invasive ventilation; HFOV = high frequency oscillatory ventilation; HFV = high frequency ventilation due to flow interruption; Noi = inhaled nitric oxide; PPE = personal protective equipment.

the high risk of Burnout (state of emotional, physical, and mental exhaustion caused by excessive and prolonged stress)[52].

We recommend guiding and instructing all awake patients to cough correctly during physiotherapy procedures: when coughing or sneezing, cover the mouth and nose with the forearm or a handkerchief, which should be immediately discarded. Then wash hands with soap and water or 70% gel alcohol[52].

The interventions that include the participation of a physical therapist are listed in table 1 and must consider the severity of the disease infection for the indication or not of the procedures.

## CONCLUSIONS

The Sars-CoV-2 infection is a new challenge for all healthcare professionals. In children and adolescents, frequently, the disease is milder in clinical and radiologic aspects if compared to adults, but critically ill pediatric patients have been described in all ages. Several approaches as important as respiratory support must be considered. The analysis of radiologic findings, adequate fluid therapy, hemodynamic support, early nutritional therapy, and physiotherapy are essential during treatment. Other therapeutics (corticosteroids, antiviral therapy, antithrombotic therapy, and use of immunoglobulins) are controversial but can be useful after solid investigation. We emphasize the importance of a multi-professional approach for adequate recovery.

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### Authors Contribuition

Juliana Ferreira Ferranti; Isadora Souza Rodriguez; Emiliana Motta; Cíntia Johnston; Werther Brunow de B Carvalho; Artur Figueiredo Delgado - Contribution: bibliographic survey, design, critical analysis, writing and agreement on the conclusions.

**RESUMO**

*A síndrome respiratória aguda grave (SRAG) pelo novo coronavirus (SARS-CoV-2) é um novo desafio para todos os países e crianças estão predispostas a adquirir a doença. Alguns estudos demonstraram quadros mais graves em adultos, mas crianças criticamente doentes foram descritas em todas as idades. O envolvimento pulmonar é a principal característica e a necessidade de suporte ventilatório é comum nos casos mais graves. Entretanto, outras abordagens terapêuticas importantes devem ser consideradas. Nesse artigo revisamos extensamente a literature médica até o momento a fim de citar os principais recursos terapêuticos para o manejo dos pacientes pediátricos durante o período de suporte ventilatório. Achados radiológicos, terapia fluídica, terapia antiviral, o uso de corticosteroides, terapia antitrombótica e o uso de imunoglobulinas foram analisados a fim de guiar os profissionais durante o período de hospitalização desses pacientes. Nós reforçamos a importância de uma abordagem multiprofissional para recuperação adequada.*

PALAVRAS-CHAVE: *Criança. Coronavirus. SARS-CoV-2. COVID-19.*

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REVIEW ARTICLE

# Ventilatory support recommendations in children with Sars-CoV-2

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## INTRODUCTION

COVID-19 is a new respiratory illness that can rapidly deteriorate into severe respiratory distress. Since a specific antiviral treatment is still under investigation, the main way to reduce morbidity and mortality is early and strong intervention when it comes to respiratory support[1]. Initially thought to have flu-like symptoms, this disease has shown that it can present itself as severe pneumonia with a non-uniform presentation: in some cases with preserved compliance and altered perfusion, and sometimes with very low compliance, similarly to acute respiratory distress syndrome.

Recently, one study from Gattinoni et al.2 describes two types of lung lesions: type L and type H. Type L (Fig. 1) patients may have subpleural interstitial edema (ground-glass injuries), low elastance (and high compliance), low ventilation/perfusion ratio (V/Q) – gas volume is nearly normal, and what leads to hypoxemia is altered perfusion and loss of hypoxic vasoconstriction and they also have low lung recruitability; this kind of pattern usually appears at the onset of the disease, and patients can either improve or deteriorate into a more severe case. Type H patients (Fig. 2), approximately 20-30%, behave more similarly to CARDS, with low compliance, decreased gas volume due to edema, V/Q mismatch, and a possibility of lung recruitment. Considering the possibility of severe cases, respiratory support should be given to those with signs of respiratory failure

Considering the possibility of severe cases, respiratory support should be given to those with signs of respiratory failure such as SpO2 ≤ 93%, increased work of breathing and tachypnea (for age), low PaO2/FiO2 ratio, high oxygenation index (OI) or high oxygen saturation index (OSI)[3].

Given the paucity of information regarding respiratory support of pediatric patients with Sars-CoV-2, we believe these recommendations may guide the ventilatory therapy in those children.

## NONINVASIVE RESPIRATORY SUPPORT

Nasal prongs/reservoir mask (Low flow < 4L/min): Should only be used in mild respiratory illness, with no respiratory distress[4], since they do not generate recruitment of the lungs. If used, it may improve oxygenation but not the PaO2/FiO2 ratio and may delay other ventilatory therapies[3].

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High flow nasal cannula (HFNC): May be used in cases with no severe hypoxemia. Response to treatment has to be assessed within 30-60 minutes from the initiation of therapy. If no response (SpO2/FiO2 < 220 or FiO2 > 0,4 for SpO2 > 92%)[5], other respiratory support should be considered. This therapy generates aerosol[6] and should never be used if there is no appropriate airborne isolation (negative pressure and >12 air changes per hour) and adequate personal protective equipment (PPE)[4,6].

Continuous positive airway pressure (CPAP)/ Bilevel positive airway pressure (BiPAP): Can be used in moderate cases, if SatO2/FiO2 is between 221-264. A trial can be done during 60-90 minutes and response to treatment has to be assessed. If no response (SpO2 < 92% and/or FiO2 > 0,6) tracheal intubation is recommended[5]. Like in HFNC, this kind of support is also aerosol-generating and should only be used if appropriate precautions are available. A helmet is the preferable interface[8] (watch out for risk of self-inflicted lung injury), if not available, a full face mask is the second choice. There can be no leaks during its use and it is necessary to use an adequate filter (HEPA or HMF).

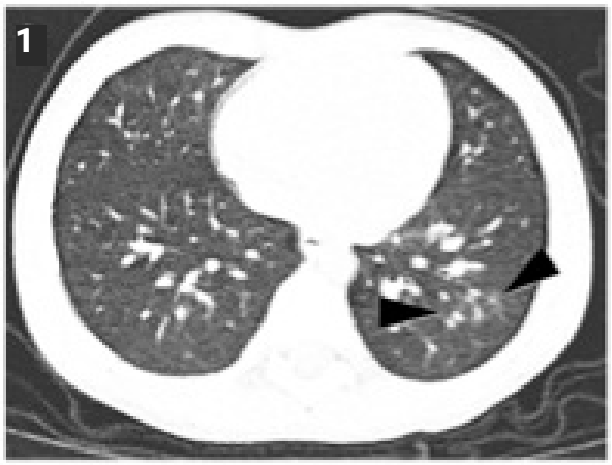
## AIRWAY MANAGEMENT

Intubation is a critical procedure for patients with COVID-19 and also for healthcare workers. It has a high risk of viral shedding, so when it is performed, some important precautions are suggested[9,10]:

- Preferably negative pressure ventilation rooms with ante-room to minimize exposure to aerosol or droplets
- Adequate PPE: Impervious gown, theatre hat, gloves, N95 facial mask, protection goggles, face shield[11]
- Disposable equipment is preferred over reusable equipment
- Closed-circuit aspiration
- Pre-oxygenation should be performed using a occlusive face mask with a viral filter (HEPA or HMF) or maintain the previously used device
- Avoid bag-mask ventilation if possible
- Intubation should be performed by the most experienced professional available and there must be a limited number of healthcare professionals to avoid exposure
- Use rapid sequence intubation to minimize exposure to droplets and aerosol: we suggest using fentanyl(1-2mcg/kg), midazolam (0,1-0,2mg/kg), and rocuronium (1-2mg/kg). Use atropine (0,02mg/kg) in younger infants.
- Video laryngoscope is preferable but should be used by airway operators who are proficient in their use.
- Use cuffed cannulas (inflate the tracheal tube cuff up to 20cmH2O initially). We suggest occluding the cannula with a clamp to avoid exposure to droplets and aerosol.

## INVASIVE RESPIRATORY SUPPORT

Mechanical ventilation is essential when it comes do COVID-19 treatment, and it seems that the



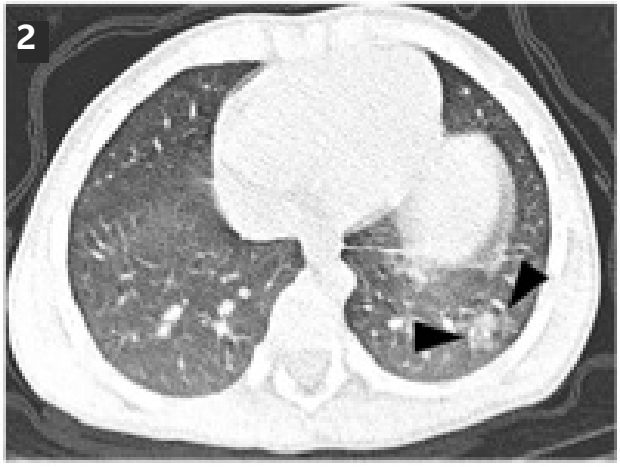




**FIGURE 1.** Patchy ground-glass opacification (arrowheads).

**FIGURE 2.** Also ground-glass but with more severe opacifications and edema. Adapt. from Wei Li, Huaqian Cui, Kunwei Li, Yijie Fang, Shaolin Li. Chest computed tomography in children with COVID-19 respiratory infection. Pediatric Radiology. doi: 10.007/soo247-020-04656-7

hypoxemic respiratory failure resulting from COVID-19 may be different from usual types of acute respiratory distress syndrome (ARDS)[14]. As we described, there seem to be two different types of pulmonary injuries and they require different ventilation strategies. We recommend compliance evaluation at least twice a day, using electric impedance tomography (EIT) without perfusion analysis, if available, or performing respiratory mechanics to determine which type of pulmonary pattern seems more predominant.

For type L patients (high compliance), we suggest using PEEP around 8cmH2O for infants, toddlers, and preschoolers, and PEEP around 10cmH2O for children older than 6 years old. Tidal volume should be around 6-8ml/kg of predicted body weight (PBW)[15,16], and up to 8-9ml/kg PBW may be tolerated. Inspiratory time should be age-appropriate with a decelerating flow. Plateau pressure (Pplateau) should be as low as possible, maintaining adequate PEEP and maximum driving pressure of 15cmH2O. Respiratory rate should be enough to keep pH > 7,25 and inspired oxygen fraction (FiO2) should be <60%. We do not recommend using recruitment maneuvers for this type of patient.

Type H patients (low compliance) are recommended to be treated with protective ventilation[14]. Maintaining 3-6ml/kg PBW of tidal volume, initial PEEP should be around 10cmH2O and titrated up to 12cmH2O (similarly to low PEEP table from ARDS network[17]), keeping in mind that excessive fluids may influence in inadequate PEEP titration. Plateau pressure should be < 30cmH2O, FiO2 < 60%, inspiratory time should be age-appropriate with a decelerating flow, the respiratory rate should be enough to keep pH > 7,25, pCO2 should be monitored by capnography (preferably volumetric capnography) and we recommend using permissive hypercapnia (pH > 7,2). Goal SpO2 is 93-96%, as supraphysiologic arterial oxygen can be associated with higher mortality[18]. Regarding ventilatory modes, we suggest using pressure-controlled modes.

Some patients may present with wheezing or some kind of lower airway obstruction, and they should be treated with bronchodilators (preferably dosimetric or spray inhalers) and magnesium sulfate if necessary (initial dosing of 50mg/kg, infusion during at least 30 minutes). We recommend using low respiratory frequencies, inspiratory/expiratory time ratio of 1:3-1:4, and the lowest PEEP possible, avoiding auto-PEEP.

## ANALGESIA, SEDATION AND NEUROMUSCULAR BLOCKING AGENTS

Appropriate administration of analgesia and sedation is an essential component in the care of mechanically ventilated patients. The promotion of comfort and lowering of anxiety, fear, and anguish is part of the routine. However, the use of excessive dosage or the fear of undersedation is a difficulty in the management of these patients.

The use of excessive of sedation indicated a strong association with poor outcomes, including a longer period of immobilization, more weakness, sleep-wake disturbance and delirium, increase in time of mechanical ventilation and hospital length of stay, higher mortality, cognitive decline, and psychological complications.[18,19]

Recent studies and the last adult (2018) Guideline – Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU- shows that light sedation should be achieved to make the patient comfortable, calm and cooperative, resulting in an improvement of all poor outcomes described above and facilitating patient-ventilator interactions.[19-21]

All sedation strategies should start by assessing and reaching adequate pain control; the priority is effective analgesia and, consequently, a calm patient. To achieve good management of analgesia and sedation, nowadays, the use of scales (grade of recommendation A) is recommended. The pain scale recommended and appropriate is the FLACC. The name FLACC is an acronym of five categories: Face, Legs, Activity, Cry, Consolability. Each category scores 0 to 2 points, totaling 10 points. The resulting scores correlate with the degree of pain: 0 for no pain or comfortable; 1-3 for mild pain; 4-6 for moderate pain; and 7-10 for intense pain. It can be used in many age groups, clinical settings, and cognitive states.[19,20,21,23]

In the initial management, analgesia may be the priority to achieve adequate pain control and level of sedation. So, the use of a strong opioid is recommended, being fentanyl the preferred. Fentanyl can be initiated intermittent and titrated to a continuous infusion to achieve adequate analgesia, guided by the FLACC scale.[19-22]

In the past, the primary sedation strategy in mechanically ventilated patients was deep sedation; however, a light level of sedation with an analgesia-first approach is recommended currently. The

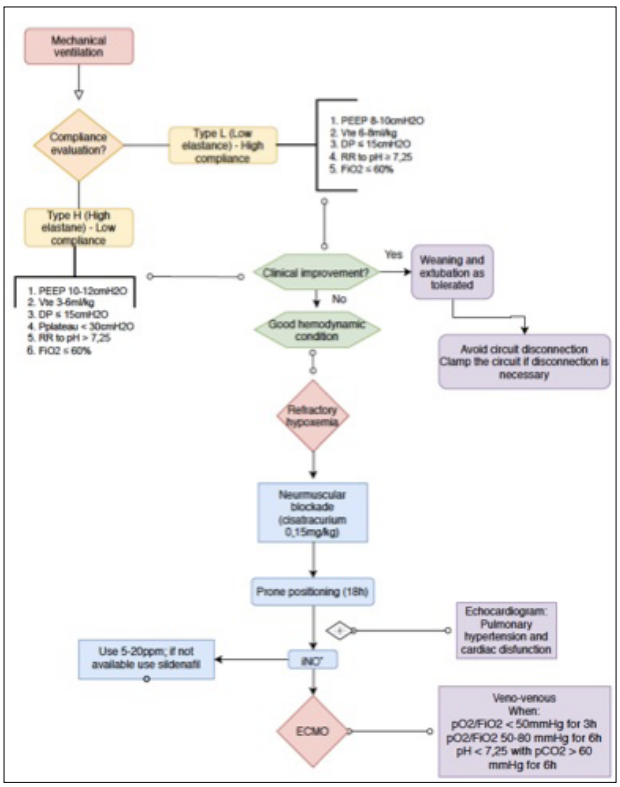



**FIGURE 3.** Mechanical ventilation management flowchart in critically ill pediatric patients

administration of sedation should only be considered after achieving adequate analgesia. As is the case with analgesia, bedside scales may be used to avoid deep sedation, prolonged ventilation, longer ICU and hospital stay, delirium, and weakness. The ESPNIC recommendation is the COMFORT Behavior scale (level A evidence). The COMFORT-B scale aggregates six behavioral parameters, in which 1 indicates deeper sedation and 5 more agitation for each parameter. Their sum should guide the titration of sedative drugs (<11: oversedation; 11-22: adequate sedation; >22: undersedation).[20,23,24] The choice of the ideal sedative agent is difficult and must take into account the pharmacology of the drugs and the different pathologies. The most frequently used sedatives in the pediatric ICU are benzodiazepines – midazolam. The initial use of the sedative drug must be after adequate analgesia in acute respiratory distress to help with patient management and avoid patient-ventilator asynchrony. However, it is still important to keep using scales to avoid unnecessary deep sedation, resulting in less delirium, shorter duration of mechanical ventilation, and improved mortality. [20,21,22]

With the use of continuous fentanyl and midazolam, it is important to consider the association of another drug. The emerging pediatric literature suggests the benefits of dexmedetomidine, an α-2 agonist, improving outcomes.[24] Dexmedetomidine has both analgesic and sedative effects, and, unlike other sedatives, does not depress the respiratory drive. Multiple clinical trials have demonstrated its efficacy and safety when used for longer-term sedation in the ICU. The 2018 PADIS guidelines recommend dexmedetomidine for sedation over benzodiazepines.[21,22] In cases associated with asthma, consider the association of ketamine with fentanyl and midazolam.

However, several management aspects of acute respiratory distress can make light-sedation strategies (as described) challenging, including low tidal volume ventilation, high positive end-expiratory pressure (PEEP), prone and lateral positioning, and the patient evolving with refractory hypoxemia. On this occasion, consider the need for deeper sedation associated with neuromuscular blockade (NMB). This strategy may help improve hypoxemia by decreasing inflammation, decreasing oxygen consumption, increasing alveolar recruitment, improving patient-ventilator synchrony, and improving oxygenation by preventing the contraction of respiratory muscles when cisatracurium is administered in the first 48 hours. [22,25,26] However, another study showed that among those who were treated with a higher PEEP strategy, the administration of continuous cisatracurium did not result in significantly lower mortality at 90 days.[27] Therefore, we recommend, in cases of refractory hypoxemia, to associate intermittent BNM, which can improve oxygenation with lower barotrauma and without ICU weakness. In view of all of the above, consider, if possible, the use of Bispectral Index (BIS) to titrate sedative doses within BNM infusion, to ensure an adequate level of sedation.[5,8,29]

## REFRACTORY HYPOXEMIA

A patient can be considered to have refractory hypoxemia when SpO2 < 90%, FiO2 > 60%, driving pressure > 15cmH2O, Pplateau > 30cmH2O, and pCO2 has no response to ventilation and dead space reduction. If they have some of those features we recommend using the following strategies:

- Prone position: It is known that prone position decreases the V/Q mismatch due to pulmonary shunting[14] and optimizes ventilation. We suggest a trial and, if there is good response (pO2 increases more than 20mmHg, SpO2 > 93%, improvement in EIT and ventilation), maintain

it for 18h with 6h intervals (if high workload, the patient can be kept in the prone position for up to 24h), and repeat if necessary. If the use of the prone position is not possible, the patient should be lateralized, keeping the more affected lung upwards.

- Nitric oxide: A potent pulmonary vasodilator, inhaled nitric oxide was used as rescue therapy in patients with refractory hypoxemia because it enhances pulmonary perfusion to areas with better ventilation; in the same way, it can be associated in patients with Sars-Cov-2 pulmonary thrombosis. It may show a transient improvement in PaO2/FiO2 ratio. We suggest an initial dosing of 5 parts per million (ppm) to 20ppm. If nitric oxide is not available, we suggest using sildenafil (0.5-2 mg/kg/dose, every 4-6 hours with a maximum of 20 mg/dose, every 8 hours).
- Recruitment maneuvers: We do not recommend the routine use of recruitment maneuvers. They can be performed if there is adequate monitoring, expertise, and clinical condition - we suggest a trial of step-by-step titration of PEEP. Beware of mechanical complications such as barotrauma and hemodynamic instability.
- High-frequency oscillatory ventilation (HFOV): We recommend against its use due to the risk of contamination of healthcare workers and other caregivers. It may be used in units with adequate isolation.
- Extracorporeal membrane oxygenation (ECMO): Consider veno-venous ECMO if in an experienced center, when the patient maintains pO2/FiO2 < 50 for 3h, or pO2/FiO2 50-80 for 6h, and pH < 7,25 with pCO2 > 60 for 6h, and when the patient doesn't meet the exclusion criteria (multiple organ dysfunction, severe neurologic dysfunction, palliative care).[30]

## WEANING/ EXTUBATION

Like it is with intubation, extubation is a critical moment in the care of critically ill patients with COVID-19. We recommend achieving very low ventilator settings before extubation (FiO2 < 30%, pressure support ≤ 10cmH2O and PEEP ≤ 7cmH2O). We also suggest performing a spontaneous breathing test (SBT) with a T-piece for better evaluation of successful extubation. It is also important to test gag reflex and other airway protection reflexes prior to extubation as there have been reports of re-intubation in patients with aspiration or excessive airway secretions, some of them even requiring bronchoscopy[31].

In pediatric patients, unplanned extubation is more frequent, so they should be closely monitored to minimize those events.

## CONCLUSION

Although some cases of Sars-CoV-2 may behave similarly to ARDS, they have different pathological findings and should not be treated as the same illness. In addition, not every approach is equal. Children appear to have milder cases, but there have been some reports of severe cases[32] that require mechanical ventilation. The suggested flowchart may contribute to the bedside management of severe pediatric cases of Sars-CoV-2 infection.

KEYWORDS: *Sars-CoV-2, pacientes graves, ventilação mecânica, suporte respiratório, crianças, adolescentes.*

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REVIEW ARTICLE

# What do we know about COVID-19? A review article

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## SUMMARY

OBJECTIVES: *To bring summarized information about what has been published so far regarding Covid-19, facilitating the access to information and a better understanding of this pandemic, and to contribute to the medical community in the decision-making against this virus.*

METHODS: *This review article brings collected information from different articles published since the beginning of the pandemic of the 2019 novel coronavirus.*

KEY RESULTS: *This paper aggregates and consolidates some epidemiological parameters and clinical knowledge about the novel coronavirus and brings what is new in the search for pandemic control.*

MAJOR CONCLUSIONS: *Governments and health authorities are under increased pressure to control the COVID-19 spreading. In this scenario, the scientific community is working hard to produce relevant papers which will help in the next steps against coronavirus. Our review summarized the latest news about SARS-CoV2, evidencing what we know about COVID-19 until now.*

KEYWORDS: *Coronavirus. Covid-19. Respiratory insufficiency. Pneumonia. Pandemics.*

## INTRODUCTION

The epidemic of the 2019 novel coronavirus (severe acute respiratory syndrome coronavirus 2 - SARS-CoV-2), which was first identified in Wuhan, a city in the Hubei province in China, is being exported to a growing number of countries. Early efforts were focused on describing the clinical course, counting severe cases, and treating the disease[1]. Covid-19 has spread rapidly and has been shown to have a wide spectrum of severity. The World Health Organization (WHO) has recently declared coronavirus disease 2019 (Covid-19) a public health emergency of international concern[2].

So far, according to the World Health Organization[3], COVID-19 has affected globally 1.210.956 individuals and accounted for over 67.594 deaths.

Since this is a new disease, the scientific community

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is engaged in new research that better explains the pathophysiology, diagnosis, clinical course, and treatment of coronavirus. Many works are published daily showing different outcomes of the disease, mainly regarding the symptoms and the treatment, which does not have one specific path so far, making it difficult to follow and understand the updates. This study will discuss information on what we know about Covid-19 so far to summarize and facilitate the access to information and a better understanding of this pandemic in order to contribute to the medical community in the decision-making and direct new studies on issues that remain limited about SARS-CoV2.

## MATERIALS AND METHODS

Our study brings whats is known about the coronavirus so far and aims to gather essential information to better understand this pandemic and help on the next steps that the scientific community must take. This is a review article that brings collected information from different articles published since the beginning of the epidemic of the 2019 novel coronavirus [Pubmed "covid-19"; "coronavirus"; "H1N1 infection"]. There were no date or language restrictions. Information was collected in cohort studies[4], case series[11], non-randomized clinical trials[1], review articles[7], and others. The search was for information about the epidemiology, rate of infection, hospital care, incubation period, signs and symptoms, risk factors, confounding factors, and current treatment. The majority of the data on COVID-19 come from Asia. The electronic databases were last searched on 06 April 2020. The main papers used are listed in Table 1.

## RESULTS

### Rate of Infection

At the beginning of the outbreak, an association between the origin of COVID- 19 and the wet animal market in Wuhan City, where live animals are routinely sold, was identified[19]. But after the progression of the virus, the person-to-person transmission became the most important way of transmission. It occurs primarily via direct contact or through droplets spread by the coughing or sneezing of an infected individual[19]. Recently, SARS-Cov-2 was isolated from feces of patients with Covid-19 by Chinese researchers, indicating the potential of fecal-oral transmission[24]. Moreover, a study detected a low prevalence of patients with positive results for SARS-CoV2 on RT-PCR in conjunctival swabs and suggested the possibility of transmission through the eyes[7]. Currently, there is no evidence for intrauterine vertical transmission of COVID-19[24].

Based on observations of data from the early outbreak in China, the trend of an increasing incidence largely follows exponential growth, and the mean basic reproduction number (R0) was estimated from 2.24 to 3.58[20].

The fraction of undocumented cases with mild, limited, or no symptoms is critical to the spread of coronavirus. Li et al.[25] estimated the prevalence and contagiousness of these undocumented cases with a mathematical model of simulation. They found that patients with no reported infection are half as contagious, per individual, as reported ones. However, 86.2% (95%CI: 81.5-89.8) of all infections were from undocumented cases. Their simulation predicted that 78.8% of reported infections should have been reduced without transmission from undocumented cases[25].

## INCUBATION PERIOD

The incubation period is critical to understand the infectiousness of COVID-19, its epidemic size, and the ideal time for the quarantine period. It is defined as the period between the day of infection and the illness onset. Linton et al.[15] found an average incubation period of 5.6 days (95%CI: 5.0,6.3) (n=158). Most infected people that present symptoms will do so within 12 days of the primary contact and the current period of active monitoring (14 days) is well supported by the evidence[26].

## SIGNS AND SYMPTOMS

The symptoms may vary, according to studies, due to different samples, the period of analysis of the patients, and subjectivity of data. However, this review enabled a satisfactory survey of the main signs and symptoms. The most common symptoms at the onset of illness, according to the case series analyzed and represented in Table 2, were fever, cough, myalgia, fatigue, sputum production, and dyspnea [Table 2]. Some patients had radiographic evidence of pneumonia with bilateral diffuse airspace opacities. Some of which needed supplemental oxygen too[6]. Less common symptoms included hemoptysis, abdominal pain, diarrhea, nausea, and vomiting[5]. Sore throat and nasal congestion occurred in only around 5-10% of patients[22].

**TABLE 1.** MAIN PUBLICATIONS USED IN THIS REVIEW.

| Study design | Author / Country | Title |
|---|---|---|
| Case Series | Mao, et al. (China) | Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: a retrospective case series study. |
| | Wang, et al. (China) | Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. |
| | Young, et al. (EUA) | Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. |
| | Wu, et al. (China. March 2020) | Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei Province, China. |
| | Bordi, et al. (Italia. February 2020) | Differential diagnosis of illness in patients under investigation for the novel coronavirus (SARS-CoV-2) |
| | Shen, et al. (China. March 2020) | Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. |
| | Yang, et al. (China, 2020) | Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): A multi-center study in Wenzhou city, Zhejiang, China. |
| | Liu, et al. (China, March 2020) | CT manifestations of coronavirus disease-2019: a retrospective analysis of 73 cases by disease severity. |
| | Huang, et al. (China) | Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China |
| | Wang, et al. (China) | The clinical dynamics of 18 cases of COVID-19 outside of Wuhan, China. |
| | Kong, et al. South Korea | Early Epidemiological and Clinical Characteristics of 28 Cases of Coronavirus Disease in South Korea. |
| Cohort | Linton, et al. (China. February 2020) | Incubation Period and Other Epidemiological Characteristics of 2019 Novel Coronavirus Infections with Right Truncation |
| | Guan, et al. | Clinical Characteristics of Coronavirus Disease 2019 in China. |
| | Wu, et al. (China. March 2020) | Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. |
| | Zhou, et al. (China) | Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. |
| Non-randomized Clinical Trial | Gautret, et al. (France. March 2020) | Hydroxychloroquine and Azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. |
| Review Article | Lipsitch, et al. (EUA. February 2020) | Defining the Epidemiology of Covid-19 — Studies Needed. |
| | Rothan, et al. (February 2020) | The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. |
| | Lai, et al (February 2020) | Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. |
| | Wu, et al (February 2020) | The SARS-CoV2 Outbreak: WhatsApp se know. International Journal of Infectious Diseases. |
| | Thomas-Rüddel, et al. (Germany. March 2020) | Coronavirus disease 2019 (COVID-19): update for anesthesiologists and intensivists March 2020. |
| | Chen, et al. (February 2020) | Convalescent plasma as a potential therapy for COVID-19. |
| | Jiang, et al. (March 2020) | Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). |

**TABLE 2.** MOST COMMON CLINICAL CHARACTERISTICS OF THE RESEARCHED STUDIES

| Author | Date (MM/YY) | N | N(%) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Fever | Cough | Myalgia | Fatigue | Sputum production | Dyspnea |
| Liu, KC [11] | 05/20 | 73 | 68 (93) | 60 (82) | - | 55 (75) | 39 (53) | - |
| Yang, W [12] | 04/20 | 149 | 114 (76.51) | 87 (58.39) | 5 (3.36) | - | 48 (31.21) | 2 (1.34) |
| Wang, L [13] | 03/20 | 18 | 16 (94.4) | 10 (55.6) | 2 (11.1) | - | - | 4 (22) |
| Wang, D [14] | 02/20 | 138 | 136 (98.6) | 82 (59.4) | 48 (34.8) | 96 (69.6) | - | 43 (31.2) |
| Kui, L [15] | 02/20 | 137 | 112 (81.8) | 66 (48.2) | 44 (32.1) | 44 (32.1) | - | - |
| Kong, I [16] | 02/20 | 28 | 9 (32.1) | 5 (17.9) | 4 (14.3) | - | 5 (17.9) | - |
| Huang, C [17] | 01/20 | 41 | 40 (98) | 31 (76) | 18 (44) | 18 (44) | 11 (28) | 22 (55) |

Neurological signs and symptoms were also described, such as headache, dizziness, impaired consciousness, ataxia, acute cerebrovascular disease, epilepsy, hypogeusia, and hyposmia[4]. Organ dysfunction and death can occur in severe cases[5].

Wu et al.[7] analyzed some confirmed or very suspected cases of COVID-19 to see what are the ocular manifestations and its relation with coronavirus disease. They concluded that 31.6% (95% CI: 17.5-48.7) of the patients had ocular abnormalities which are more

prevalent in severe (dyspnea, blood oxygen saturation of 93% or less) or critical cases (respiratory failure or shock or multiple organ dysfunction). The most common ocular symptoms were conjunctivitis, conjunctival hyperemia, epiphora, chemosis, and increased secretions. In addition, those patients had higher white blood cell, neutrophil, procalcitonin, C-reaction protein, and lactate dehydrogenase[7].

Laboratorial parameters may be useful to help the diagnosis, but the virus isolation and viral nucleic acid detection are the exams that confirm the infection. Other nonspecific parameters may be helpful, mainly in the early stage of the disease, like leukopenia, or a normal number of leukocytes with lymphopenia or increased monocytes[21]. A procalcitonin, C-reaction protein, or lactate dehydrogenase increase also appears in COVID-19 infection[7].

Image abnormalities could appear in COVID-19 infection and vary with age, underlying diseases, immunity, and stage of the infection at the moment of scanning. Some patterns at the chest X-ray or CT Scan are multiple small patchy shadows, interstitial changes, bilateral multiple ground-glass opacity, infiltrating shadows, and pulmonary consolidation[21].

## RISK FACTORS

Although most patients are thought to have a favorable prognosis, older ones and those with chronic underlying conditions may have worse outcomes[16].

A study in China reported the clinical characteristics and risk factors associated with developing acute respiratory distress syndrome (ARDS) after hospital admission and progression from ARDS to death in patients with COVID-19 pneumonia. The study shows that older age (≥65 years old), high fever (≥39 °C), comorbidities (eg, hypertension, diabetes), neutrophilia, lymphocytopenia, elevated end-organ related indices, elevated inflammation-related indices, and elevated coagulation function–related indicators were significantly associated with higher risks of unfavorable outcomes and the development of ARDS[16].

## HOSPITAL CARE X INTENSIVE CARE UNIT

In a study from China, they obtained data regarding clinical symptoms and outcomes for 1099 patients. A primary outcome event occurred in 67 patients (6.1%), including 5.0% who were admitted to the intensive care unit (ICU), 2.3% who underwent invasive mechanical ventilation, and 1.4% who died[2].

In another observational study in China with 158 patients, they found that the average time from illness onset to hospital admission was different for living and deceased cases, the former was estimated at 3.3 days (95%CI:2.7,4.0) and the latter was 6.5 days (95%CI:5.2,8.0)[15]. The mean time from hospitalization to death was 8.8 days (95%CI:7.2,10.8)[15].

## MORTALITY

Studies conducted with Chinese patients showed a mortality rate (the number of reported deaths divided by the reported cases) of 3.6%[28]. According to the WHO data until 06 March 2020, the rate is also between 3-4%[29]. A retrospective cohort with 191 patients found that older age, higher Sequential Organ Failure Assessment (SOFA) score, and d-dimer greater than 1um/mL at admission were associated with higher in-hospital death risk[17].

However, those estimated mortality rates are not representative of the actual death rate because the actual number of infected patients could not be identified. Not all cases are tested, including most asymptomatic ones or patients with very mild symptoms. Therefore, the mortality rate is probably overestimated[18].

## CONFOUNDING FACTORS - DIFFERENTIAL DIAGNOSIS

The infection by SARS-CoV-2 causes many nonspecific symptoms that are shared by other infectious diseases of the respiratory tract, like influenza, parainfluenza virus, adenovirus, respiratory syncytial virus, rhinovirus, and others previously-known human coronaviruses. The diagnosis cannot be definitively made without microbiologic testing[8,21].

## CURRENT TREATMENT

Until this moment, there are no specific antiviral drugs or vaccines against the COVID-19 infection for potential therapy in humans. One of the options available is the use of broad-spectrum antiviral drugs like nucleoside analogs and HIV-protease inhibitors, which could attenuate virus infection[19].

A great deal of effort has been made to find effective drugs against the virus in China. The State Council of China held a news briefing indicating that chloroquine

phosphate (CQ) and hydroxychloroquine sulfate (HCQ), old drugs used for the treatment of malaria, had demonstrated efficacy and acceptable safety in treating COVID-19-associated pneumonia in multicenter clinical trials conducted in China[30]. The oral absorption of both drugs in humans is very efficient. As in the case of SARS-CoV, the virus transport of SARS-CoV2 from endosomes to endolysosome appears to be a requirement to release the viral genome, and both CQ and HCQ have been able to block it. The anti-SARS-CoV2 activity seems to be more potent with CQ; however, HCQ has been shown to be much less toxic than it. Until now, the inhibition of SARS-CoV2 in vitro has been efficient with HCQ using a safe dosage but this awaits confirmation by clinical trials[31].

Gautret and collaborators conducted an open-label non-randomized clinical trial to investigate the effect of HCQ and Azithromycin in virological clearance, clinical follow-up, and occurrence of side-effects in patients with COVID-19 infection. In this study, 26 patients received HCQ (200mg three times per day for ten days) and 16 were the control group. Among the patients treated with HCQ, six received Azithromycin (500mg on day 1, followed by 250mg per day, for the next four days). The results were very promising; at day 6 post-inclusion, the group treated with both drugs had 100% of virological cure compared with 57,1% of patients treated with HCQ only, and 12,5% with no drugs. Further works are needed to investigate these effects with a greater sample and a longer follow up, but also to investigate potential side effects (QT prolongation, ventricular arrhythmia, and retinopathy)[18].

The convalescent plasma containing neutralizing antibodies or immunoglobulins has been used as a last resource to improve the clinical conditions of patients with ARDS. Moreover, studies have shown a shorter hospital stay and lower mortality in patients treated with convalescent plasma than in those who were not treated with it[9,23].

An effective treatment is an urgent need to treat symptomatic cases and decrease the transmission of coronavirus in the community by reducing the virus carriage[18].

## PUBLIC HEALTH AND ECONOMIC IMPACTS

In the absence of a Covid-19 vaccine or proven and safe treatment, our better protection against coronavirus is social isolation. This measure aims to decrease contact rates in the population in order to reduce the transmission of the virus. Quarantine brings enormous social and economic costs in the short, mid, or long-term[32].

Many countries made hard decisions to control this epidemic. China locked down whole cities, Italy imposed severe restrictions on the population, and the United States subjected part of the country to quarantine and part to a recommended "self-quarantine" and banned non-US nationals from entering the country[33].

## DISCUSSION

Knowledge about the 2019 novel coronavirus remains limited, but we need to learn and collect quality information about this clinical threat to deal and respond to the consequences of the pandemic.

The infection by COVID-19 is gradually being elucidated by the scientific community, contributing to new steps towards the control of the disease and the search for its treatment. According to this study review, coronavirus has an infection rate (R0) that varies between 2 and 3 people and an incubation period of around 5.6 days. This information is essential for the development of preventive measures and epidemiological simulations.

It is important to highlight that the rate of infection and death are very different within the countries. This might be caused because each country followed different protocols. Some with early person-to-person isolation, others with vertical isolation, and others with no isolation. Another possible cause of this huge difference in the infection and death rates are the capability of each country to test their individuals. While some are testing all individuals at risk, others have no epidemiologic, economic, and political condition to do the same, thus causing unreliable data and underreporting of the disease in most countries.

The disease presents, in most cases, with fever, cough, myalgia, fatigue, and dyspnea, but it has a wide spectrum of severity, which can cause respiratory failure and require ICU admission for advanced ventilatory support. Knowing the natural history of the disease is essential to think about possible treatments and prepare the health system in the most appropriate way, such as increasing ICU beds and respirators.

As most studies in the literature are quite recent and use different methodologies, this review aims to facilitate the dissemination of knowledge among

scientists and health care professionals through clear data and information.

The most effective way to prevent the disease so far is social isolation, which aims to reduce the rate of disease transmission. However, this decision also leads to economic issues and we must not be blind to these effects of the pandemic. Countries with major economic influence in the world are stopping all activities for at least 14 days. This may increase the unemployment rate and the indebtedness of the countries.

## LIMITATIONS OF THE STUDY

Our study has some limitations because different types of studies were analyzed (observational, experimental, review articles, clinical trials) but most of the information was consistent between them. Another limitation is the short review time for these papers, considering the urgent need for the infection diagnosis, treatment, and pathogenesis.

## CONCLUSION

During a pandemic, scientific knowledge advances in an accelerated way. In the race for rapid epidemic control, every minute is important and discoveries cannot be delayed. Governments and health authorities are under increased pressure to control the COVID-19 spreading. In this scenario, the scientific community is working hard to produce relevant papers which will help in the next steps against the coronavirus. Our review summarized clearly the latest news about SARS-CoV2, evidencing what we know about COVID-19 until now. Further studies are needed to fill the existing gaps in this epidemic knowledge.

### Conflict of interest

The authors declare no conflicts of interest.

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### Authors Contribuition

All authors have made substantial contributions to this work. Júlia Vieira, Olívia Ricardo, and Carolina Hannas conducted the data analysis and writing. Fábio Kanadani, Tereza Kanadani, and Tiago Prata drafted and revised the paper. All authors have seen and approved the manuscript and contributed significantly to the work.

RESUMO

OBJETIVOS: *Trazer de forma resumida as informações que têm sido publicadas sobre o novo coronavírus, facilitando o acesso à informação e o melhor entendimento dessa pandemia, como também contribuir para a comunidade médica nas decisões para conter o vírus.*

METODOLOGIA: *Este artigo de revisão coletou informações de diferentes artigos publicados desde o início da pandemia do novo coronavírus.*

RESULTADOS: *Este artigo consolida alguns parâmetros clínicos e epidemiológicos do novo coronavírus e traz o que tem de novo no controle da pandemia.*

CONCLUSÃO: *Os governos e autoridades de saúde estão sob pressão constante para conter o alastramento do coronavírus. Nesse cenário, a comunidade científica tem trabalhado e produzido muitos estudos e artigos que têm ajudado a guiar os próximos passos na contenção dessa pandemia. Nossa revisão faz um compilado dos últimos artigos e estudos, trazendo o que sabemos até então sobre a Covid-19.*

PALAVRAS-CHAVE: *Coronavírus. Covid-19. Insuficiência respiratória. Pneumonia. Pandemias.*

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REVIEW ARTICLE

# Guidance on breastfeeding during the Covid-19 pandemic

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## SUMMARY

OBJECTIVE: *These recommendations aim to provide guidance on breastfeeding for mothers with suspected or confirmed Covid-19.*

METHODS: *We performed a review of the recent medical literature on breastfeeding mothers with suspected or confirmed Covid-19, focusing on the neonatal period.*

RESULTS: *We analyzed 20 recent publications on breastfeeding, Covid-19, and its transmission through breastmilk. We presented possible options for breastfeeding and their consequences for the mother and the child.*

CONCLUSION: *All maternal decisions in relation to breastfeeding are justifiable since the infection by Covid-19 is still poorly known. However, puerperal women and their families must be very well informed to make a conscious choice based on the information available in the literature so far.*

KEYWORDS: *Infant, newborn. Breastfeeding. Neonatology. Coronavirus. COVID-19.*

## INTRODUCTION

The impact of infections by the new coronavirus (Covid-19) has been increasing rapidly as the pandemic spreads and the number of patients affected grows exponentially.

The repercussions of this infection for pregnant women and newborns (NB) are still not well known, with sparse scientific evidence about its behavior in mothers and children. Reports and case series from the first epicenter of the epidemic, China, suggest that, unlike other infections caused by coronaviruses and the H1N1 virus, the effect in pregnant women is similar to that of adults of the same age group[1-3]. There is no evidence of greater clinical severity during pregnancy, nor of a higher prevalence of obstetric complications in patients infected by Covid-19[3-5]. A study that included nine patients with pneumonia caused by Covid-19 did not find the presence of the virus in samples of six patients, collected from amniotic liquid, blood from the umbilical cord, breastmilk, and oropharynx swab of the NB[3]. Thus, the existing data

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so far, although not very solid from a scientific point of view, suggest that the main route of transmission of Covid-19 to neonates is by infected droplets from caregivers or, secondarily, through contact with contaminated biological material. The vertical mother-fetus transmission seems to be possible but is not documented, neither seems to be frequent. Zeng et al.[6] reported 33 newborns of mothers infected by Covid-19 who showed mild to moderate signs and symptoms of early neonatal infection. Three of these NB presented molecular tests positive for Covid-19, and the authors questioned the existence of possible vertical transmission of the virus since all measures recommended for infection control were adopted. However, the samples of amniotic fluid, umbilical cord blood, and breastmilk did not show the presence of the virus.

In the face of the existing evidence so far, the concerns regarding the care of newborns whose mother have a suspected or proven infection by Covid-19 is focused on two aspects: 1) avoiding the infection of NB after birth, and 2) avoiding the infection of health professionals present in the delivery room and neonatal unit[1,2].

On the other hand, the Chinese consensus is contrary to the evidence available; they have affirmed the possibility of vertical transmission of the new coronavirus and through breastmilk; for this reason, they recommend separating the mother and child and interrupting breastfeeding, even in suspected cases. In their publications, they advise that breastfeeding and/or extraction of breast milk are allowed only in the case of a negative PCR test for Covid-19 in the mother and breastmilk[4]. Thus, if these tests are not negative, the NB should be fed with breastmilk from a donor and/or formula.

## PROTOCOLS AVAILABLE FOR GUIDANCE ON BREASTFEEDING FOR MOTHERS WITH SUSPECTED OR CONFIRMED COVID-19

Two reviews, one by the North-American Centers for Disease Control and Prevention[7] and another by the Royal College of Obstetricians and Gynaecologists, London[8], concluded that if the mother is willing and in clinical conditions to breastfeed her child, she must be well-informed and agree with the preventive measures necessary. The initiation and continuation of breastfeeding must be determined by the puerperal woman, along with their families and health professionals.

Recently, Eidelman A. made a contribution along the same line, stating that: "given the fact that mothers infected with the coronavirus have probably already colonized their babies, and ongoing breastfeeding has the potential to transmit protective maternal antibodies to infants through breastmilk. Therefore, breastfeeding should continue with the mother carefully washing her hands and wearing a mask during the procedure in order to minimize the NB's additional viral exposure"[9].

Based on the evidence available and the recommendations listed above, the Brazilian Federation of the Gynecology and Obstetrics Associations (Febrasgo) published a note highlighting that the benefits of breastfeeding outweigh any potential risks of virus transmission through breast milk[10]. Therefore, they recommended that women infected by Covid-19 who wish to breastfeed should be encouraged to do so[10].

The World Health Organization (WHO)[11], the Ministry of Health[12,13], the Secretary of Health of the State of São Paulo[14], the Brazilian and Global Network of Human Milk Banks[15], the Pediatrics Society of São Paulo[16,17], the Brazilian Society of Pediatrics[1,2], and the American Academy of Pediatrics[18], considering that mothers infected with the new coronavirus have probably already colonized their children, the benefits of breastfeeding for the health of the child and women[19], and the absence of scientific evidence on the transmission of Covid-19[3] and other respiratory viruses[7] through breastfeeding, recommend that breastfeeding is maintained with the necessary precautions in case of infection by Covid-19; this guidance is valid only if the mother wishes to breastfeed her child and is in clinical conditions to do so. Skin-to-skin contact in the delivery room and breastfeeding within the first hour of life should be suspended. Puerperal women and their NBs can stay in the same room, provided they are asymptomatic, there is a distance of 2 meters between the maternal bed and the NB cradle, and all the safety precautions described below are observed[12-14]. If the woman does not feel safe to breastfeed while infected, it is recommended that their milk is extracted and offered to the child.

It is recommended, therefore, that the precautions ahead are followed since an infected mother can pass the virus through respiratory droplets when in contact with the child, including during breastfeeding:[7,12-15]

- Washing hands for at least 20 seconds before touching the baby or extracting breastmilk (manual extraction or by pump).

- Wearing a face mask (completely covering the nose and mouth) and avoiding talking or coughing during breastfeeding.
- Immediately changing masks in case of coughing or sneezing, or at every feeding.
- In the case of manual or mechanical extraction of human milk, strictly observe the guidelines available in the document: http://bvsms.saude.gov.br/bvs/publicacoes/cartilha_mulher_trabalhadoraamamenta.pdf. If possible, ask for help from a trained professional of the Human Milk Bank.
- Strictly follow the recommendations for cleaning the pumps for milk extraction after each use according to the manufacturer's specifications.
- Consider the possibility of asking for help from someone who is healthy to feed the newborn with the breastmilk using a cup or spoon.
- It is necessary that the person who will feed the NB with breastmilk learns how to do this with the help of a healthcare professional.

## CONSEQUENCES OF MATERNAL CHOICES IN RELATION TO BREASTFEEDING

As described above, mothers with suspected or confirmed Covid-19 may, after receiving all necessary information, choose to breastfeed their NBs, extract the breast milk and ask a professional or healthy companion to feed it to the NB, or even not to feed the child breastmilk. Whatever the choice, it should be respected without reprimands. Puerperal women are often going through a very difficult time, fragile, afraid of their diagnosis, and the consequences it might ensue. They will always choose what they think is best for their child. Thus, their choice reflects their state of mind and should be heeded, whatever it is.

### A. Option for starting and maintaining breastfeeding

This is a WHO recommendation[11], which must be respected provided the mother and NB are in good clinical conditions. The mother should be encouraged to breastfeed her child, always complying with the protection standards described above; it is essential she receives all the support and guidance necessary from the multi-professional team, including regarding mental health, in this particularly difficult time. The presence of a healthy companion is allowed, but must not of visitors; this tends to be a cause of sorrow for the mother because she is not able to share her happiness and worries with other family members.

Breastfeeding protects against morbidity and mortality in the neonatal and post-neonatal periods, as well as throughout childhood. Its benefits extend also to adolescence and adulthood and include the prevention of dental malocclusion, overweight and obesity, allergic and chronic diseases. It also favors the bond between mother and child, provides higher intellectual coefficients, and greater professional success, with higher monthly incomes in the future[11,18-20].

Regarding immunological protection, its effect is particularly important against infectious diseases that benefit from the direct transfer of antibodies and other anti-infectious factors, favoring also the lasting transfer of immunologic competence and memory[11,19].

We must not forget, also, of the protection conferred by breastfeeding to the maternal health, providing less postpartum bleeding, aiding in the reduction of weight gained during the pregnancy, reducing the risk of breast and ovarian cancer, diabetes type 2, and postpartum depression. Exclusive breastfeeding also provides a contraceptive effect which assists in the spacing between pregnancies, even when no other method is used for such purposes[19,20].

The contact between mother and child during breastfeeding will certainly benefit her from an emotional point of view, providing the necessary support to cope with this difficult period of quarantine and social isolation. The mother should be well-informed about the absence of data, so far, that proves vertical transmission and infection through breast milk[3,6]. On the other hand, there are reports of cases in which the NB contracted the disease, usually with a not severe presentation, through respiratory droplets from the mother or health professionals; hence the importance of, at all times, complying with the protection practices during the period of viral transmissibility[3-6].

### B. Option for not breastfeeding and extracting breastmilk

Women who are not in good clinical conditions or who do not feel safe to maintain direct contact with their child should opt for the extraction of breastmilk and get help from a trained professional to feed the NB using a cup or spoon or instruct a healthy companion on how to do so. The extraction of milk should also be an option when the NB is premature, or even when they are not in clinical conditions that allow sharing the same room.

The raw milk must be extracted in an isolated room, preferably with the aid of a trained professional of the Human Milk Bank (HMB), and can be stored for up to 12 hours in the refrigerator. The milk extracted from mothers with a suspected or confirmed Covid-19 infection should not be kept inside the HMB; the fridge must be located outside and exclusive, although there is no evidence of viral excretion in breast milk.

It is important that mothers are aware of the importance of providing their milk to the NB, and professionals should inform them of all the benefits listed above. It is also recommended that the mother be informed of the frequency of extraction, i.e., four to six times a day or more, to maintain milk production until the end of isolation[12-15].

## OPTION FOR NOT BREASTFEEDING AND NOT EXTRACTING BREASTMILK

Women may fear transmitting the virus to the NB, both by contact and through breastmilk; they also may not yet be in clinical conditions to breastfeed or extract their milk. In this situation, they will be separated from their child, who will not be offered their milk during the period of isolation. Such an option, if maintained after clarification by professionals, should be respected.

As reported above, the Chinese consensus is to separate the mother from the child and interrupt breastfeeding, even in suspect cases. Breastfeeding and/or the extraction of breast milk are allowed only in the case of negative PCR tests for Covid-19 in the mother and breastmilk[4]. Thus, if these tests are not negative, the NB should be fed with breastmilk from a donor and/or formula. In Brasil, according to the protocols described above, the recommendation is different, but the will of the mother is paramount and must be accepted.

Once again it is recommended to inform the mother on the frequency of at least four to six daily extractions to maintain the milk production until the cure of the infectious process; this milk will, unfortunately, be discarded[15].

The NB will be separated from the mother and, during the period recommended, will be preferably supplied with breast milk from a healthy donor. A bottle should not be used for the administration of milk, if possible, so that there is the possibility of resuming breastfeeding after the isolation period; the use of a cup or spoon is recommended. A nasogastric tube is used in premature NBs (with gestational age less than 34 weeks) or with respiratory insufficiency. It is known that the donor milk can only be offered to the NB after pasteurization; although this process maintains the nutritional value of the milk, it reduces its immunological properties by about 30% to 40%. Regarding its nutritional components, only lipase and some thermolabile vitamins are inactivated in pasteurized milk[15,18].

We must highlight here the importance of Human Milk Banks. In Brasil, there are approximately 225 Human Milk Banks and 212 Units of Human Milk Collection, which provide donor milk for NBs who do not receive milk from their own mothers. These numbers are growing because the Brazilian Network, which served as a basis for the implementation of the Global Network of Human Milk Banks, is very active and recognized at a world level (https://rblh.fiocruz.br)[15]. We are in the final stage of implementing a Human Milk Bank in the Neonatal Center of the Children's Institute of Hospital das Clínicas and the Faculty of Medicine of the University of São Paulo, which is likely to become a reference in Brasil and abroad. The project should be completed shortly, by the end of 2020.

The offer of the pasteurized donor milk is a valid option in the situations mentioned above, much better than the administration of formula. This features nutritional elements that are not always suitable for the nutrition of NB, proteins that form bigger curds of difficult digestion and provide immunological factors[19]. There is also the possibility of, after a single ingestion of formula, the NB developing cow's milk protein allergy. We also have to consider the cost of the product, often inaccessible for Brazilians with low purchasing power and difficulty to work in the current scenario we are going through[20].

There is the possibility of weaning if the precautions mentioned above are not taken. Milk production may decrease gradually if the frequency of extraction is not maintained; the NB may become accustomed to the bottle nipple and, thus, refuse the mother's breast when breastfeeding is attempted. Walters et al.[20], in 2019, published an article that describes the billionaire costs of not breastfeeding. The research was conducted for six years, in more than 100 countries. The absence of breastfeeding and the interruption of exclusive breastfeeding in the first six months led to, according to their calculations, the loss of 341.3 billion dollars annually due to childhood

diseases and deaths, loss of productivity by early mortality, cognitive loss in children who were not breastfed, maternal deaths due to diabetes, breast cancer, and ovarian cancer. We should also include the thousands of cases of childhood obesity, which also increase morbidity and mortality. The authors completed the study by stating that "the human and financial costs of not breastfeeding highlight the importance of fostering a culture that supports breastfeeding at a global scale."

Considering everything that has been exposed, it can be concluded that all the options regarding breastfeeding are justifiable since the infection by Covid-19 is still very new and little known. However, puerperal women and their families must be very well informed to make a conscious choice based on the information available in the literature so far.

## Author contributions

All authors contributed equally to this study.


### RESUMO

OBJETIVO: *Estas recomendações têm como objetivo orientar o aleitamento materno de mães com Covid-19 suspeita ou confirmada.*

MÉTODO: *Foi realizada revisão da literatura médica recente sobre aleitamento materno de mães com Covid-19 suspeita ou confirmada, focando o período neonatal.*

RESULTADOS: *Foram analisadas 20 publicações recentes sobre aleitamento materno, Covid-19 e sua transmissão pelo leite. Foram apresentadas as possíveis opções maternas em relação ao aleitamento e suas consequências para o binômio mãe-filho.*

CONCLUSÃO: *Todas as opções maternas em relação à amamentação são justificáveis, porque a infecção por Covid-19 ainda é pouco conhecida. Porém, as puérperas e seus familiares devem ser muito bem orientados, realizando uma opção consciente e baseada nas informações disponíveis na literatura até o momento.*


PALAVRAS-CHAVE: *Recém-nascido. Aleitamento materno. Coronavírus. Neonatologia. Covid-19.*

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REVIEW ARTICLE

# Sars-CoV-2: A clinical update - II

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## SUMMARY

INTRODUCTION: *A covid-19 pandemic decreed by WHO has raised greater awareness of it.*

EPIDEMIOLOGY: *The infection, reached the mark of 2,000,000 patients in 33 countries and caused the risk of the presence of comorbidities and advanced age.*

TRANSMISSIBILITY: *The transmissibility calculated so far is similar to the H1N1 epidemic, but with lower mortality rates.*

PHYSIOPATHOLOGY: *The SARS-CoV-2 virus, of the Coronaviridae family, has the capacity for cellular invasion through the angiotensin-converting enzyme 2 does not have a lower respiratory epithelium and in the cells of the small intestine mucosa.*

CLINICAL MANIFESTATIONS: *a presentation can be divided into mild (fever, fatigue, cough, myalgia, and sputum) and severe (cyanosis, dyspnoea, tachypnea, chest pain, hypoxemia and need for clinical measurement) and has an estimated estimate of 2%.*

DIAGNOSIS: *allows the detection of viral load in CRP-TR of patients with high clinical suspicion.*

TREATMENT: *based on supportive measures and infection control. In severe cases, the use of medications such as hydroxychloroquine and azithromycin or medication can be promising. Take care to avoid the use of corticosteroids. There are no restrictions on the use of resources and IECAs / BRAs.*

KEYWORDS: *Public health. Coronavirus. COVID-19. Pandemics. Respiratory tract infections. Review.*

## INTRODUCTION

Originally discovered in poultry in the 1930s, several coronaviruses cause respiratory, gastrointestinal, liver, and neurological disease in animals. Only seven coronaviruses are known to cause disease in humans. Four of these (229E, OC43, NL63, and HUK1) more often cause symptoms of a common cold. On rare occasions, there may be a severe infection of the lower respiratory tract, such as pneumonia, especially in children, the elderly, and immunocompromised patients[1].

The three coronaviruses that cause the most severe respiratory infections in humans, sometimes even fatal, are considered zoonoses and are described below:

- Sars-CoV-2 is the new betacoronavirus identified on 31/12/2019 as the etiological agent of the disease caused by coronavirus 2019 (Covid-19) described in Wuhan, China.
- Mers-Cov was identified in 2012 as the cause of the Middle East Respiratory Syndrome (Mers).

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- Sars-CoV was identified in 2002 as the cause of an outbreak of Severe Acute Respiratory Syndrome (Sars).

It is believed that Covid-19 (Sars-CoV-2) originated in Chiroptera mammals (bats), since they have been reported to a local animal trade in Wuhan, and due to its close genetic similarity to infectious coronavirus in this genre[1].

## EPIDEMIOLOGY AND RISK FACTORS

Only 71 days after the discovery of Covid-19 (and 59 days from its genetic sequencing), on 11/03/2020 The World Health Organization declared a pandemic. Thirty-five countries have already registered Covid-19 cases, totaling at least 2 million cases and 115,000 deaths to the date this article was updated. A large global economic impact has been estimated due to the saturation of health systems and quarantine state, with an expected GDP recession of 30% in the most affected quarter in the US[3]. Due to the extreme current relevance of the infection and its extension, the writing of this review became necessary to provide medical knowledge and guide the conduct of recently-graduated doctors and others engaged in the fight against this pandemic.

The average age of infected individuals ranges between 49 and 56 years, and the conditions in rare in individuals younger than 20 years (children, in general, are asymptomatic)[4]. Severity increases with age, and the mean age of deaths in Italy (the second epicenter of the pandemic) is 79.5 years.

Among the known risk factors for severe symptomatic presentation are cardiovascular (hypertension) and pulmonary (smoking, asthma) comorbidities and advanced age (over 60 years)[4].

## TRANSMISSIBILITY

Transmissibility is mainly by droplets - close interpersonal contact (less than 2 meters - 6 feet, for a prolonged time) - and fomites[4]. Studies in the USA with 445 contacts of infected individuals found a rate of social contagion of 0.45%. Fecal-oral transmission is possible (due to the presence of ACE2 in the gastrointestinal tract and presence of positive RT-PCR in stool samples), however, it has yet to be documented[5,6]. There have been reports of intrauterine vertical transmission in the third quarter, with an asymptomatic newborn with increased cytokines and positive IgM[7].

A very important quantification of viral transmissibility is the basic reproduction number, which is usually denoted by $R_0$ (pronounced "R-naught"). The epidemiological definition of $R_0$ is the average number of people who contract a disease from a contagious person. It applies specifically to a population of people who previously were free of infection and were not vaccinated. There are three possibilities for the potential spread or decline of disease, depending on the value of $R_0$:

- If $R_0$ is less than 1, each existing infection generates less than 1 new infection. In this case, the disease will decrease and eventually disappear.
- If $R_0$ is equal to 1, the disease will remain alive, but there will be no epidemic.
- If $R_0$ is greater than 1, the cases will grow exponentially and cause an epidemic or even a pandemic.

As far as we currently know, the $R_0$ value calculated for 2019-nCoV is significantly greater than 1. The preliminary estimate of a 1.4-2.5 $R_0$ was presented on the WHO declaration about the 2019-nCoV outbreak on January 23, 2020. Studies had estimated the average $R_0$ for 2019-nCoV in the initial stage of the outbreak ranging from 3.3 to 5.5 (likely lower than 5, but above 3 with increased rate), which was slightly higher than those of Sars-CoV ($R_0$: 2-5), indicating that 72-75% of transmissions must be avoided to stop the growing trend. In contrast, previous studies had suggested that the $R_0$ for Mers-CoV is less than 1, which means that it is unlikely to cause a pandemic. Super-spreading events have been implicated in the transmission of 2019-nCoV, as was the case with Sars-CoV and Mers-CoV, but its relative importance remains unclear and it is difficult to trace the super-spreaders[1]. In addition, $R_0$ can change seasonally according to climate or annual gatherings[1].

Transmissibility seems to be reduced in hot and humid climates[8].

## PHYSIOPATHOLOGY

Although the reservoir of SARS-CoV-2 animals main remains unknown for a long time, what we have learned so far is that the genomic characterization of the SARS-CoV-2 has shown phylogenetic distance from the coronaviruses previously identified as causes of human diseases; it shared only 79% and 50% of its identity with SARS-CoV and Mers-CoV, respectively.

**TABLE 1.** COMPARISON BETWEEN THE MAJOR CURRENT CONTAGIOUS DISEASES AND COVID-19 REGARDING MORTALITY AND $R_0$ Chen[1].

| Virus | Fatal Cases (%) | Transmissibility (R) |
|---|---|---|
| Covid-19 | 3 | 1.4 - 5.5 |
| Sars-CoV | 10 | 2 - 5 |
| Mers-CoV | 40 | <1 |
| Avian H7N9 (2013) | 40 | <1 |
| H1N1 (2009) | 0.03 | 1.2 - 1.6 |
| H1N1 (1918) | 3 | 1.4 - 3.8 |
| Rhinovirus | <0.01 | 6 |
| Ebola | 70 | 1.5 - 2.5 |
| Smallpox | 17 | 5 - 7 |
| Measles | 0.3 | 12 - 18 |
| HIV | 80 | 2 - 4 |

Despite these differences, several studies have reported that SARS-CoV-2 explores the same angiotensin-converting enzyme 2 (ACE2) as Sars-CoV to obtain access to its target cells but it presents more binding affinity. It is known that the two main types of ACE can be found in the lung epithelium, and ACE is classically related to the conversion of angiotensin I into angiotensin II, whose effects are vasoconstriction and cardiac remodeling. ECA2, however, is a membrane-bound carboxypeptidase that cleaves a single residue of angiotensin I (Ang I), generating Ang 1-9, and a single residue of angiotensin II (Ang II) to generate Ang 1–7, whose functional effects of vasodilation, antiproliferation, and antifibrotic oppose those of the Ang II generated by the angiotensin-converting enzyme (ACE). It is known that, by inhibiting ACE (with ACE and ARB antihypertensive drugs), the number of ECA2 in the renal epithelium membrane and in the heart increases, with a theoretical potential of increase in other tissues, increasing infectivity and predisposing to a more serious disease (considering that most critically ill Covid-19 patients were hypertensive, and most hypertensive patients are treated with an angiotensin-converting enzyme inhibitor - ACEI or angiotensin receptor blockers - ARB). The presence of cardiomyopathy due to Covid-19 has been demonstrated, with a heart failure prevalence rate in critically ill patients above 40% [9].

A recent study showed that ACE2 is highly expressed in the mouth and tongue, to facilitate the virus entry into the host. In normal human lungs, ACE2 is expressed in the lower lungs in type I and II alveolar epithelial cells. After infection, the entry of Sars-CoV-2 begins with the binding of the peak glycoprotein expressed in the viral envelope for ACE2 on the alveolar surface. The binding of Sars-CoV-2 to ACE2 stimulates the clathrin-dependent endocytosis of the entire Sars-CoV-2 and ACE2 complex, inducing fusion in the cell membrane The entry of Sars-CoV-2 endosomal cells is facilitated by endosomal cathepsins, cysteine endosomal proteases of low pH[10].

Once inside the cells, Sars-CoV-2 explores the endogenous transcriptional mechanism of alveolar cells to replicate and spread throughout the lung Given the critical role of Sars-CoV-2's acid endosomal pH in its processing and internalization, it has been suggested that the antimalarial drug chloroquine could have a potent antiviral effect due to its ability to increase the endosomal pH. From within the cells, chloroquine quickly becomes protonated and is concentrated in the endosomes. The positive charge of chloroquine increases the pH of the organelle by revoking the virus-endosome fusion, ultimately inhibiting the infection. In addition to chloroquine, hydroxychloroquine was considered as a possible candidate for treatment trials in the short term[11]. In addition, amiodarone has also been suggested as a possible inhibitor of the Sars coronavirus, which spreads due to its ability to interfere in the endocytic pathway[12].

When Sars-CoV-2 infects most ciliated cells in the alveoli. When the normal activity of these cells, which consists of clearing the airways, is disturbed, there is a consequent progressive accumulation of debris and fluid in the lungs and acute respiratory distress syndrome (ARDS)[13]. There is the possibility of bacterial superinfection, given the aforementioned pathophysiology and the biphasic clinical scenario (evolution to ARDS after 5-8 days of illness).

Since it has been demonstrated that the ACE2-binding affinity is the main determinant of Sars-CoV-2 infectivity, experiments have been carried out at the atomic resolution level of the virus-receptor interaction to identify the precise glycoprotein receptor-binding domain (RBD) of the peak glycoprotein in the viral envelope involved in the Sars-CoV-2 interaction with ACE2. In this study, the author found that the Sars-CoV-2 RBD sequence is similar to that of Sars-CoV, further confirming the hypothesis that ACE2 is the entry receptor for Sars-CoV-2[10,12]. Notably, it has also been found that the Sars-CoV-2 RBD features a unique mutation that significantly increases its affinity to ACE2 binding, suggesting that Sars-CoV-2 may have evolved with a greater ability to infect and spread among humans

Although the potential of the aforementioned ACE inhibitors enable a severe clinical picture, in vitro

studies suggest that the increase of ACE2 attenuates the lung injury caused by Covid-19 infections[10,13]. There are two main theories for this finding:

- First, the entry of Sars-CoV-2 into the target cells is a regulated, multi-step process, of which ECA2 binding is only the initial step. In fact, TMPRSS2 is an essential serine protease necessary for the glycoprotein peak initiated after the ACE2 binding. The increased expression of ACE2 by ARB could induce the sequestration of Sars-CoV-2 in the cell membrane, which, however, may not be parallel to an increase in TMPRSS2, thus limiting the viral infection If that is the case, the TMPRSS2 inhibitor, camostat mesylate, which has been approved for some forms of cancer and hepatitis, can be a valuable treatment option to block various entry routes for Sars-CoV-2. In addition, membrane-bound ACE2 is processed by the metalloproteinase ADAM17, which cleaves the ACE2 ectodomain that can be released in soluble form Even though ARBs can increase the expression of ACE2 in the lungs, we still do not know whether this also results in an increased rate of ACE2 shedding, which would act as a decoy receptor that reduces Sars-CoV-2 circulation and limits viral entry into the target cells[13].
- Second, the ARBs allow an increased availability of Ang II by competing with the same AT1R. The increased levels of Ang II become substrates available for the ACE2. The engagement of the ACE2 catalytic domain by its substrates can induce a major conformational change in the three-dimensional structure of this receptor, making it unfavorable to Sars-CoV-2 binding and internalization. In addition, the generation of Ang 1-7 and Ang II by the ACE2 can create a cytoprotective environment in the lungs that can counterbalance the vasoconstriction and profibrotic processes, an important protection mechanism during coronavirus infection, consistent with the protective role of ACE2 in acute lungs[13].

The aforementioned study and the theories it implies encourage and mitigate the concern of cardiology and nephrology societies about the need to discontinue antihypertensive medication in cases of Covid-19 infection in hypertensive patients.

Studies indicate that the viral load detected in asymptomatic patients was similar to that found in symptomatic patients; however, the viral loads in patients with serious diseases were higher than those of patients with mild to moderate presentations. In addition, higher viral loads were detected in the nasal mucosa than in the oropharynx. This suggests the effectiveness of an upper swab of the nasal mucosa, which presents less risk to the professional in charge of sample collection[14].

The incubation period ranges from 2 to 14 days (average of 5.2 days). The average time between the first symptoms and the development of acute respiratory distress syndrome (ARDS) is eight days[15]. A possible explanation for such rapid and serious deterioration is the cytokine release syndrome (CRS), or 'cytokine storm', an overproduction of immune cells and cytokines, which leads the system of multiple organs to fail and causes fatal damage to the tissues of the lungs, kidneys, and heart.

The current trend to release Covid-19 convalescent individuals from quarantine raises the hypothesis of whether or not reinfection exists. Although other coronaviruses allow reinfection and there have been cases of this process reported in Covid-19, there is no elucidation so far if this is a possibility. Coronavirus infection is known to elicit a short- and medium-term response that suppresses new early reinfections in humans. Research carried out on primates has failed to demonstrate the presence of Covid-1916 reinfection[16]. Previous data suggest that the IgG for coronavirus peaks in four months and remains positive for three years. However, it is not known whether this conferred immunity is sufficient to provide cross-protection against Covid-19 mutations or other respiratory viruses.

## CLINICAL PRESENTATIONS

It is estimated that most individuals are asymptomatic or present only mild symptoms (85%), including fever, fatigue, cough, myalgia, and sputum. There may be anosmia (initial symptom), loss of taste (pre-hospitalization symptom in 91% of patients[17]), nausea, headache, emesis, abdominal pain[6], diarrhea, odynophagia, and rhinorrhea. Severe cases (15%) may include chest pain, dyspnea, cyanosis, tachypnea, signs of respiratory distress, hypotension, decompensation of underlying diseases, and lymphopenia, and must be treated in a hospital bed. RR >30 bpm, $SatO_2$ <93%, $PaO_2/FiO_2$<300 were indicators of poor prognosis and progression for mechanical ventilation (risk factors for mechanical ventilation: hypertension, diabetes mellitus, and age over 65 years). The mortality rate is

around 2.9% (95% CI 1,4-4,3%), lower than SARS (10%)[15]. In patients that require intensive care, mortality can be up to 26%[18].

In severely immunosuppressed patients (transplanted), the initial presentation may be gastrointestinal (diarrhea and fever), progressing to respiratory involvement in 48h[19].

A study with dermatologists identified cutaneous manifestations in the course of Covid-19 infection. The manifestations were erythematous rash (14 out of 88 patients), generalized urticaria (3 out of 88 patients), and varicella-type lesions (1 patient). The torso was the main area involved. Pruritus was low or absent, and lesions usually healed in a few days. Apparently, there was no correlation with the severity of the disease[20].

A cohort of 99 patients in Wuhan identified changes in liver and canalicular enzymes (GGT, AST, and bilirubin) in up to 54% of patients[6]. The actual meaning of this clinical finding is still unknown. It is known that other coronaviruses do not have the ability to cause encephalitis, and, recently, a case report identified Sars-CoV-2 in a patient's CSF. However, there are no reports yet of neuroinvasive and symptomatic Covid-19 cases[21].

The most common finding on computed tomography scans of the chest in patients was ground-glass opacity nodules with peripheral and lowe-lobe bilateral involvement. Such findings may occur even in asymptomatic patients, but are more common in patients with Covid-19-related pneumonia. The presence of a fine fibrotic layer (fine reticular opacities) indicates a good prognosis of the disease, with progression in remission[15].

Convalescence lasts for one to three weeks for mild cases and from two to six weeks for severe cases[22].

## DIAGNOSIS

Clinical suspicion is based on the presence of fever and respiratory symptoms (cough, dyspnea). The presence of compatible epidemiology (contact with a suspected or confirmed case, travel to an endemic location in the previous 14 days) increases suspicion of Covid-19 at the expense of other respiratory syndromes and should be an indication for a RT-PCR test[15].

The diagnosis is currently possible only through a positive RT-PCT test. It the test is not available, the presence of high clinical suspicion (compatible clinic signs + favorable epidemiology + blood count suggestive of viral infection) associated with a CT with bilateral peripheral ground-glass opacity pattern of the lower lobes may be sufficient to reach a diagnosis[22].

## TREATMENT

The treatment is supportive (antipyretics and hydration).

Epidemiological measures of infection control management must be carried out. Mild cases should be treated on an outpatient basis, with home isolation, and instructing all household individuals on sanitary practices (the patient must be restricted to the bedroom, with the door closed and well ventilated, fomites must be sanitized with soap and water or alcohol 70° by the patient, minimal agitation and handling of clothing, frequent sanitation of hands by the patient and other household members, quarantine of all household members for 15 days)[2]. These patients should, ideally, be followed up by the Primary Care team every 48 hours via telephone or teleconsultation. It is recommended to instruct their return if there is a clinical worsening and offer work leave for domestic contacts for 14 days.

Severe cases ($SatO_2$ <95%, tachypnea, tachycardia, decompensation of comorbidities) must be hospitalized in isolation, 2 meters away from other suspected cases, and with the necessary precautions. Hand washing and the correct use of PPE by health professionals (gloves, disposable gowns, and N95 masks when entering a room, and caps and face protections during invasive procedures) are indicated, as well as the provision of masks for patients with respiratory symptoms at the hospital reception and in a separate waiting room[2,14].

General measures such as oxygen supplementation if $SatO_2$ is below 94%, hydration, symptom, and decompensated comorbidity control are recommended. Upon medical discharge, the patient must be instructed on possible clinical worsening 5-8 days after the onset of symptoms[2].

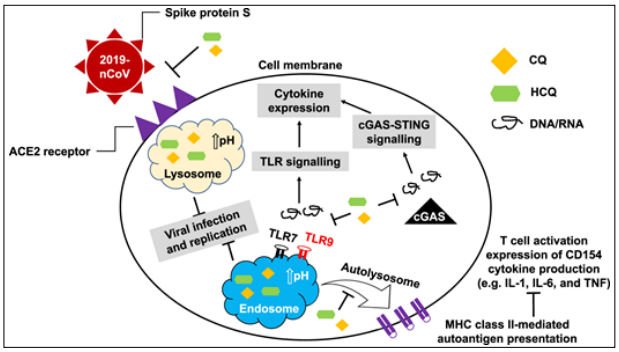
In the case of SBP <90 mmHg, DBP <60 mmHg, or persistence of $SatO_2$ <94% despite supplementation with a 5l / min nasal catheter, monitoring in an ICU bed and early tracheal intubation is indicated. NIV should be used with caution: although it is effective in preventing the intubation of patients with respiratory distress, it can cause dispersion of droplets and is indicated for 30 minutes only in a private room with negative pressure. Thus, it is recommended to maintain

a negative fluid balance of 0.5-1L/day in case of ARDS, maintenance of the MBP between 65-70 mmHg (in cases of shock, supply isotonic hydration at 30 ml/kg, proceeding to vasoactive drugs if refractory), protective mechanical ventilation (tidal volume 4-8 mL/kg, plateau pressure <30 $cmH_2O$, PEEP according to the ARDSnet chart), intermittent nocturnal sedation for early weaning, prevention of DVT/PE (stimulate ambulation, use of compression tights/intermittent pneumatic compression, low-molecular-weight heparin), correction of acid-base and hydroelectrolytic disorders, prevention of nosocomial infection (pneumonia associated with mechanical ventilation, infections due to catheters), prevention of decubitus ulcers (change of decubitus every 2 hours) are essential and must be implemented in cases of Covid -19[2,23].

Early open and non-random clinical trials with small samples were promising for use of hydroxychloroquine + azithromycin and remdesevir (antiviral drug developed against the Ebola Virus). Previous results from new randomized studies with larger samples, however, have failed to replicate this efficacy[25,26].

Hydroxychloroquine (HQ) and chloroquine (CQ) are immunomodulators implicated in the inhibition of lysosomal activation of antigen-presenting dendritic cells and in the suppression of TRL binding, thus attenuating the production of IL-1, IFN-1, and TNF. The first action would reduce the excessive secretion of cytokines, delaying the overactivation of the immune system triggered by the disease. In addition to this role in modulating the immune response, HCQ and CQ inhibit binding to the receiver and fusion of the membrane, the two main steps necessary for the cell entry by coronaviruses: interfering in the glycosylation of the angiotensin-converting enzyme 2 (ACE2) (the cell receptor of Sars-CoV) and blocking the binding of the virus to the host cell. In addition, they significantly raise the endosomal pH, interrupting the action of proteases and activation of the endosome for virus endocytosis. It is recommended that a dose of 400 mg twice a day of hydroxychloroquine sulfate administered orally, followed by a maintenance dose of 200 mg twice a day for four days. Gastrointestinal responses, such as vomiting and diarrhea are the most common adverse effects of these two drugs. Patients with exposure to CQ exceeding five years suffer severe side effects, such as retinopathy, circular defects (bulls-eye maculopathy), and cardiomyopathy. There is no contraindication to HQ during pregnancy[11,24].

**FIGURE 1.**

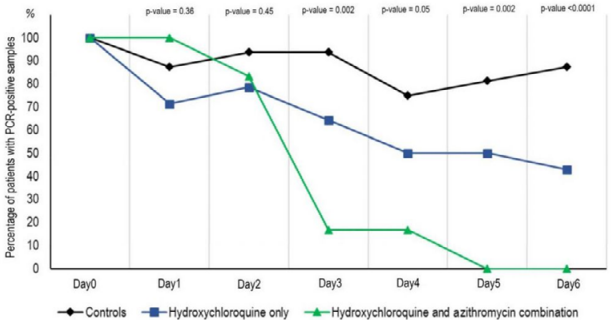



Antiviral mechanisms of CQ and HCQ. Both chemicals may interfere in the glycosylation of ACE2 and reduce the efficiency of binding between ACE2 in host cells and spike protein (S) on the surface of the coronavirus. They can also increase the pH of endosomes and lysosomes, thus preventing the process of binding of the virus with host cells and its subsequent replication. When HCQ enters APCs, it prevents antigen processing and the presentation of autoantigen mediated by class II MHC in T cells. The subsequent activation of T cells and the expression of CD154 and other cytokines are suppressed. In addition, HCQ interrupts the interaction of DNA / RNA with TLRs and the nucleic acid sensor cGAS and, therefore, the transcription of proinflammatory genes cannot be stimulated. As a result, the administration of CQ or HCQ not only blocks the invasion and replication of coronaviruses but also mitigates the risk of a cytokine storm, Yao, Ye, Zhang. [24]

Azithromycin, an antimicrobial derived from the macrolide class, has proven in vitro efficacy against the Ebola and Zika viruses[27,28]. Its mechanism of action against these viruses is not yet fully understood; it acts mainly in inhibiting replication. In addition, it is believed that it can shorten respiratory viral infection by preventing bacterial superinfections.[23]

The combination of hydroxychloroquine 200 mg 12/12 hours and azithromycin 500 mg in a single daily dose in a French small sample study had encouraging results (70% of viral load clearance with hydroxychloroquine D6 versus 12.5% with the placebo)[23], as shown in the chart below.

**CHART 1.** COMPARISON OF VIRAL CLEARANCE WITH A PLACEBO, HYDROXYCHLOROQUINE, AND AZITHROMYCIN. GAUTRET *ET AL.*[23]




Remdesevir is a promising drug along with HQ[15,29]. Although this antiviral was tested in a study without a control group and with a small sample, it was related to a reduction in the in vitro viral load and a decrease

in the severity of the condition. A dose of 200 mg in D1, followed by 100 mg/day for nine days in single daily doses is recommended[15].

The use of corticosteroids has been associated with a worse clinical outcome and is not routinely recommended. Its use in initial presentations was related to a higher viral load, and its use during the period of severe pneumonia was related to delayed clearance of the viral load, as well as the decompensation of diabetes mellitus and the presence of psychosis[15,19]. However, it should be considered in the presence of septic shock refractory to vasopressors and with suspected adrenal insufficiency.

A recent review that included 11,321 individuals from 14 countries showed that vitamin D supplementation decreased the risk of acute respiratory infections (ARI) in both those with vitamin D deficiency and those with adequate levels. Specific studies for Sars-CoV-2 are underway to elucidate the real application of these results[30].

Measures such as self-quarantine or temperature control at borders should not be very effective since half of the infections are asymptomatic and 44% of the patients do not present fever. Currently, there is a consensus regarding the closing of schools and restrictions of social gatherings (including the closure of workplaces) to limit population movements and introduce the so-called sanitary cordons (quarantines at a cities or region scale). The implementation of these interventions (including sanitary cordons, traffic restrictions, social distancing, centralized quarantine, and universal symptom research) has been temporarily associated with a reduction in the effective number of Sars-CoV-2 infections (secondary transmission) and in the number of confirmed cases per day in groups of age, sex, and geographic regions[31]. There is less consensus regarding which measure should be the first to be implemented, in which combination, and when. The World Health Organization recommends universal testing with subsequent isolation of positive asymptomatic patients (effective measure to control the spread of the virus)[14].

The return to daily activities is still uncertain. It is suggested that, with universal testing, non-transmitting convalescents (IgG positive, PCR-TR negative) may return from isolation and collaborate with the production chain (lockdown reduction). Recently, the World Health Organization suggested the possibility of loosening quarantine for regions with controlled rates of transmissibility, a health system capable of detecting, isolating, and treating all newly infected individuals, control of the risk of imported cases and sanitary control of risk locations (such as long-stay institutions), and a community that is aware and capable of complying with the new standards[14].

It is worth noting that discontinuing ACE/ARB antihypertensive drugs is not recommended due to the potential for cardiac decompensation, as well as the non-use of ibuprofen - when there is no other alternative to this NSAID - is not recommended[13,15,19]. Passive immunoprophylaxis with convalescent serum in mice has shown a significant reduction in viremia. However, it did not significantly alter the evolution to pulmonary disease[32].

## DIFFERENTIAL DIAGNOSES IN PEDIATRICS

Current data indicate that symptomatic pediatric cases are rare, as are severe cases in individuals younger than 20 years without comorbidities. Thus, faced with a case of pediatric respiratory syndrome, one of the differential diagnoses below should be considered:

### Acute viral rhinopharyngitis

It is the most common infectious disease during childhood (children younger than five years usually present from five to eight episodes per year)[33,34].

The most common etiologic agents are rhinovirus, coronavirus, respiratory syncytial virus (RSV), influenza, parainfluenza, coxsackie, and adenovirus. The transmission is by droplets and direct contact with the mucous membranes, and the incubation period is of 2-5 days. The affected individual presents a risk of contagion in the one-day period before the onset of symptoms and two days after it.

The clinical presentation lasts from five days to seven days and includes rhinorrhea, nasal obstruction, dry coughing, sneezing, pharyngitis, and fever of variable intensity. There may be hyperemia of the tympanic membrane, changes in sleep, and irritability in infants. The adenovirus and RSV may generate lower airway infection (leading to tachypnea, retractions, and grunting). The influenza virus is implicated in a more severe clinical presentation, with diarrhea, abdominal pain, prostration high fever, and myalgia, which puts the clinical presentation of a common cold (coryza, nasal obstruction, cough, and pharyngitis) in the background. Both RSV and rhinovirus can trigger asthma episodes[34,35]. There may be complications with

acute otitis and sinusitis due to the obstruction of the ostia of the paranasal sinuses and eustachian tube, secondary to the inflammatory process or indiscriminate use of decongestants.

The diagnosis is clinical and should be differentiated from hepatitis A (onset of jaundice, increased direct bilirubin and transaminases), measles (intense cough, conjunctivitis with photophobia, exanthema, and enanthema of koplik), pertussis (severe cough, and may cause vomiting and dyspnea, duration of six to ten weeks, absence of vaccination), rhinitis (AURTI caused by winter, positive family history and personal history of atopy, remission after use of nasal corticosteroids), streptococcal pharyngitis, and mononucleosis (both with intense hyperemia of the oropharynx, petechiae on the palate, hypertrophy of the tonsils and purulent plates). The detection of the virus is unnecessary.

The treatment consists of rest during the febrile period, nasal instillation of isotonic saline solution (3-5 mL in each nostril every 2 hours), and antipyretic medication. In adults with influenza A, one can resort to amantadine 200 mg every 24 hours (pre-contact prophylaxis with 70-80% of effectiveness, equally effective treatment with a reduction of the symptomatic period)[34]. In children older than 12 years or weighing over 40 kg and adults with suspicion of influenza type A or B, oseltamivir 75 mg can be used every 12 hours for five days (pre-contact prophylaxis with 92% efficiency, reduces the severity and duration of symptoms, can be used in children over 1 year)[34]. The use of probiotics and vitamin C in high doses (>1g/day) has proven effective in the prevention of rhinopharyngitis in athletes, as well as in the reduction by 20% of the duration of the condition in children. Caretakers should be instructed on the need for hand hygiene at home and to return in case of clinical worsening.

### Acute sinusitis

Defined as a bacterial infection of the paranasal sinuses, with a duration of fewer than 30 days. Acute sinusitis is rare in small children since the maxillary and ethmoidal sinuses are reduced before the age of 2 years, and the frontal and ethmoidal sinuses develop from the age of 4 years[34,35].

The most frequent etiological agents are Moraxella catarrhalis, Hamophilus influenza, and Streptococcus pneumoniae[35].

Acute sinusitis is suspected when there is the persistence of AURTI exceeding ten days or recurrence after clinical improvement. The symptoms include nasal obstruction, purulent rhinorrhea, halitosis, coughing with worsening at night, fever, and frontal tension headache (may also present as pain in teeth). There may be osteomyelitis, periorbital cellulitis (a sign of ethmoiditis), meningitis, thrombosis of the cavernous sinus, and brain abscess.

The diagnosis is clinical and an x-ray of the paranasal sinuses is usually unnecessary. It must be differentiated from adenoiditis (snoring, epistaxis, acute otitis media) and nasal foreign body (obstruction and asymmetrical rhinorrhea, history of foreign body insertion). It may be necessary to have a specialized assessment if sinusitis lasts for over 90 days or in case of recurrent sinusitis. It may be necessary to have a computed tomography of the skull in refractory cases or in case of suspected complications[34].

The treatment consists of rest, antipyretics, nasal instillation of isotonic saline solution every 2 hours, topical or systemic corticosteroids (in case of a history of asthma), and antimicrobial agents. The first choice is amoxicillin clavulanate 875+125 mg every 12 hours for seven days (or ten days in case of resistance factors)[34]. Other options are cefuroxime, clarithromycin, or azithromycin. In the absence of a response after 48 hours, consider doubling the dose or changing the medication. Instructions to avoid decongestants and diving during periods of AURTI, avoid smoking (active and passive), and proper treatment of allergic rhinitis.

Children with allergic rhinitis can present chronic or repetition sinusitis[35].

### Streptococcal pharyngitis (SAP)

SAP is an acute infection of the oropharynx by *Streptococcus pyogenes* (group A beta-hemolytic). It is transmitted via droplets or direct contact with patients, presents incubation of two to five days, and represents 15% of AURTI[34,35].

The most common clinical presentation is high fever, odynophagia with sudden onset, pharyngeal hyperemia, hypertrophy of the tonsils and tonsillar exudate, associated or not with prostration, cervical adenopathy, vomiting, and abdominal pain. It can complicate with cervical lymph node abscesses, acute otitis media, post-streptococcal glomerulonephritis, reactive arthritis, rheumatic fever, and sepsis[35].

The diagnosis is clinical, and a quick test can be used. It must be differentiated from scarlet fever (strawberry tongue, exanthema with signs of Pastia - increase of the flexural exanthema, and Filatov - perioral pallor), viral pharyngitis (coryza, absence tonsil

hypertrophy, and exudate), diphtheria (predominant diarrhea, grayish-white plates in the oropharynx that may invade the uvula) and infectious mononucleosis (generalized adenopathy, exanthema after the use antimicrobial agents)[35].

The treatment is based on rest, instillation of warm saline solution in the oropharynx, antipyretics, and antibiotics (the drug of choice is benzathine penicillin G 600 thousand or 1.2 million IU IM single dose, for <27 kg and >27 kg, respectively)[34]. The treatment is less painful if a heated solution used for dilution. In the case of allergy to penicillin, the drug of choice is erythromycin estolate 40 mg/kg/day in 2-3 administrations. Instruct the patient to return in case of dysphagia and muffled/nasalized voice (tonsillar abscess), dyspnea, exanthema, or clinical worsening. Instruct to be absent from nursery/school and work activities for 48 hours after starting the treatment[35].

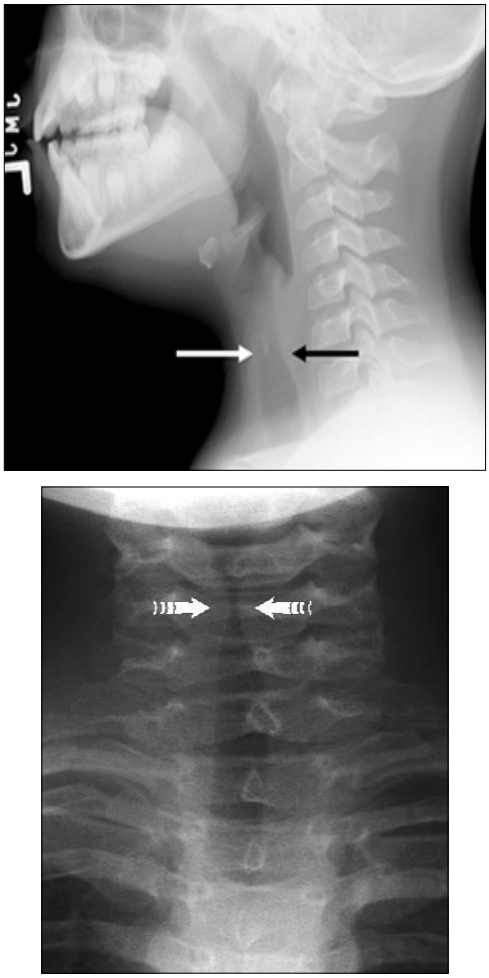
## Viral croup

This is subglottic laryngitis, a viral infection with a variable degree of congestion and obstruction of the airways. It is often caused by RSV and parainfluenza I and II, presents a natural history of partial obstruction of the airways for 2-3 days, with remission after five days[35].

Clinical manifestations include prodromes (runny nose, dry cough, nasal obstruction, and fever) and frank laryngitis (hoarse cough, dysphonia/aphonia, and inspiratory stridor). There may be signs of respiratory failure (nasal flaring, subcostal retraction, tachypnea, cyanosis/pallor) and progression to airway obstruction and death.

The diagnosis is clinical and can be aided by radiography (laryngeal narrowing with pencil-point sign). It must be differentiated from a foreign body (sudden onset of airway obstruction, with cyanosis and cough), a congenital malformation of the airway (repeat laryngitis), spasmodic laryngitis (absence of prodromes, nocturnal onset, spontaneous regression, personal history of GERD, and improvement with humidification) and allergic laryngeal edema (history of exposure to allergens or drugs, presence of angioedema, and other stigmata of anaphylaxis)[33].

**FIGURE 2.** CERVICAL RADIOGRAPHS THAT ARE SUGGESTIVE OF VIRAL CROUP. IMAGE BY JOHN MCBRIDE, MD.



The treatment is based on the humidification of the environment and hydration, as well as symptomatic treatment. In severe cases (progressive or at rest stridor, signs of respiratory failure, toxemia), use inhaled corticosteroids and consider tracheal intubation[35].

## RESUMO

INTRODUÇÃO: *A pandemia de Covid-19 decretada pela OMS suscita maior conhecimento acerca da doença.*

EPIDEMIOLOGIA: *A infecção atingiu a marca de 2 milhões de pacientes em 33 países e levantou como fatores de risco a presença de comorbidades e a idade avançada.*

TRANSMISSIBILIDADE: *A transmissibilidade calculada até o momento é similar à da epidemia de H1N1, contudo, com taxa de mortalidade inferior.*

FISIOPATOLOGIA: *O vírus Sars-CoV-2, da família Coronaviridae, tem capacidade de invasão celular através da enzima conversora de angiotensina 2 presente no epitélio respiratório inferior e nas células da mucosa do intestino delgado.*

MANIFESTAÇÕES CLÍNICAS: *A apresentação pode ser dividida em leve (febre, fadiga, tosse, mialgia e escarro) e grave (cianose, dispneia, taquipneia, dor torácica, hipoxemia e necessidade de ventilação mecânica) e tem mortalidade estimada de pouco mais de 2%.*

DIAGNÓSTICO: *Dá-se pela detecção da carga viral no PCR-TR de pacientes com alta suspeição clínica.*

TRATAMENTO: *Baseado em medidas de suporte e de controle de infecção. Em casos graves, uso de medicamentos como hidroxicloroquina e azitromicina ou remdesevir pode ser promissor. Deve-se evitar o uso de corticosteroides. Não há evidências suficientes para abster-se do uso de ibuprofeno e IECAs/BRAs.*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# Comment on: "Basic Life Support: an accessible tool in layperson training"

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We read with great interest the article by Bonizzio et al.[1] entitled "Basic Life Support: an accessible tool in layperson training". Basic life support (BLS) is a very important concept, and people should be able to do it correctly if they are trained to do so. It is sad to know that the knowledge of BLS is poor in many countries, and both health professionals and laypeople must be trained regularly to save more lives[1,2].

Bonizzio et al.[1] stated that there was no significant difference in knowledge between health care professionals and laypeople. This finding is really important because we assume that health care professionals would be better at BLS. A study conducted on nurses showed that if the training for cardiopulmonary resuscitation (CPR) is not repeated at 6 months intervals, the knowledge decreases[3]. It is possible that the lower than expected knowledge of health care professionals is caused by insufficient CPR courses. If compulsory CPR training in hospitals and health institutions is repeated every 6 months, CPR knowledge in health care professionals will gradually increase. They will also learn the innovations in the guidelines through their instructors.

Layperson training is very important because not everyone is lucky to pass out in a health facility. In a study conducted by Pergola and Araujo[4], 31% of the participants did not know the telephone number of the emergency services. The public should be aware of the importance of CPR knowledge. Bonizzio et al.[1] show us an easy and applicable way of BLS training. Dummies made to train laypeople are cheap and easy to make with materials used daily. With this method, layperson training will be cheap with the help of volunteer health care professionals. If BLS training is added to the curriculum of senior medical students, a large number of educators will emerge. Since these students are trained at an instructor level, their knowledge will increase automatically.

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# Comments: "Association between Hemogram Parameters and Coronary Collateral Development in Subjects with Non-ST Elevation Myocardial Infarction"

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The severity of atherosclerotic heart diseases can be predicted by coronary collateral circulation, which is a consequence of coronary collateral development (CCD). Subjects who suffer from coronary artery disease with adequate CCD can benefit from an alternative blood supply of collateral vessels[1]. Cardiac morbidity and mortality rates are lower in patients with sufficient CCD compared to those without adequate CCD, since these collateral vessels make a natural arterial bypass[2].

Laboratory and clinical determinants of CCD are a matter of debate. While statin use has been supposed to be related to better CCD[3], increased inflammatory markers, such as c-reactive protein, are suggested to be associated with poor CCD[4]. Interestingly, anemia was also related to better development of coronary collateral circulation independent from erythropoietin level[5].

In the article by Sincer et al.[6], the authors reported that elevated platelet distribution width (PDW) was associated with better development of coronary collateral vessels. PDW is a marker of thrombocyte activation and refers to the size variability of circulating platelets. It has a potential role in the pathogenesis of myocardial infarction[7]. Moreover, the authors found that it was associated with type 2 diabetes mellitus and diabetic nephropathy[8]. Sincer et al.[6] evaluated the grade of CCD by Rentrop grading, in which grade 0 and 1 were classified as insufficient CCD, and grade 2 and 3 were classified as sufficient CCD. Their study design and interpretation of the results are justified. Increased PDW, as a result of increased platelet activation, could promote angiogenesis and better development of coronary artery vessels.

In conclusion, due to its nature of being easy to assess and repeat, increased PDW could be a promising predictor of CCD in patients with coronary heart disease.

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