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Elevated alanine transaminase is nonlinearly associated with in-hospital death in ICU-admitted diabetic ketoacidosis patients

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ABSTRACT

Aims: To investigate the association between alanine transaminase (ALT) and in-hospital death in patients admitted to the intensive care unit for diabetic ketoacidosis (DKA).
Methods: A cohort of 2,684 patients was constructed from the eICU Collaborative Research Database. Baseline demographic and clinical characteristics were summarized. Cox regressions with restricted cubic spline functions were modelled to explore the association between alanine transaminase and in-hospital death. Subgroup analyses were conducted between sexes, age groups, and people with/without obesity.
Results: After adjusting multiple confounders, a nonlinear, S-shaped association between ALT and in-hospital death was found. Compared to patients at median ALT, patients at the 90th percentile of ALT have a 1.88 (95 % confidence interval [CI]: 1.34–2.62) times higher hazard of in-hospital death in the unstratified cohort. Similar results were found in males (hazard ratio [HR] = 1.69, 95 % CI: 1.24–2.30); patients aged under 65 years (HR = 1.65, 95 % CI: 1.09–2.49); patients aged 65 years or above (HR = 3.45, 95 % CI: 1.67–7.14); non-obese patients (HR = 1.52, 95 % CI: 1.00–2.32); and obese patients (HR = 2.76, 95 % CI: 1.38–5.54).
Conclusions: Elevated ALT is robustly associated with in-hospital death in ICU-admitted DKA patients across several subgroups. Close monitoring of ALT in these patients is recommended.

1. Introduction

Diabetes mellitus (DM) is a chronic noncommunicable disease in which the body cannot efficiently utilize blood glucose and the existence of abnormally high blood glucose for prolonged periods.

Newly diagnosed DM patients or those with a long duration of diabetes are more prone to complications [1]. Among all the acute complications, diabetic ketoacidosis (DKA) is a major metabolic complication caused by the coexistence of low effective insulin levels and high counterregulatory hormone levels [2]. Patients with type 1 diabetes mellitus (T1DM) are vulnerable to DKA by nature, as their bodies produce insufficient insulin [3]. A study in 2014 reported a 31.1 % prevalence of DKA in T1DM patients below 19 years old [4], while up to 75 % of admitted DKA patients have T1DM [5]. In type 2 diabetes mellitus (T2DM) patients, who have increased insulin resistance, DKA can be caused by treatment nonadherence, pulmonary/urinary infection, stroke, and other diseases [6]; approximately 5.7 % of young T2DM patients experience DKA [4].

DKA accounts for up to 50 % of all deaths among children and young T1DM patients [6]. The mortality of DKA varies across countries, ranging from<1 % in developed Western countries [7] to 30 %, as reported in a study in India [8], with age-specific differences. In the current context of the COVID-19 pandemic, DKA patients infected with COVID-19 suffer higher mortality irrelevant of age and type of diabetes [9].

The liver can be regarded as a starting point and the main organ in DKA development. The dysregulation of insulin and counterregulatory hormones (e.g., glucagon) facilitates hepatic glucose production,

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CI, confidence interval; DKA, diabetic ketoacidosis; DM, diabetes mellitus; HR, hazard ratio; ICU, intensive care unit; ICD-9, International classification of diseases version 9; IQR, interquartile range; NAFLD, non-alcoholic fatty liver disease; RCS, restricted cubic spline; SD, standard deviation; T1/T2DM, type 1/type2 diabetes mellitus; ULN, upper limit of normal.

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leading to hyperglycemia. The elevated level of glucagon accelerates the decomposition of triglycerides in the liver, which generates free fatty acids that are then oxidized to ketone bodies. The low level of effective insulin in patients with diabetes cannot inhibit the production of ketone bodies, thus leading to a continuous increase in ketones [6].

The association between DM and the liver can be seen as a bidirectional "vicious circle" [10]. Oxidative stress induced by hyperglycemia and insulin resistance may damage liver tissue [11,12]. Dysregulated hepatic lipid metabolism in patients with diabetes results in hepatic injury and steatosis [13]. Patients with a long duration of DM are at higher risks for non-alcoholic fatty liver disease (NAFLD) and cirrhosis. DM is also associated with increased severity of hepatic diseases [14]. Conversely, most patients with cirrhosis have glucose intolerance, and 30 % may be clinically diabetic [14]. NAFLD, a precursor of cirrhosis, is also a risk factor for DM [10].

Alanine transaminase (ALT) mainly exists in the cytoplasm of liver cells. It is a specific marker of hepatocellular injury. Elevated ALT is positively associated with all-cause mortality [15–17], non-liver disease mortality [16], and standardized mortality rate [18] in the general population and T2DM patients. Nonetheless, there are inconsistencies regarding the direction and strength of the association between ALT and mortality. One study on 484,472 general Korean participants demonstrated a positive association between ALT and all-cause mortality [15]. A study in the Netherlands showed a U-shaped association between ALT and all-cause mortality in T2DM patients [17]. One Australian study reported an inverse linear association between ALT and all-cause mortality when ALT was below 50 U/l [19]. Another population-based study using the National Health and Nutrition Examination Survey demonstrated an inverse ALT-mortality association only when ALT $<$ 17 U/l, and no significant association was found at higher ALT levels [20].

Considering the acute manifestation, high prevalence, and lethality of DKA, together with the liver's role in glycaemia regulation, it is necessary to explore the association between the liver and mortality in DKA patients. Nonetheless, to the best of our knowledge, existing studies on the liver and mortality showed inconsistencies, and research on the liver in DKA patients is scarce. To bridge the knowledge gap, this research explored the association between ALT and in-hospital death in ICU-admitted DKA patients using a large-scale, multicenter database; to offer possible clinically meaningful findings in the management of DKA patients.

2. Material and methods

Research data were extracted from the eICU Collaborative Research Database, which included medical information on 200,859 ICU admissions for 139,367 unique patients who were admitted to 335 ICUs across 208 hospitals in the USA between 2014 and 2015 [21]. The corresponding author has completed PhysioNet training and was authorized to access the eICU database.

2.1. Study population

A total of 3,658 DKA patients were initially identified by looking for International Classification of Diseases version 9 (ICD-9) code 250.1 (Diabetes with ketoacidosis) and the text "DKA/diabetic ketoacidosis" in the diagnosis datafile. The exclusion criteria included: (1) discharged within 24 h after ICU admission; (2) incomplete demographic data; (3) no laboratory record of ALT; and (4) ALT or aspartate transaminase (AST) $\geq$ 1000 U/l by ICU admission. For patients with multiple ICU admissions, only the first admission record was kept. A total of 2,684 DKA patients entered the study cohort.

2.2. Sample size justification

One large-scale epidemiological study with a study size of 20,756 general people showed an average hazard ratio (HR) of 1.22 in the association between elevated ALT and all-cause mortality [16]. The required sample size to measure this hazard ratio was 1,276 people at a two-sided significance level of 0.05, with 90 % power. Our study size was 2,684 people. It has a power of 99.91 % to identify the published HR of 1.22 at a significance level of 0.05. In addition, with the same significance level and a 90 % power, our research can identify a minimum effect size of 0.135 (i.e., HR = 1.135); the sample size of our research was justified.

2.3. Selection of lab test results

In one ICU stay, a lab item (e.g., glucose) could be repeatedly tested as treatment proceeded. To capture the value of lab items most representative of a patient's baseline status at the time of ICU admission, the test result of a lab item which record time was closest to the ICU admission time and within 24 h of ICU admission was used. Lab data have been technically validated and checked for integrity following a series of procedures stated in the database document [21].

2.4. Exposure and outcome measurements

The exposure of this study was a patient's ALT measured at the time closest to the ICU admission time and within 24 h of ICU admission. The "labResultOffset" column of the "lab" table in the eICU database stored the interval between a patient's ICU admission time and the time a biomarker's lab value was drawn. By joining the "lab" table with patient information and selecting the minimum offset value, the exact ALT value measured closest to the ICU admission of each patient was identified.

The study outcome was in-hospital death. In-hospital death was defined as death occurring on or before the day of hospital discharge. It was identified by examining the "hospitalDischargeStatus" and "unitDischargeStatus" of the patient table. The general introduction of table structure and database schema can be freely accessed at https://eicu-crd.mit.edu.

2.5. Identification of covariates

Based on clinical knowledge and a series of existing publications on DKA, both demographic, medical, and lab test covariates were selected [2,3,6,22]. Body mass index (BMI) was calculated as admission weight in kilograms divided by the square value of admission height in meters. Ethnicity was categorized as White, Black, Asian and others, as documented in the database. Complications diagnosed during the ICU stay were identified by examining ICD-9 codes and diagnosis text of the Philips eCareManager system from the database. The complications included in this research were hypertension (401. *), myocardial infarction (410. *), heart failure (428. *), stroke (430–434. *), pulmonary infection (480–486. *, 491. *, 507. *), chronic liver disease (571. *), chronic kidney disease (585. *), and urinary infection (595. *, 599.0). Lab test items were alkaline phosphatase, albumin, serum creatinine, glucose, and anion gap.

2.6. Statistical analysis

Baseline characteristics of the study cohort were stratified by the quartile of their baseline ALT levels. Continuous data were presented as the mean (standard deviation [SD]) for normally distributed data and the median (interquartile range [IQR]) for skewed data. Categorical data were presented as the total number of an item with column percentage (n [%]) unless otherwise specified. Crude comparisons between strata were performed using Kruskal-Wallis rank test for continuous data and chi-square tests for categorical variables.

Based on existing studies, a nonlinear association between baseline ALT and in-hospital mortality was hypothesized. Cox proportional hazards models with restricted cubic spline functions (RCSs) were created to test the nonlinear hypothesis. The outcome event was the in-

hospital death of a patient. The follow-up period was defined as the interval between ICU admission and the outcome event or hospital discharge if no event occurred.

The restricted cubic spline function is a widely used approach to investigate the nonlinear effects of continuous variables [23,24]. As recommended, RCS with 3 ~ 5 knots was constructed, and the model with the lowest Akaike information criterion value was selected [25]. The reference ALT value was set at the median of the ALT of the study cohort. Subgroup analysis was conducted between male and female patients with a sex-specific upper limit of normal (ULN) for ALT at 33 U/l for males and 25 U/l for females, as defined by the American College of Gastroenterology in 2017 [26]. In addition, the associations in younger and older adults (cutoff value: age 65), and non-obese and obese patients (cutoff value: BMI 30 kg/m^2) were explored.

Sensitivity analysis was performed to evaluate the effect of using the ALT percentiles as the study exposure. Considering that 21.4 % (784 out of 3,658) of the entire study population had no ALT records and were excluded, the baseline characteristics of people with and without ALT records were compared to evaluate missing data. Univariate Cox regression was performed to evaluate the association between missing data and in-hospital death. Analyses were performed using STATA 16.0/MP (StataCorp, USA). A two-sided P value < 0.05 was considered statistically significant.

2.7. Ethical approval

The study was exempt from institutional review board approval due to the retrospective design, lack of direct patient intervention, and security schema, for which the reidentification risk was certified as meeting safe harbor standards by an independent privacy expert (Privacert, Cambridge, MA; Health Insurance Portability and Accountability Act Certification no. 1031219–2).

3. Results

3.1. Baseline characteristics

During a median follow-up time of 3.30 days, a total of 78 deaths occurred in the cohort. Significant differences in baseline characteristics including sex, in-hospital death, ethnicity, BMI, chronic liver disease, ALT, alkaline phosphatase, albumin, serum creatinine, and blood glucose were found among baseline ALT quartiles (Table 1).

3.2. Association between ALT and in-hospital death

Following the Akaike information criterion, a total of 3 knots were used in modeling. Knot positions were selected at the 10th, 50th, and 90th percentiles of baseline ALT levels [24], among which the 50th percentile was selected as the reference value. In the unstratified cohort, a consistently significant nonlinear association (P for nonlinearity < 0.001) between baseline ALT and in-hospital death was observed after adjusting for multiple confounders. In the final adjusted model (Model 3), starting from the minimum level of baseline ALT (4 U/l), the hazard ratio of in-hospital death had a steep S-shaped increase until ALT reached the 90th percentile point (ALT = 72 U/l), where the hazard ratio was 1.88 (95 % CI: 1.34–2.62). Above 72 U/l, the hazard ratio had a relatively flat increase (Fig. 1).

By sex, 37.51 % (521 out of 1389) of males and 41.70 % (540 out of 1295) of females had ALT levels that exceeded the sex-specific normal upper limit of ALT (male: 33 U/l, female: 25 U/l). In the male cohort, a significant nonlinear, S-shaped association (P for nonlinearity < 0.001) similar to that of the unstratified cohort was observed between ALT and in-hospital death after adjusting for multiple confounders. The magnitude of the association at the 90th percentile of baseline ALT was slightly attenuated (HR = 1.69, 95 % CI: 1.24–2.30) compared to the unstratified cohort (HR = 1.88, 95 % CI: 1.34–2.62). In the female cohort, no significant nonlinear association was observed (P for nonlinearity = 0.31). The possible linear association between ALT and in-hospital death in females was explored using Cox regression, and no significant association (P = 0.86) was observed (Fig. 2).

Table 1
Baseline characteristics of 2,684 ICU-admitted DKA patients stratified by ALT Quartile.

Baseline characteristics	Overall	ALT Quartile				P-value
		Q1 (The lowest)	Q2	Q3	Q4 (The highest)	
Number of patients, n (row %)	2684 (100.00)	768 (28.61)	618 (23.03)	628 (23.40)	670 (24.96)	–
In-hospital death, n (%)	78 (2.91)	14 (1.82)	12 (1.94)	13 (2.07)	39 (5.82)	< 0.001
Male, n (%)	1389 (51.75)	316 (41.15)	315 (50.97)	360 (57.32)	398 (59.40)	< 0.001
Age at admission, mean (SD) (year)	46.10 (17.48)	46.56 (18.17)	46.02 (17.97)	46.14 (17.20)	45.60 (16.49)	0.87
Ethnicity, n (%)						
White	2039 (75.97)	559 (72.79)	464 (75.08)	493 (78.50)	523 (78.06)	< 0.001
Black	402 (14.98)	127 (16.54)	95 (15.37)	83 (13.22)	97 (14.48)	< 0.001
Asian and others	243 (9.05)	82 (10.68)	59 (9.55)	52 (8.28)	80 (7.46)	< 0.001
Body mass index, mean (SD) (kg/m^2)	27.29 (7.68)	26.82 (7.20)	26.84 (7.24)	27.37 (7.73)	28.15 (8.45)	0.05
Complications, n (%)						
Chronic kidney disease	191 (7.12)	63 (8.20)	31 (5.02)	53 (8.44)	44 (6.57)	0.06
Chronic liver disease	52 (1.94)	4 (0.52)	6 (0.97)	13 (2.07)	29 (4.33)	< 0.001
Heart failure	53 (1.97)	20 (2.60)	8 (1.29)	11 (1.75)	14 (2.09)	0.35
Pulmonary infection	128 (4.77)	37 (4.82)	20 (3.24)	35 (5.57)	36 (5.37)	0.20
Urinary infection	137 (5.10)	49 (6.38)	24 (3.88)	30 (4.78)	34 (5.07)	0.20
Hypertension	261 (9.72)	64 (8.33)	58 (9.39)	72 (11.46)	67 (10.00)	0.26
Stroke	22 (0.82)	3 (0.39)	9 (1.46)	5 (0.80)	5 (0.75)	0.18
Myocardial infraction	59 (2.20)	11 (1.43)	12 (1.94)	18 (2.87)	18 (2.69)	0.23
Blood chemistry						
Alanine transaminase, median (IQR) (U/l)	25 (22)	13 (6)	21 (4)	31 (5)	61 (53)	< 0.001
Alkaline phosphatase, mean (SD) (U/l)	132.81 (93.02)	112.69 (53.83)	125.10 (49.12)	135.06 (80.97)	160.86 (147.29)	< 0.001
Albumin, mean (SD) (U/l)	3.65 (0.82)	3.51 (0.81)	3.74 (0.81)	3.71 (0.81)	3.65 (0.85)	< 0.001
Serum creatinine, mean (SD) (mg/dL)	1.58 (1.49)	1.53 (1.48)	1.52 (1.36)	1.65 (1.61)	1.64 (1.50)	0.01
Blood glucose, mean (SD) (mg/dL)	399.63 (245.07)	377.07 (216.26)	408.42 (244.17)	390.93 (233.66)	425.55 (279.64)	0.04
Anion gap, mean (SD) (mEq/L)	22.86 (7.83)	22.45 (7.73)	22.74 (7.57)	22.86 (7.90)	23.43 (8.09)	0.18

ALT alanine transaminase; IQR interquartile range; SD standard deviation.
% is column percentage unless otherwise specified.

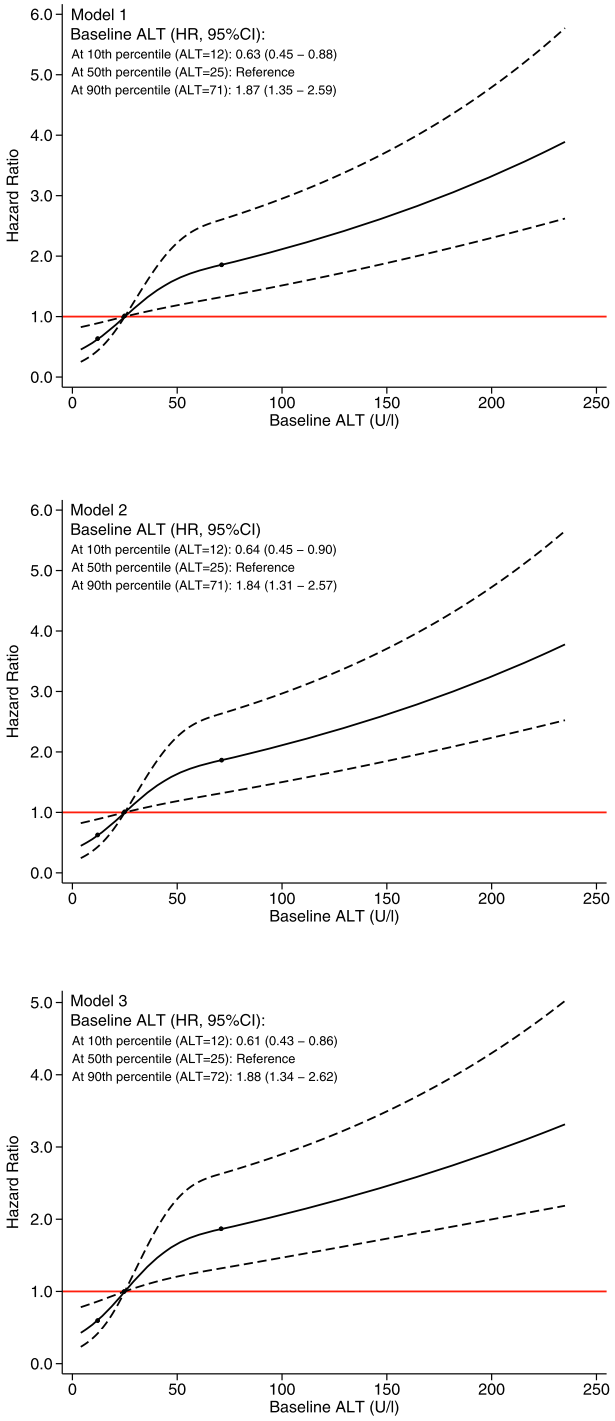

Fig. 1. Nonlinear association between ALT and in-hospital death in the unstratified cohort. (From top to bottom) Model 1 was adjusted for sex, age at admission, ethnicity, and body mass index. Model 2 was adjusted for the variables in Model 1, plus chronic kidney disease, heart failure, pulmonary infection, urinary infection, hypertension, stroke, myocardial infarction, and chronic liver disease. Model 3 was adjusted for the variables in Model 2, plus blood glucose, anion gap, serum creatinine, alkaline phosphatase, and albumin. The dashed lines indicate the 95% confidence intervals. The dots indicate the 10th, 50th, and 90th percentile of ALT. ALT alanine transferase; CI confidence interval; HR hazard ratio.

Age under 65 years had a significant nonlinear association (P for nonlinearity < 0.001). At ALT levels above the median (ALT = 25 U/l), there was a marginally significant association with a lower limit of 95 % CI very close to 1.0. On average, patients at the 90th percentile of ALT have a 1.65 times higher hazard of in-hospital death (HR = 1.65, 95 % CI: 1.09–2.49). At an ALT above the 90th percentile, ALT was significantly associated with in-hospital death. In people over 65 years, ALT showed a significant dose–response association (P for nonlinearity < 0.001) with in-hospital death. Patients above the ALT median had hazard ratios with 95 % CIs clearly above 1.0. Patients at the 90th percentile of ALT had a 3.45 times higher hazard of in-hospital death (HR = 3.45, 95 % CI: 1.67–7.14) than patients at the reference ALT level (Fig. 3).

In both non-obese and obese patients, ALT showed a significant nonlinear association with in-hospital death (P for nonlinearity < 0.05). The magnitude of the association was higher in obese people. At the 90th percentile of ALT, obese people had a 2.76 times (95 % CI: 1.38–5.54) higher hazard of in-hospital death than people with reference ALT. In non-obese people, this effect was attenuated to 1.52 (95 % CI: 1.00–2.32; Fig. 4).

3.3. Sensitivity analyses

Sensitivity analyses using the percentiles of ALT as the study exposure showed findings similar to the main analysis that used ALT values. Compared to people in the 50th percentile of ALT, people in the 90th percentile of ALT had a 2.40 times higher hazard of in-hospital death on average (HR = 2.40, 95 % CI: 1.39–4.13). Below the 50th percentile of ALT, no significant association was observed between the ALT percentile and in-hospital death (Supplementary Figure 1).

Analysis of the missingness of ALT showed that people without ALT records were at a younger age, black ethnicity, fewer chronic liver diseases/urinary infections, more hypertensive/stroke, and had lower alkaline phosphatase/albumin/blood glucose/anion gaps (Supplementary Table 1). No significant association between the missingness of ALT and in-hospital death was found (P = 0.11).

4. Discussion

This study demonstrated that ALT was an independent risk factor for in-hospital death in ICU-admitted DKA patients. After adjusting for multiple confounders, ALT was S-shaped and nonlinearly associated with in-hospital death. The findings remained consistent in the unstratified cohort and the male cohort, age-specific cohorts, and obesity-specific cohorts. The sensitivity analysis results supported the main analysis, and the missingness of ALT was not significantly associated with in-hospital death.

The reasons behind the positive association we found between ALT and in-hospital mortality can be elaborated in physiological terms. Elevated serum ALT has been recognized as a biomarker of hepatocyte damage. High ALT may imply hepatic damage in which the liver glycogen storage capacity is impaired. It should be noted that liver abnormalities are common in patients with diabetes [27]. One pathological study of 16 patients who died from their first DKA manifestation showed that 93.75 % (15 out of 16) of patients had steatosis, and 87.50 % (14 out of 16) of patients had fibrosis, together with nine cases of liver inflammation [28]. In compensated cirrhotic patients whose ALT levels were commonly high, the hepatic glycogen storage capacity was around 66 % of that in healthy people, with a 3.5-fold lower net hepatic glycogenolysis [29]. With a similar glucose production rate between healthy and cirrhotic patients, the gluconeogenesis rate in cirrhotic patients must be increased to maintain glucose production for peripheral metabolism [29,30]. The same phenomenon was also found in patients with noncirrhotic liver abnormalities [31]. Patients with diabetes are characterized by a prolonged duration of high blood glucose; thus, an increased gluconeogenesis rate is very likely to lead to hyperglycemia,

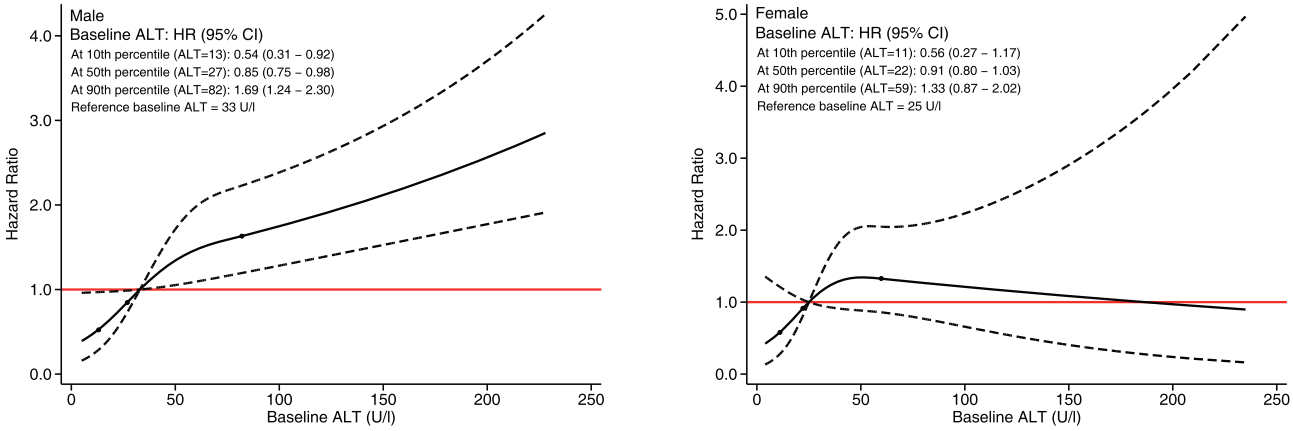

Fig. 2. Sex-specific association between ALT and in-hospital death in the study cohort. Models were adjusted for sex, age at admission, ethnicity, body mass index, chronic kidney disease, heart failure, pulmonary infection, urinary infection, hypertension, stroke, myocardial infarction, chronic liver disease, blood glucose, anion gap, serum creatinine, alkaline phosphatase, and albumin. The dashed lines indicate the 95% confidence intervals. The dots indicate the 10th, 50th, and 90th percentile of ALT. ALT alanine transferase; CI confidence interval; HR hazard ratio.

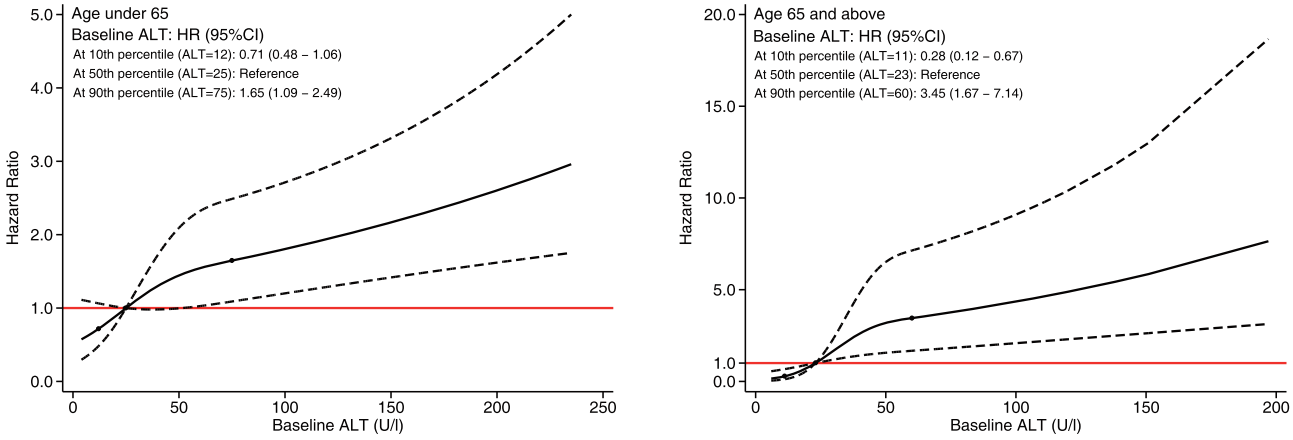

Fig. 3. Age-specific association between ALT and in-hospital death in the study cohort. Models were adjusted for sex, age at admission, ethnicity, body mass index, chronic kidney disease, heart failure, pulmonary infection, urinary infection, hypertension, stroke, myocardial infarction, chronic liver disease, blood glucose, anion gap, serum creatinine, alkaline phosphatase, and albumin. The dashed lines indicate the 95% confidence intervals. The dots indicate the 10th, 50th, and 90th percentile of ALT. ALT alanine transferase; CI confidence interval; HR hazard ratio.

which independently facilitates the production of oxidative stress biomarkers and proinflammatory cytokines (e.g., thiobarbituric acid and interleukin-6), even in the absence of ketoacidosis [32]. These proinflammatory cytokines can stimulate lipolysis [33], which generates free fatty acids and ketone bodies [2], thus exacerbating DKA and increasing the risk of death.

In our study, low ALT levels had no significant association with mortality. This is inconsistent with several studies [15,17,34],. One theory behind the association between low ALT levels and mortality is that frailty is a mediator of the pathway between low ALT levels and mortality [35]. However, this theory is not without controversy. A multicenter study found minor changes in the association between ALT and all-cause mortality after adjusting for frailty and its biomarkers, suggesting a less important mediating role of frailty [19]. Moreover, frailty is a consequence of age-related degradation of multiple systems [36], and its prevalence is approximately 5 % in people aged below fifty [37]. Studies that observed an association between low ALT and mortality [15,17] have populations older (mean age: 53–67 years) than our study cohort (mean age: 46.10 years). Our young study cohort may have a very low prevalence of frailty, and thus, no association between low ALT and mortality was observed.

No significant association between ALT and in-hospital death was found in females. This finding was supported by one study [16]. Nonetheless, it remained controversial, as another study found similar associations in both sexes [18]. Several possible reasons may contribute to the inconsistency in our sex-specific findings. First, the difference in reaction to alcohol and the effect of sex hormones may be attributable to the inconsistent findings. Males are more likely to die from chronic liver disease [38]. Second, male DKA patients have significantly higher in-hospital mortality than female DKA patients [39]. Third, the difference in study population and outcome among studies may generate diverse conclusions. Despite all the above reasons, the sex-specific role of the liver and liver enzymes are unclear and require further exploration.

As expected, the association between ALT and in-hospital death has a larger magnitude in patients aged 65 or above and those with obesity. The decrease in ALT level along with aging indicates that hepatocellular damage that caused ALT elevation could be more severe in elderly patients than in younger patients [40]. The aging liver has delayed restoration of liver function and a decreased mass of functional liver cells,

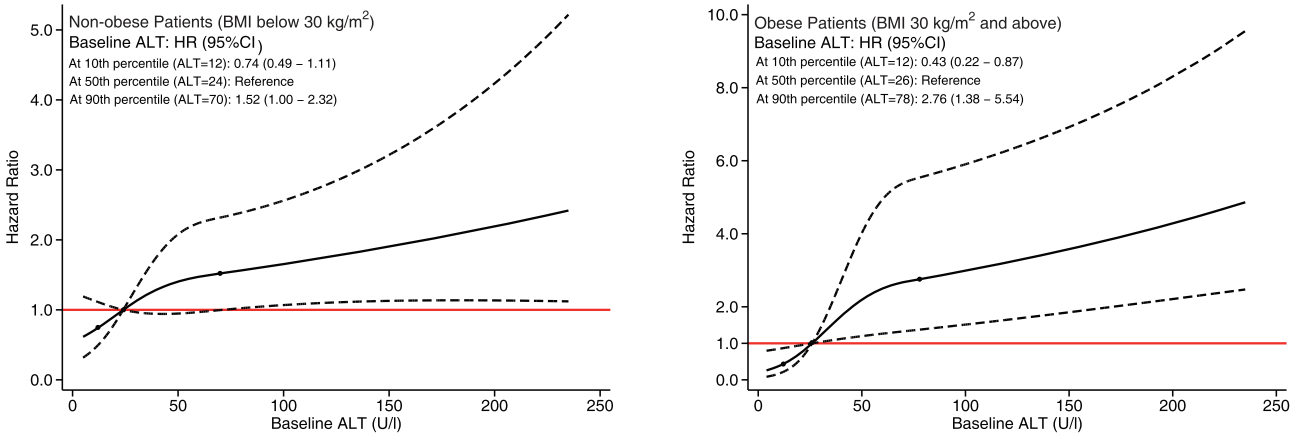

Fig. 4. Obesity-specific association between ALT and in-hospital death in the study cohort. Models were adjusted for sex, age at admission, ethnicity, body mass index, chronic kidney disease, heart failure, pulmonary infection, urinary infection, hypertension, stroke, myocardial infarction, chronic liver disease, blood glucose, anion gap, serum creatinine, alkaline phosphatase, and albumin. The dashed lines indicate the 95% confidence intervals. The dots indicate the 10th, 50th, and 90th percentile of ALT. ALT alanine transferase; CI confidence interval; HR hazard ratio.

implying vulnerability to prolonged metabolic dysfunction [41], which contributes to the severity of DKA. Obesity is associated with increased in-hospital mortality in DKA patients [39]. Obesity is also associated with an increased risk of steatosis and cirrhosis. In the presence of NAFLD, obese patients have a faster fibrosis progression [42]. All these diseases may manifest as elevated ALT levels.

The strengths of this study are its large size, cohort design, multicenter data source, and overall consistent results in subgroups. Nevertheless, limitations should be considered in interpreting our results. First, our models did not adjust for blood pH, which is an important biomarker of DKA severity. It was because 47 % (1,274 out of 2,684) of patients had no pH data. Using complete case analysis would have greatly reduced the sample size and the power, and using multiple imputation is not recommended with this large proportion of missing data [43]. Second, glycated hemoglobin and duration of diabetes were not adjusted due to data availability. It is recognized that glycated hemoglobin is a biomarker of long-term glycemic control and reflects a patient's average blood glucose level in the past two to three months. Higher glycated hemoglobin indicates insufficient control of blood glucose, and thus may have a higher chance of DKA manifestation. Patients with a long duration of diabetes are more common to have severe liver disease, including cirrhosis which leads to elevated ALT [14,44,45]. Should glycated hemoglobin or the duration of diabetes be adjusted, it is expected that our findings will be attenuated. We expected to include these data in future research in a different dataset. Third, the eICU database does not include the time when a lab specimen was collected from patients. Instead, it reports the time when a lab value is available. The latter was used as a proxy for specimen collection time in our study. This may introduce bias because patient status may change during the time interval between specimen collection and lab value release. However, this is regarded as a nondifferential misclassification and will not affect the estimation. Fourth, as patients could be admitted to the ICU at any time, no specific time patterns of blood collection could be identified. This may introduce bias as the possible diurnal variation of biomarkers was left unadjusted. Fifth, only complications documented within the ICU stay were recorded in the database. There may be omitted complications that, if adjusted for, will attenuate the magnitude and strength of our reported findings. Last, lifestyle, diet pattern, and medication adherence were not adjusted, as they were not covered by the database.

5. Conclusion

In conclusion, our study indicated that the level of serum alanine transferase was nonlinearly associated with in-hospital mortality in ICU-admitted DKA patients. With adjustments for multiple confounders, the adjusted hazard of in-hospital mortality was significantly higher in patients with ALT above the 50th percentile of the study cohort. Patients with obesity and those aged 65 years or above with elevated ALT were more vulnerable to in-hospital death than their non-obese and younger counterparts. No association between ALT and in-hospital death was observed in females; further research on female patients is needed. In sum, ICU-admitted DKA patients with elevated alanine transferase above the population median should be paid close attention to in clinical settings.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2023.110555.

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