The Association Between Serum Liver Enzymes And Cancer Mortality

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Abstract

BACKGROUND & AIMS: Interpreting levels of liver enzymes is often challenging because they may be influenced by metabolic processes beyond the liver. Given their pathophysiologic roles in inflammation and oxidative stress, higher levels of these enzymes may be associated with increased risk of mortality. However, studies have found inconsistent results. Thus, we examined the association of liver enzymes levels with cancer mortality in the general U.S. adult population.

METHODS: We used the US National Health and Nutrition Examination Survey from 1999 to 2016. Kaplan-Meier survival curve comparisons were examined across quartiles of liver enzymes. Cox proportional hazards models were built to examine the relationship between cancer mortality and liver enzymes quartiles without and with adjustment for potential confounding factors.

RESULTS: During the 338,882 person-years follow-up, 1059 participants had cancer-related deaths. There was a nonlinear U-shaped relationship between serum alanine and aspartate aminotransferase (ALT and AST) levels and cancer mortality. There was no relationship between cancer mortality and gamma glutamyltransferase (GGT), however, each 10 IU/L increase in GGT after median was associated with 1% higher mortality risk (HR=1.01; 95% CI=1.00, 1.02; P=0.001). Only subjects with high levels of alkaline phosphatase (ALP) had higher cancer mortality (HR=1.63; 95CI=1.30, 2.05; P<0.001 and HR=1.52; 95%CI=1.20, 1.94; P=0.001 respectively).

CONCLUSIONS: Only the lowest and highest serum ALT and AST levels are associated with increased cancer mortality. For ALP, the relationship is present at higher levels. The association with GGT was not robust to different analyses. The mechanisms underlying the observed relationships need further exploration.

Introduction

Serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyltransferase (GGT), and alkaline phosphatase (ALP) are commonly used biomarkers for liver disease because of their abundance in hepatocytes.[1] Besides, because of their presence in other tissues, these enzymes may also be potential biomarkers for various diseases.[2–4] Previous studies suggested a correlation between serum liver enzymes levels and visceral adiposity.[5–7] Other studies have shown associations between elevated liver enzymes levels and risk of type 2 diabetes mellitus (T2DM) and metabolic syndrome (MS) even in absence of liver disease such as viral hepatitis, and both are well known risk factors for numerous adverse health outcomes.[4,5,8,9] A possible role of liver enzymes as markers of all-cause mortality and mortality from non liver diseases, such as cancer, is yet to be clarified. Further, there are concerns for chronic exposure to low concentration toxins and inflammation. Toxins and chronic inflammation are often associated with both low grade liver damage as well as various cancers. This hypothesis can explain the liver enzymes-cancer relationship by means of ‘systemic chronic inflammation (SCI)’ and environmental toxicant exposures across life span. The perturbation in the

balance between pro- and anti-inflammatory responses is a potential driver of tissue damage and carcinogenesis. One of the chronic inflammatory states linked to liver damage and risk of malignancy is NAFLD, Although usually associated with obesity, NAFLD can also develop in non-obese individuals. This subpopulation of individuals, known to have 'lean NAFLD' or 'non-obese NAFLD', is growing in prevalence.[11] Cancer-related mortality is among the top three causes of death in individuals with NAFLD.[10]

While there is significant evidence for an association between liver enzymes elevation and all-cause mortality outcomes, the data on cancer-related mortality is limited and controversial.[20,21] Prospective epidemiological studies have demonstrated an association between elevated liver enzymes and risk for cancer mortality in certain subpopulations. For example, studies have reported an association between elevated ALT levels and cancer mortality among male Korean workers[22] and in the elderly Italian population[23]. Similarly, elevated GGT levels have been associated with a higher risk of cancer mortality; several population-based Austrian cohorts of healthy men and women found a dose-response relationship of GGT with cancer incidence and mortality[3,24,25]. Although elevated liver enzyme levels have been associated with cancer mortality in subgroups of populations[26], such association remains unclear in the general population[22]. Prior studies reported inconsistent results and had limitations such as lack of generalizability to the general population, short duration of follow-up, small sample size, retrospective study design, and lack of adjustment for important confounders such as smoking[1,23]. To address these shortcomings, and to study the relationship between serum levels of liver enzymes and cancer mortality in the general population, we examined this relationship in a large sample representative of the general adult population of the United States using the National Health and Nutrition Examination Survey (NHANES).

Materials And Methods

Study Population: The NHANES is an ongoing cross-sectional, complex, multistage, stratified, clustered sampling design survey representative of the civilian, non-institutionalized population of the United States. NHANES was approved by the Centers for Disease Control and Prevention's Institutional Review Board and all participants provided written informed consent. A detailed description of the survey and its sampling procedures are available on its web site [11]. Participants from nine survey cycles (1999-2016) who were older than 18 years, had serum liver enzyme levels measured, and had information on their vital status were included in this study.

Variable Definitions: Participants self-reported their age, sex, and race. Participants were categorized as smokers if they were actively smoking at baseline, ever smokers if they had smoked at least 100 cigarettes during their lifetime, and nonsmokers if they had never actively smoked. Individuals who drank fewer than 12 drinks in a lifetime were defined as 'nondrinkers', those who drank five or fewer drinks/day were defined as 'light drinkers', whereas individuals who drank more than five drinks were defined as 'heavy drinkers'. Participants were classified as hypertensives if they were taking antihypertensive

medications, had an average systolic blood pressure more than 140 mmHg, or an average diastolic blood pressure more than 90 mmHg. The mean systolic and diastolic blood pressures were calculated from up to four readings obtained in a seated position and using sphygmomanometers. Body mass index (BMI) was calculated as kilograms divided by height in meters squared. Individuals were classified as diabetics if they were taking medications for diabetes mellitus or had a hemoglobin A1C > 7%. Plasma glucose, serum total cholesterol, and serum triglycerides levels were measured by using standardized methods. Hemoglobin A1C was measured on the fully automated glycohemoglobin analyzer. Creatinine was measured using the Jaffe rate method to determine the concentration of creatinine in serum. Glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.

Serum samples were collected and shipped at -20°C to the processing laboratory. Serum ALT, AST, ALP, and GGT levels were assayed by using a Hitachi 737 Analyzer (Boehringer–Mannheim Diagnostics, Indianapolis, IN) at the White Sands Research Center, Alamogordo, New Mexico. Each enzyme activity was measured using an enzymatic method that monitors the rate of change in absorbance over a fixed-time interval. The rate of change in absorbance is directly proportional to the liver enzyme activity in the sample. Data on mortality status were obtained using a probabilistic match between NHANES and the National Death Index (NDI) death certificate records. The NDI is a National Center for Health Statistics (NCHS) centralized database of all USA deaths beginning in 1979. Time at risk was from the date of the NHANES examination to the date of death or to December 31, 2016. The cause of death was attributed by NCHS based on the International Classification of Diseases (ICD), 9th or 10th revision. Outcomes for this analysis consisted of all-cause and cause-specific mortality (in this case cancer mortality (ICD-9: 140 to 239. ICD-10: C00-D48).[27] For each death, the underlying cause is selected from an array of conditions reported in the medical certification section on the death certificate using the Automated Classification of Medical Entities (ACME). The conditions are translated into medical codes through the use of the classification structure, and the selection and modification rules contained in the applicable revision of the ICD, published by the World Health Organization (WHO).

Statistical Analysis: All analyses were conducted taking into account the complex survey sampling design of the NHANES. Survey weights were generated from the nine 2-year cycles for the complete dataset so that the results are representative of the US population. For descriptive statistics, data were summarized as frequencies (percentages), or means $\pm$ standard deviations (SD), as appropriate. Differences between descriptive statistics were examined using the student's t-test or chi-square test as appropriate. Kaplan-Meier survival curves were compared across quartiles of liver enzymes using a log-rank test. Using quartiles of each enzyme, hazard rate ratio (HR) estimates for mortality outcomes were calculated with Cox proportional hazard regression models which were constructed without and with adjustment for age, sex, race, BMI, hypertension, diabetes mellitus, alcohol use, cigarette smoking, and estimated glomerular filtration. The difference in years between a participant's age at the time of survey examination and death or censoring was used as the measurement of follow-up time.[28] Proportionality of hazards was confirmed visually by examining the log-log survival curves and by comparing the

observed Kaplan-Meier survival curves with Cox model predicted curves. To examine a nonlinear relationship between enzyme levels and cancer mortality, we also used a piece-wise spline with a single knot at the median. For sensitivity analysis, we used the Fine and Gray competing risk method to account for mortality due to competing risks. All analyses were performed using Stata 16.1 (StataCorp, College Station, TX). A P-value of < 0.05 was considered to indicate statistical significance.

Results

Of the 42,038 patients, 51.6% were women, 22.4% were active smokers, 69.6% were Caucasians, 30.4% were hypertensive, and 8% were diabetics. The mean (SD) age of the cohort was 47.1 (19.4) years, serum cholesterol 195.4 (43) mg/dl, and estimated GFR was 95.7 (25.4) mL/min. The mean (SD) of serum ALT was 25.2 (25.3) U/ml, of AST was 25.5 (19.0) U/ml, of GGT was 29.1 (43.9) U/ml, and of ALP was 71.9 (27.6) U/ml. During the 338,882 person-years follow-up (median = 7.67 years), 1059 participants died of a cancer-related cause. As expected, subjects who died during follow-up were older and more likely to be men, hypertensive, diabetics, smokers (active or former), with hypertriglyceridemia and hypercholesterolemia. Except for ALT and AST levels, the liver enzymes levels were higher in participants who died as compared to those who did not (**Table 1**). Participants in the highest quartile of ALT had a lower mortality rate than those in the lowest quartile (2.46 vs 3.55 per 1000 person-year) (**Supplementary Fig.1**) with an incidence rate ratio of 0.69 (95%CI=0.58 to 0.83; P<0.0001). In contrast, participants in the highest quartile of AST had a higher mortality rate than those in the lowest quartile (3.47 vs 2.92 per 1000 person-year) with an incidence rate ratio of 1.19 (95%CI = 1.00 to 1.41; P=0.04) (**Supplementary Fig.2**). Similar findings were observed with GGT and ALP; individuals in the highest quartile had higher mortality than those in the lowest quartile (4.02 vs 2.10 and 4.31 vs 2.41 per 1000 person-year respectively) with incidence rate ratios of 1.92 (95%CI = 1.59 to 2.31; P<0.001) and 1.79 (95%CI = 1.49 to 2.15; P<0.001) respectively (**Supplementary Fig. 3 and 4**). In unadjusted Cox proportional hazards models, there was no difference in cancer mortality between the lowest and highest quartiles of serum ALT levels (HR=0.86; 95%CI=0.67, 1.10; P=0.24). On the other hand, the second and third quartiles had significantly lower cancer mortality than the lowest quartile (HR=0.77; 95%CI=0.62, 0.96; P=0.02 and HR=0.76; 95%CI=0.62, 0.94; P=0.01 respectively) suggesting a non-linear relationship. In adjusted models, a similar non-linear relationship was noted; participants in the third quartile had lower mortality than those in the lowest quartile (HR=0.79; 95%CI=0.63, 0.99; P=0.04) while there was no significant mortality difference between the lowest and highest quartiles (**Table 2**). The use of piece-wise spline with a single knot at the median confirmed the nonlinear relationship (**Table 3**); each 10 IU/L increase in ALT was associated with a 30% lower adjusted mortality risk until median (HR=0.70; 95%CI=0.52, 0.94; P=0.02) while after median, each 10 IU/L increase in ALT was associated with a 2% increase in adjusted mortality (HR=1.02; 95%CI=1.01, 1.03; P<0.001). Similar results were seen with serum AST levels in both unadjusted and adjusted models (**Table 2**). In adjusted models, while there was no difference between the lowest and highest quartiles (HR=0.90; 95%CI=0.72, 1.12; P=0.35), second and third quartiles had significant lower mortality than the lowest quartile (HR=0.72; 95%CI=0.60, 0.87; P=0.001 and HR=0.69; 95%CI=0.55, 0.87; P=0.002 respectively). Adjusted piece-wise spline model confirmed nonlinear relationship (**Table 3**); each 10IU/L

increase in AST was associated with 36% lower mortality risk until median (HR=0.64; 95%CI=0.47, 0.87; P=0.004) and 3% higher risk after median (HR=1.03; 95%CI=1.02, 1.04; P<0.001). In contrast, while individuals in the lowest quartile of GGT had a lower risk of mortality than those in the lowest quartile in unadjusted models (HR=1.50; 95%CI=1.20, 1.88; P<0.001), this relationship disappeared in adjusted models (HR=1.20; 95%CI=0.94, 1.54; P=0.14). There was no mortality difference between the lowest and other two quartiles in unadjusted or adjusted models. In adjusted piece-wise spline models, there was no relationship between cancer mortality and GGT until median, however, each 10 IU/L increase in GGT after median was associated with 1% higher mortality risk (HR=1.01; 95%CI=1.00, 1.02; P=0.001) (**Table 3**). The relationship between serum ALP levels and cancer mortality was consistent between adjusted and unadjusted models; only participants in the highest quartile had higher mortality than the lowest quartile in unadjusted and adjusted models (HR=1.63; 95CI=1.30, 2.05; P<0.001 and HR=1.52; 95%CI=1.20, 1.94; P=0.001 respectively). Consistent with the findings with quartiles, adjusted piece-wise spline models found no relationship between cancer mortality ALP until median, however, each 10 IU/L increase in ALP after median was associated with 5% higher mortality risk (HR=1.05; 95%CI=1.02, 1.08; P0.001) (**Table 3**).

Sensitivity Analysis: Because patients who died due to non-cancer-related causes during follow-up could not have died due to cancer, we used competing-risk models, where deaths due to other causes were treated as competing events. Using the competing risk models, the results were similar to those obtained using the Cox proportional hazard models (**Supplementary Table 1**).

Discussion

In this study representative of the United States population, we have found a nonlinear U-shaped relationship between serum ALT and AST levels and cancer mortality. Individuals at the lower as well as at the upper end of the distributions had significantly higher cancer mortality than those in the middle of the distribution; for both enzymes, mortality risk first decreases until the median and then increases after the median. On the other hand, individuals with serum ALP levels at the higher end of the distribution were at higher risk of cancer death during follow-up. Similarly, individuals with serum GGT levels at the upper end of distribution may be at higher mortality risk than those with lower values. These results were robust to adjustment for confounding variables as well as to the underlying assumptions for the Cox proportional hazards models.

Several lines of evidence from cellular, animal models, and epidemiological studies suggest possible and plausible mechanisms for the observed association between serum levels of these enzymes and cancer mortality. The U-shaped association between serum ALT and AST levels and cancer mortality could be because a portion of serum ALT and AST originate from skeletal muscles; therefore, low serum levels may reflect sarcopenia with reduced release of ALT and AST into the blood by muscle. Sarcopenia has been associated with higher mortality, therefore, the observed increase in mortality with low ALT and AST may result from smaller muscle mass.[29,30] Moreover, low ALT and AST levels were associated with increased frailty and subsequent increased risk for mortality among the elderly population.[31,32] Thus, low ALT or AST levels might serve as a marker for sarcopenia and frailty. The association of mortality with

high levels of AST and ALT might reflect some kind of liver injury in conjunction with other systemic illnesses. The oxidative stress hypothesis may explain the associations between high serum liver enzymes and cancer mortality[33]. Subclinical inflammation may increase tissue damage and susceptibility to noninfectious diseases including cancer[34]. Another possible explanation is that aminotransferase elevation is associated with alcohol use; therefore, alcohol-related diseases, such as cancer, can occur more frequently in patients with elevated aminotransferase[35]. To date, little is known about the physiological functioning of ALP. It is strongly associated with c-reactive protein (CRP), a marker of inflammation[36], potentially explaining its association with cell injury, inflammation, and cancer-related mortality.[37] GGT is regarded as less specific for liver injury but potentially more discriminating for other diseases. GGT has long been considered a marker of excessive alcohol intake and more recently has been suggested to reflect oxidative stress[38] and exposure to environmental pollutants[24].

The observed increased cancer mortality with elevated serum ALT, AST, GGT, and ALP levels in this study is consistent with the results from several other studies[35,39–41]. Karaphillis et al. have shown that individuals with serum ALTs < 17 IU/L were at high risk of all-cause mortality[42]. Similarly, a nationwide cohort study in Korea found that individuals with high serum ALT and AST were at higher risk of all-cause, cardiovascular, and liver-related mortality than those with levels within the normal range.[43] Oh et al reported a U-shaped relationship between ALT and all-cause mortality showing that the relationship exists both at the higher and lower end of ALT.[5] However, the three studies did not examine the cancer-specific mortality risk. Previous studies have reported AST to be a significant prognostic factor in various malignancies such as lung, colonic or pancreatic cancer.[35,39,40,44] Similarly, GGT and ALP have been shown to predict overall and cancer-free survival in cancer patients (20, 21, 22, 23, 24). The findings from our study expand on the current evidence from other epidemiological studies and show that the cancer-specific mortality risk is U-shaped for AST and ALT while it is linear for GGT and ALP.

Our study has potential limitations and several strengths. We used only a single serum enzyme level for each individual that was obtained at baseline. Changes in the levels of liver enzymes over a lifetime were not assessed resulting in potential misclassification of participants. However, such misclassification in enzyme levels would bias results toward null and the true effect size may be larger than what we reported above. A strength of our study is a large sample size and a nationally representative population, resulting in the generalizability of our findings. Further, results were robust to statistical assumptions.

Conclusion

We report a nonlinear U-shaped relationship between cancer mortality and serum ALT and AST levels and that the relationship between cancer mortality and ALP is present at higher ALP levels. From this observational study, a causal association cannot be deduced. Data supporting strong biological plausibility will be needed before a causal association can be considered. Therefore, underlying mechanisms for the observed relationship need further study, as elucidating the mechanism may reveal a pathway that may modify risk factors and reduce population morbidity and mortality. Randomized

controlled trials with medications aimed at reducing liver enzymes and, therefore cancer-related mortality, will be needed to examine a causal association; for example, a study may examine the effect of sorafenib in reducing the incidence of liver cancer that is mediated through a change in liver enzymes.

Declarations

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Consent to participate: Not applicable

Consent for publication: Not applicable

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Code availability: Not applicable

References

1. Green RM, Flamm S. AGA technical review on the evaluation of liver chemistry tests. *Gastroenterology*. 2002;123(4):1367-1384. doi:10.1053/gast.2002.36061

2. Ruhl CE, Everhart JE. Elevated serum alanine aminotransferase and gamma-glutamyltransferase and mortality in the United States population. *Gastroenterology*. 2009;136(2):477-485.e11. doi:10.1053/j.gastro.2008.10.052

3. Kazemi-Shirazi L, Endler G, Winkler S, Schickbauer T, Wagner O, Marsik C. Gamma glutamyltransferase and long-term survival: is it just the liver? *Clin Chem*. 2007;53(5):940-946. doi:10.1373/clinchem.2006.081620

4. Fraser A, Thinggaard M, Christensen K, Lawlor DA. Alanine aminotransferase, gamma-glutamyltransferase (GGT) and all-cause mortality: results from a population-based Danish twins study alanine aminotransferase, GGT and mortality in elderly twins. *Liver Int*. 2009;29(10):1494-1499. doi:10.1111/j.1478-3231.2009.02090.x

5. Oh C-M, Won Y-J, Cho H, et al. Alanine aminotransferase and gamma-glutamyl transferase have different dose-response relationships with risk of mortality by age. *Liver International*. 2016;36(1):126-135. doi:10.1111/liv.12879

6. Ruhl CE, Everhart JE. Trunk fat is associated with increased serum levels of alanine aminotransferase in the United States. *Gastroenterology*. 2010;138(4):1346-1356, 1356.e1-3.

doi:10.1053/j.gastro.2009.12.053

7. Iwasaki T, Yoneda M, Kawasaki S, Fujita K, Nakajima A, Terauchi Y. Hepatic fat content-independent association of the serum level of gamma-glutamyltransferase with visceral adiposity, but not subcutaneous adiposity. *Diabetes Res Clin Pract*. 2008;79(1):e13-14. doi:10.1016/j.diabres.2007.06.014

8. Lee DS, Evans JC, Robins SJ, et al. Gamma glutamyl transferase and metabolic syndrome, cardiovascular disease, and mortality risk: the Framingham Heart Study. *Arterioscler Thromb Vasc Biol*. 2007;27(1):127-133. doi:10.1161/01.ATV.0000251993.20372.40

9. Liu Z, Que S, Ning H, Wang L, Peng T. Elevated alanine aminotransferase is strongly associated with incident metabolic syndrome: a meta-analysis of prospective studies. *PLoS One*. 2013;8(12):e80596. doi:10.1371/journal.pone.0080596

10. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2018;67(1):328-357. doi:https://doi.org/10.1002/hep.29367

11. Albhaisi S, Chowdhury A, Sanyal AJ. Non-alcoholic fatty liver disease in lean individuals. *JHEP Rep*. 2019;1(4):329-341. doi:10.1016/j.jhepr.2019.08.002

12. Kwo PY, Cohen SM, Lim JK. ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. *Am J Gastroenterol*. 2017;112(1):18-35. doi:10.1038/ajg.2016.517

13. Tariq R, Axley P, Singal AK. Extra-Hepatic Manifestations of Nonalcoholic Fatty Liver Disease: A Review. *J Clin Exp Hepatol*. 2020;10(1):81-87. doi:10.1016/j.jceh.2019.07.008

14. VanWagner LB, Rinella ME. Extrahepatic Manifestations of Nonalcoholic Fatty Liver Disease. *Curr Hepatol Rep*. 2016;15(2):75-85. doi:10.1007/s11901-016-0295-9

15. Ding W, Fan J, Qin J. Association between nonalcoholic fatty liver disease and colorectal adenoma: a systematic review and meta-analysis. *Int J Clin Exp Med*. 2015;8(1):322-333.

16. Allen AM, Therneau TM, Larson JJ, Coward A, Somers VK, Kamath PS. Nonalcoholic fatty liver disease incidence and impact on metabolic burden and death: A 20 year-community study. *Hepatology*. 2018;67(5):1726-1736. doi:10.1002/hep.29546

17. Furman D, Campisi J, Verdin E, et al. Chronic inflammation in the etiology of disease across the life span. *Nat Med*. 2019;25(12):1822-1832. doi:10.1038/s41591-019-0675-0

18. Greten FR, Grivennikov SI. Inflammation and Cancer: Triggers, Mechanisms, and Consequences. *Immunity*. 2019;51(1):27-41. doi:10.1016/j.immuni.2019.06.025

19. Thompson PA, Khatami M, Baglole CJ, et al. Environmental immune disruptors, inflammation and cancer risk. *Carcinogenesis*. 2015;36(Suppl 1):S232-S253. doi:10.1093/carcin/bgv038

20. Liu Z, Ning H, Que S, Wang L, Qin X, Peng T. Complex association between alanine aminotransferase activity and mortality in general population: a systematic review and meta-analysis of prospective studies. *PLoS One*. 2014;9(3):e91410. doi:10.1371/journal.pone.0091410

21. Kunutsor SK, Apekey TA, Seddoh D, Walley J. Liver enzymes and risk of all-cause mortality in general populations: a systematic review and meta-analysis. *Int J Epidemiol*. 2014;43(1):187-201. doi:10.1093/ije/dyt192

22. Kim HC, Nam CM, Jee SH, Han KH, Oh DK, Suh I. Normal serum aminotransferase concentration and risk of mortality from liver diseases: prospective cohort study. *BMJ*. 2004;328(7446):983. doi:10.1136/bmj.38050.593634.63

23. Mazza A, Casiglia E, Scarpa R, et al. Predictors of cancer mortality in elderly subjects. *Eur J Epidemiol*. 1999;15(5):421-427. doi:10.1023/a:1007543725207

24. Strasak AM, Rapp K, Brant LJ, et al. Association of gamma-glutamyltransferase and risk of cancer incidence in men: a prospective study. *Cancer Res*. 2008;68(10):3970-3977. doi:10.1158/0008-5472.CAN-07-6686

25. Strasak AM, Pfeiffer RM, Klenk J, et al. Prospective study of the association of gamma-glutamyltransferase with cancer incidence in women. *International Journal of Cancer*. 2008;123(8):1902-1906. doi:10.1002/ijc.23714

26. Kunutsor SK, Apekey TA, Van Hemelrijck M, Calori G, Perseghin G. Gamma glutamyltransferase, alanine aminotransferase and risk of cancer: systematic review and meta-analysis. *Int J Cancer*. 2015;136(5):1162-1170. doi:10.1002/ijc.29084

27. Sondik EJ, Madans JH, Rothwell CJ. National Center for Health Statistics. :71.

28. Thiébaut ACM, Bénichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. *Stat Med*. 2004;23(24):3803-3820. doi:10.1002/sim.2098

29. Bigaard J, Frederiksen K, Tjønneland A, et al. Body fat and fat-free mass and all-cause mortality. *Obes Res*. 2004;12(7):1042-1049. doi:10.1038/oby.2004.131

30. Fisher AL. Of worms and women: sarcopenia and its role in disability and mortality. *J Am Geriatr Soc*. 2004;52(7):1185-1190. doi:10.1111/j.1532-5415.2004.52320.x

31. Le Couteur DG, Blyth FM, Creasey HM, et al. The association of alanine transaminase with aging, frailty, and mortality. *J Gerontol A Biol Sci Med Sci*. 2010;65(7):712-717. doi:10.1093/gerona/glq082

32. Elinav E, Ackerman Z, Maaravi Y, Ben-Dov IZ, Ein-Mor E, Stessman J. Low alanine aminotransferase activity in older people is associated with greater long-term mortality. *J Am Geriatr Soc*. 2006;54(11):1719-1724. doi:10.1111/j.1532-5415.2006.00921.x

33. Meisinger C, Döring A, Schneider A, Löwel H, KORA Study Group. Serum gamma-glutamyltransferase is a predictor of incident coronary events in apparently healthy men from the general population. *Atherosclerosis*. 2006;189(2):297-302. doi:10.1016/j.atherosclerosis.2006.01.010

34. Park JH, Watt DG, Roxburgh CSD, Horgan PG, McMillan DC. Colorectal Cancer, Systemic Inflammation, and Outcome: Staging the Tumor and Staging the Host. *Ann Surg*. 2016;263(2):326-336. doi:10.1097/SLA.0000000000001122

35. Stocken DD, Hassan AB, Altman DG, et al. Modelling prognostic factors in advanced pancreatic cancer. *Br J Cancer*. 2008;99(6):883-893. doi:10.1038/sj.bjc.6604568

36. Toiyama Y, Inoue Y, Saigusa S, et al. C-reactive protein as predictor of recurrence in patients with rectal cancer undergoing chemoradiotherapy followed by surgery. *Anticancer Res*. 2013;33(11):5065-5074.

37. Zhong C, You S, Chen J, et al. Serum Alkaline Phosphatase, Phosphate, and In-Hospital Mortality in Acute Ischemic Stroke Patients. *Journal of Stroke and Cerebrovascular Diseases*. 2018;27(1):257-266. doi:10.1016/j.jstrokecerebrovasdis.2017.08.041

38. Sakuta H, Suzuki T, Yasuda H, Ito T. Gamma-glutamyl transferase and metabolic risk factors for cardiovascular disease. *Intern Med*. 2005;44(6):538-541. doi:10.2169/internalmedicine.44.538

39. Rawson NS, Peto J. An overview of prognostic factors in small cell lung cancer. A report from the Subcommittee for the Management of Lung Cancer of the United Kingdom Coordinating Committee on Cancer Research. *Br J Cancer*. 1990;61(4):597-604. doi:10.1038/bjc.1990.133

40. Thornburg JM, Nelson KK, Clem BF, et al. Targeting aspartate aminotransferase in breast cancer. *Breast Cancer Res*. 2008;10(5):R84. doi:10.1186/bcr2154

41. Hao H, Chen L, Huang D, Ge J, Qiu Y, Hao L. Meta-analysis of alkaline phosphatase and prognosis for osteosarcoma. *European Journal of Cancer Care*. 2017;26(5):e12536. doi:10.1111/ecc.12536

42. Karaphillis E, Goldstein R, Murphy S, Qayyum R. Serum alanine aminotransferase levels and all-cause mortality. *Eur J Gastroenterol Hepatol*. 2017;29(3):284-288. doi:10.1097/MEG.0000000000000778

43. Lee H, Shin DW, Lee TH, et al. Association Between Change in Serum Aminotransferase and Mortality: A Nationwide Cohort Study in Korea. *Medicine*. 2016;95(12):e3158. doi:10.1097/MD.0000000000003158

44. Lindmark G, Gerdin B, Påhlman L, Bergström R, Glimelius B. Prognostic predictors in colorectal cancer. *Dis Colon Rectum*. 1994;37(12):1219-1227. doi:10.1007/bf02257785

Tables

Table 1. Characteristics of the study population comparing those who died from cancer with those who did not.

Variable	Dead (N=1,059)	Alive (N=40,979)	P-value
Age, years	66.3 (14.1)	46.6 (19.2)	<0.0001
Females, N (%)	420 (42.2)	21,243 (51.8)	<0.0001
Estimated GFR, mL/min	77.2 (23.4)	96.1 (25.2)	<0.0001
BMI, kg/m^2	28.2 (5.9)	28.5 (6.7)	0.57
Race			<0.0001
White, N (%)	583 (75.7)	18,688 (69.5)	
Black, N (%)	224 (11.6)	8,397 (10.7)	
Other, N (%)	252 (12.7)	13,894 (19.7)	
CRP, mg/dl (median(IQR))*	0.29 (0.54)	0.20 (0.40)	<0.0001
Hypertension, N (%)	621 (54.4)	13,813 (29.9)	<0.0001
Diabetes mellitus, N (%)	188 (14.5)	4,364 (7.9)	<0.0001
Cholesterol, mg/dl	198.8 (44.0)	195.3 (42.9)	0.005
Smoking			<0.0001
Current Smokers, N (%)	256 (27.6)	8,112 (22.3)	
Past Smoker, N (%)	431 (40.2)	9,361 (24.2)	
Non-Smoker, N (%)	365 (32.2)	20,633 (53.4)	
Alcohol Use			0.01
Heavy drinker, N (%)	66 (8.7)	4,416 (13.0)	
Light drinker, N (%)	675 (68.9)	22,886 (68.4)	
Nondrinker, N (%)	241 (22.4)	8,075 (18.5)	
ALT, U/ml (median(IQR))*	19 (11)	21 (12)	0.0002
AST, U/ml (median(IQR))*	23 (9)	23 (8)	0.09
GGT, U/ml (median(IQR))*	23 (21)	20 (16)	<0.0001
ALP, U/ml (median(IQR))*	73 (31)	68 (28)	<0.0001

Data are shown as mean (SD) unless otherwise noted. SD, standard deviation. P-values were generated using Wilcoxon rank-sum test.

BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; CRP, C-reactive protein; GFR = glomerular filtration rate

Table 2: Results of Cox proportional hazard models without and with adjustment for potential confounders

	ALT	AST	GGT	ALP
Unadjusted				
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	0.77 (0.62, 0.96); 0.02	0.68 (0.57, 0.82); <0.001	0.98 (0.77, 1.25); 0.87	1.21 (0.96, 1.53); 0.10
Quartile 3	0.77 (0.62, 0.95); 0.01	0.65 (0.53, 0.80); <0.001	1.02 (0.79, 1.32); 0.86	1.22 (0.98, 1.51); 0.08
Quartile 4	0.86 (0.68, 1.11); 0.24	0.86 (0.71, 1.04); 0.11	1.51 (1.21, 1.88); <0.001	1.63 (1.30, 2.05); <0.001
Adjusted				
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	0.80 (0.62, 1.01); 0.06	0.72 (0.60, 0.87); 0.001	0.86 (0.67, 1.10); 0.23	1.18 (0.93, 1.50); 0.18
Quartile 3	0.79 (0.63, 0.99); 0.04	0.69 (0.55, 0.87); 0.002	0.87 (0.66, 1.16); 0.34	1.16 (0.93, 1.46); 0.19
Quartile 4	0.81 (0.60, 1.08); 0.14	0.90 (0.72, 1.12); 0.35	1.20 (0.94, 1.54); 0.14	1.52 (1.20, 1.94); 0.001

Adjusted models included following variables: age, gender, hypertension, diabetes mellitus, race, smoking status, alcohol use, estimated GFR

ALT = alanine aminotransferase, AST= aspartate aminotransferase; GGT= gamma-glutamyl transferase; ALP= alkaline phosphatase

Table 3: Results of the Cox Proportional Hazards Models using Piecewise Spline with a Single Knot at Median

	Unadjusted	**Adjusted**
ALT – before median (≤19 IU/L)	0.70 (0.54, 0.92); 0.01	0.70 (0.52, 0.94); 0.02
ALT – after median (>19 IU/L)	1.02 (1.01, 1.03); <0.001	1.02 (1.01, 1.03); <0.001
AST – before median (≤23 IU/L)	0.58 (0.43, 0.76); <0.001	0.64 (0.47, 0.87); 0.004
AST – after median (>23 IU/L)	1.04 (1.03, 1.05); <0.001	1.03 (1.02, 1.04); <0.001
GGT – before median (≤18 IU/L)	1.29 (1.03, 1.61); 0.03	1.04 (0.81, 1.35); 0.75
GGT – after median (>18 IU/L)	1.02 (1.01, 1.02); <0.001	1.01 (1.01, 1.02); 0.001
ALP – before median (≤72 IU/L)	1.12 (1.02, 1.25); 0.02	1.10 (0.99, 1.23); 0.08
ALP – after median (>72 IU/L)	1.05 (1.03, 1.07); <0.001	1.05 (1.02, 1.08); <0.001

Adjusted models included following variables: age, gender, hypertension, diabetes mellitus, race, smoking status, alcohol use, estimated GFR

ALT = alanine aminotransferase, AST= aspartate aminotransferase; GGT= gamma-glutamyl transferase; ALP= alkaline phosphatase

Figures

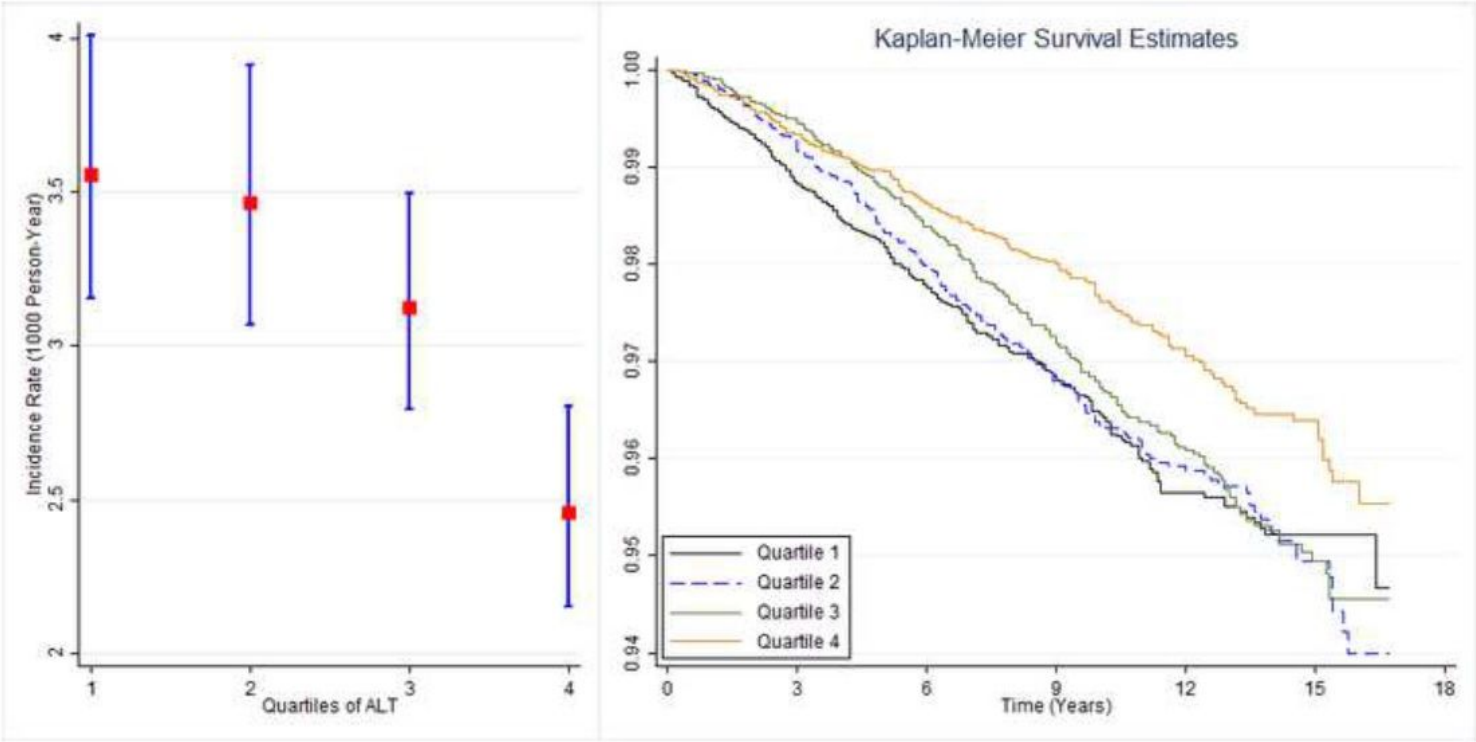

Figure 1

Mortality rate and Incidence rate across quartiles of ALT

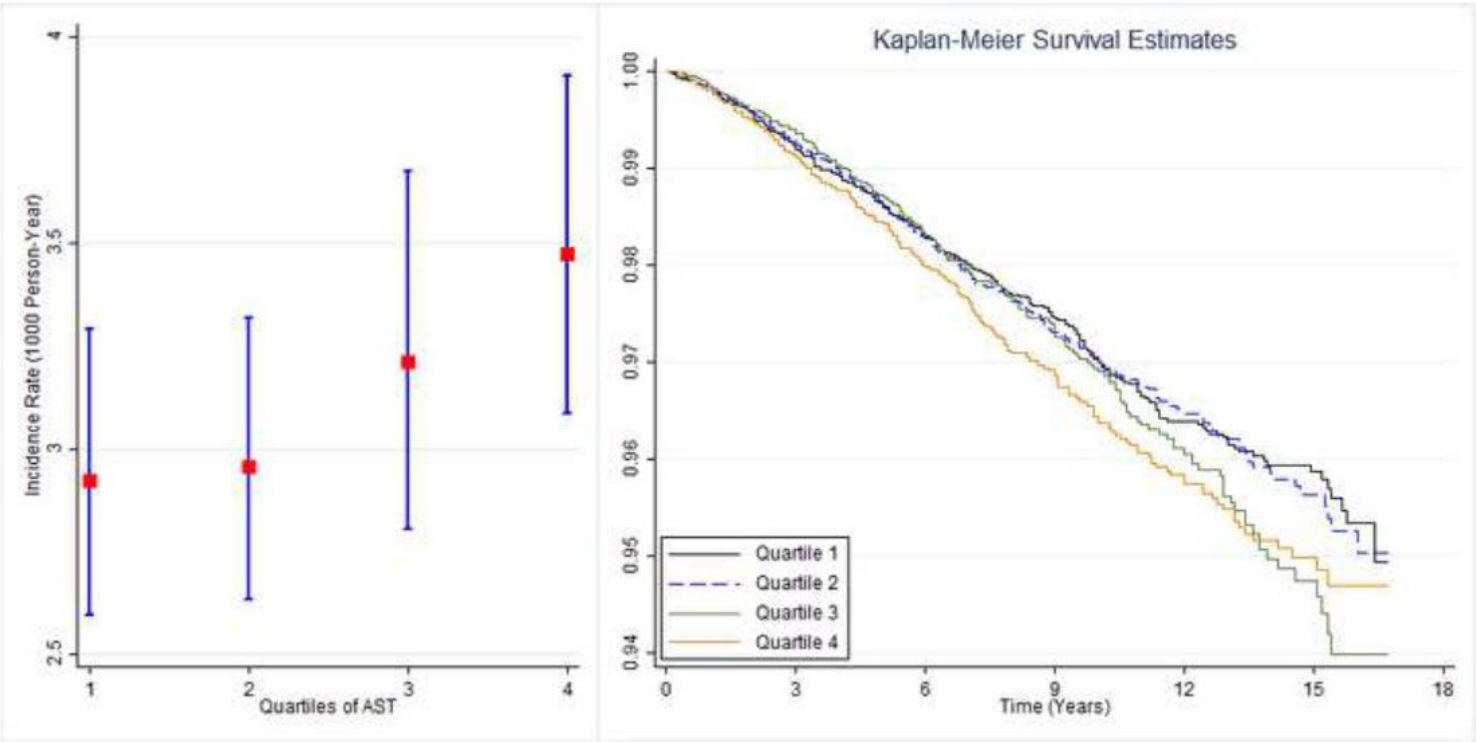

Figure 2

Mortality rate and Incidence rate across quartiles of AST

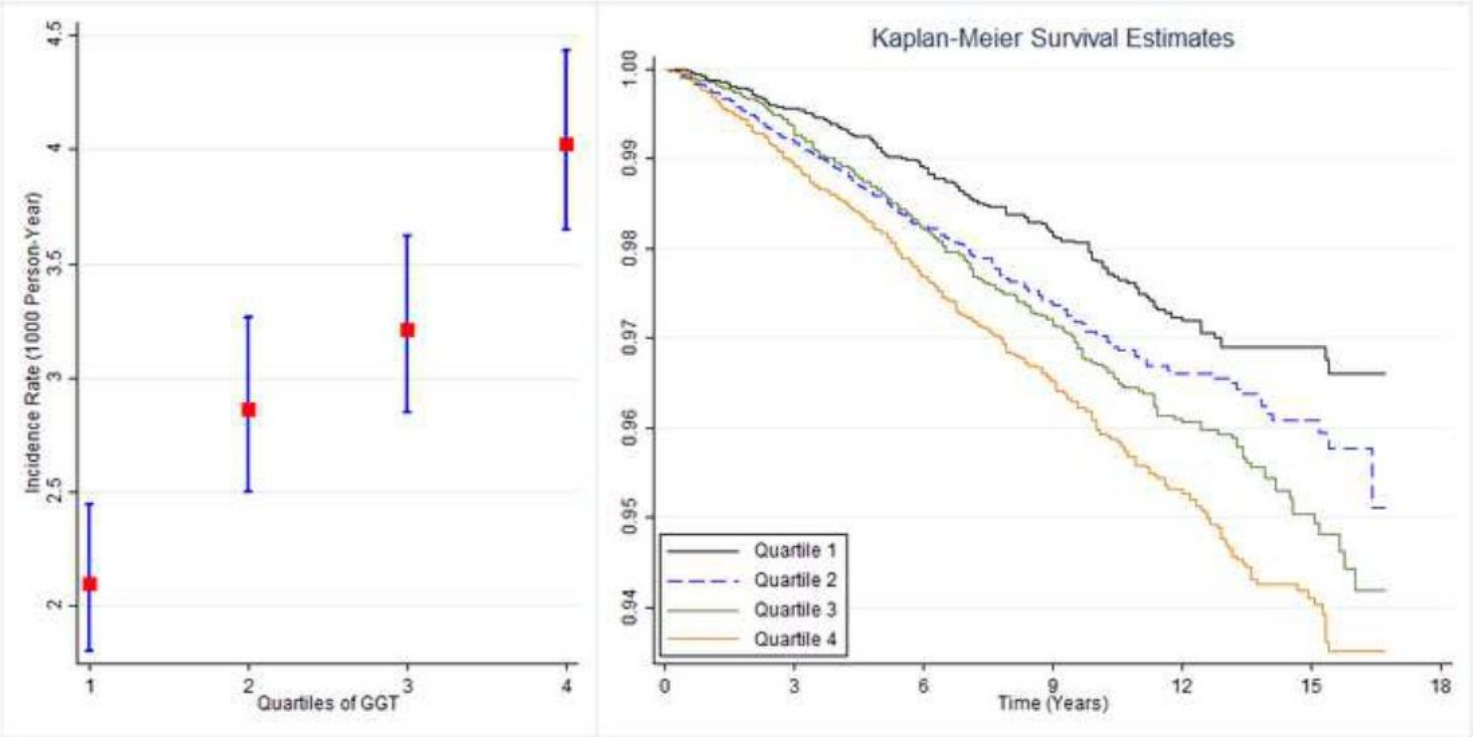

Figure 3

Mortality rate and Incidence rate across quartiles of GGT

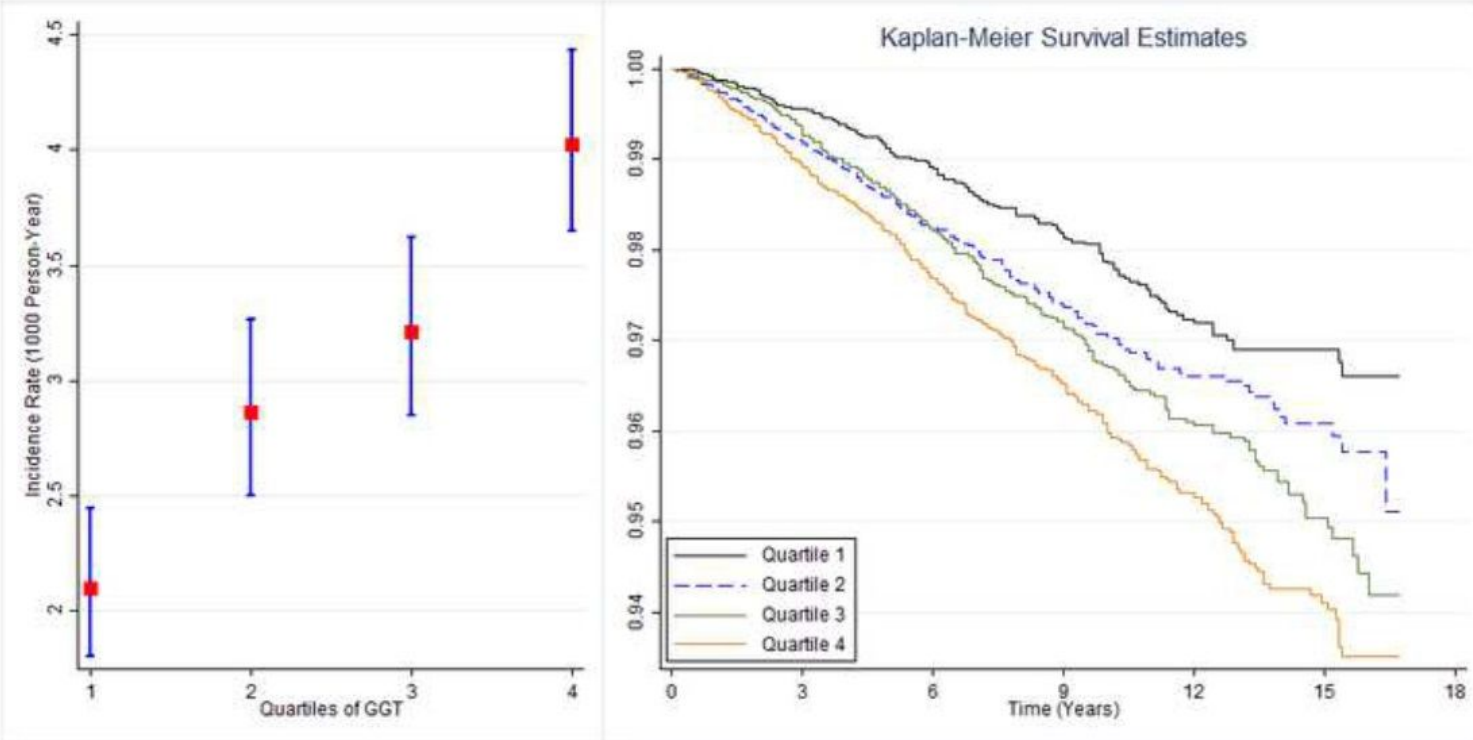

Figure 4

Mortality rate and Incidence rate across quartiles of ALP