Association Between the Non-HDL-Cholesterol-to-HDL-Cholesterol Ratio and 28-Day Mortality in Septic Patients: A Cohort Study Based on the eICU Collaborative Research Database

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Research

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Abstract

Background: Dyslipidemia contributes to the development and progression of cardiovascular disease. However, the potential association between non-high-density lipoprotein-cholesterol-to-high-density lipoprotein-cholesterol (nonHDLc/HDLc) ratio and mortality in septic patients is unclear.

Methods: This was a retrospective cohort study of patients with sepsis in the eICU Collaborative Research Database (eICU-CRD) from 208 distinct ICUs across the United States between 2014 and 2015. All-cause mortality within 28-days after ICU admission. A multivariable logistic regression model was used to estimate the risk of death.

Result: Of the 724 patients with a median age of 68 years, 43 (5.94%) died within 28 days after ICU admission. The association between the nonHDLc/HDLc ratio and the risk of all cause mortality was J shaped, and a high level was associated with increased risk of all cause mortality. The mortality rate increased when the nonHDLc/HDLc ratio higher than the turning point (≥3.41) with an adjusted odds ratio (OR) of 1.34 (95% CI: 1.07–1.67, *P*=0.010) for every 1 increment of nonHDLc/HDLc ratio. With the per-SD increase in the nonHDLc/HDLc ratio, the OR of mortality was 1.79 (95% CI: 1.15–2.80, *P*=0.010) when the nonHDLc/HDLc ratio was ≥3.41. The trend of sensitivity analysis was consistent with the main analysis.

Conclusion: For patients with sepsis, the association between the nonHDLc/HDLc ratio and the 28-day mortality risk was J shaped. A higher level of nonHDLc/HDLc ratio was associated with an increased risk of 28-day mortality. These findings need to be confirmed in other studies.

Background

Sepsis is a common and lethal syndrome. The systemic inflammatory response is biologically complex, redundant, and activated by infectious and non-infectious triggers. Its manipulation can bring benefits and harm[1]. Therefore, a closer examination of the phenotypes and subphenotypes of patients who exhibit strong survival signals in sepsis may enable us to understand novel mechanisms for improving treatment.

High-density lipoprotein-cholesterol (HDLc) or low-density lipoprotein-cholesterol (LDLc) cholesterol is inversely associated with coronary heart disease (CHD)[2, 3] and can respond differently to changes in diet and treatment. A poole of 458 population-based studies involving 82.1 million participants in 23 countries in Asian and Western found that HDL cholesterol increased in many Western countries, Japan and South Korea[4]. The non-HDLc-to-high-HDLc (nonHDLc/HDLc) ratio can be obtained from the standard lipid profile without additional cost, and is highly correlated with levels of LDL particle number[4], which has been confirmed by multiple studies shows that it is a strong cardiovascular risk marker[5, 6]. We previously shown that nonHDLc/HDLc ratio is an independent risk factor for the development of chronic kidney disease (CKD)[7].

A recent clinical study showed that during a median follow-up of 1.72 years, the mortality rate associated with the range of LDLc/HDLc ratios was U-shaped in hypertensive patients[8]. However, there is a lack of evidence to guide the emergency management of patients with sepsis.

We hypothesized that in patients with sepsis, even high and low nonHDLc/HDLc ratios are associated with a higher risk of all-cause mortality within 28-days after admission to the ICU. In this retrospective multicenter cohort study, we used the eICU Collaborative Research Database (eICU-CRD), which participated in the Philips Healthcare eICU program from 208 distinct ICUs in the United States between 2014 and 2015. We aimed to explore the threshold of the nonHDLc/HDLc ratio where risk of death significantly increases is a high priority in patients with sepsis.

Methods

Data Source

We extracted data from the eICU Collaborative Research Database (eICU-CRD)[9] in accordance with the data usage agreement of the PhysioNet Review Board (our record ID: 40859994). From 2014 to 2015, all data was automatically stored through the Philips Healthcare eICU program and retrieved electronically[9]. The eICU-CRD has been used for observational research[10–12]. Ethical approval from our local ethics committee is not required, as this is a retrospective analysis based on an anonymous database of researchers.

Study population

Briefly, all patients diagnosed with sepsis on admission to the ICU were included. Sepsis was defined as suspected or documented infection plus an acute increase in SOFA score greater than 2 points[13]. Recorded on the Acute Physiology and Chronic Health Evaluation (APACHE) IV dataset[14]. The following exclusion criteria were used: (1) Not first ICU admission; (2) ICU stay < 48 hours; (3) 18 years old; (4) Missing ICU outcome; (5) Missing total cholesterol after ICU asmission and system error. The study flowchart was presented in *Fig. 1*.

Variables

The eICU database includes demographic records, physiological indicators of bedside monitors, diagnosis via International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM) codes, and other laboratory data obtained during routine medical care.

All subject data within the first 24 hours after hospitalization admission were collected from eICU-CRD. The physiological variables, including temperature (°C), respiratory rate, heart rate (HR) and mean arterial pressure (MAP), were obtained from the table apacheApsVar. Baseline characteristics such as age, gender, ethnicity, and weight were collected from the tables of patient and apachePatientResult. The laboratory indices of total cholesterol, triglycerides, HDLc, and LDLc from laboratory tables. Non-HDL-c refers to total cholesterol (TC) minus HDLc, including cholesterol in atherogenic lipoproteins.

Outcomes

The outcome of the study was all-cause ICU mortality within 30 days after admission to the ICU. In the supplemental analysis, we also analyzed 14-days mortality rate after admission to the ICU.

Statistical analysis

Continuous variables are described as means ± SD or median and interquartile ranges (IQR). Categorical data is presented as number and percentage. The difference according to the tertiles of the nonHDLc/HDLc ratio was compared using one-way analysis of variance (ANOVA) for continuous data and Chi-squared tests for categorical variables.

We applied a Generalized Additive Model (GAM) to investigate dose-response relationship between the nonHDLc/HDLc ratio and mortality (Fig. 1). We applied logistic regression model to estimate the association between the nonHDLc/HDLc ratio and 28-day mortality. The results were presented as odds ratios (ORs) with its 95% confidence intervals (95% CIs). Crude regression estimates are presented, as well as estimates adjusted for covariates. We selected these confounders on the basis of their association with the outcomes of interest or changes in effect estimates of more than 10%[15]. After considering the clinical significance, we selected to adjust the following covariates: age (years), sex, weight, heart rate, SOFA score, and site of infection.

We further applied two-piece-wise linear regression model to examine the threshold effect of the nonHDLc/HDLc ratio on mortality (Table 3). The turning point for the nonHDLc/HDLc ratio was determined using "exploratory" analyses, which is to move the trial turning point along the pre-defined interval and pick up the one which gave maximum model likelihood. We also performed a log-likelihood ratio test and compared the one-line linear regression model with two-piece-wise linear model. As described in previous analysis[16, 17].

Table 3
Threshold effect analysis of the nonHDLc/HDLc ratio and 28-day mortality

Threshold	Per-unit increase		Per-SD increase	
	OR (95%CI)	P value	OR (95%CI)	P value
NonHDLc/HDLc ratio < 3.41	0.72 (0.47, 1.10)	0.1315	0.52 (0.22, 1.22)	0.1318
NonHDLc/HDLc ratio ≥ 3.41	1.34 (1.07, 1.67)	0.010	1.79 (1.15, 2.80)	0.010
Adjusted for age (years), sex, weight, heart rate, SOFA score, and site of infection. CI, confidence interval; OR, odds ratio.				

To examine the robustness of results, we conducted sensitivity analyses. Dummy variables were used to indicate missing covariate values, which was performed when continuous variables are missing more than 1%. The two-sided alpha level was set at 0.05. All the statistical analysis was performed using the

EmpowerStats (www.empowerstats.com, X&Y solutions, Inc. Boston MA) and R software version 3.6.1 (http://www.r-project.org).

Results

Baseline characteristics

Data from 724 patients were analyzed. The median age was 68 years (IQR 58–78 years). 334 patients (46.1%) were women. Table 1 compares the patient's demographic, vital signs, laboratory, site of infection, and severity of illness through the tertiles of the nonHDLc/HDLc ratio. Compared with subjects in the lowest tertile of the nonHDLc/HDLc ratio, subjects in the highest tertile were younger and had higher admission weight.

Table 1
Baseline characteristics and 28-day mortality according to the tertiles of nonHDLc/HDL ratio (n = 724)

	nonHDLc/HDL ratio			
Parameters	**Tertile 1**	**Tertile 2**	**Tertile 3**	P **value**
	0.28–2.24	**2.25–3.83**	**3.84-10**	
	n = 241	**n = 241**	**n = 242**	
Demographics				
Age (yr)	69.6 ± 14.0	67.2 ± 14.7	63.3 ± 15.9	< 0.001
Sex				0.578
Male	124 (51.5%)	130 (53.9%)	136 (56.2%)	
Female	117 (48.5%)	111 (46.1%)	106 (43.8%)	
Ethnicity				0.904
Caucasian	173 (71.8%)	168 (69.7%)	177 (73.1%)	
African American	29 (12.0%)	35 (14.5%)	26 (10.7%)	
Hispanic	13 (5.4%)	14 (5.8%)	15 (6.2%)	
Asian	3 (1.2%)	3 (1.2%)	5 (2.1%)	
Native American	1 (0.4%)	2 (0.8%)	0 (0%)	
Other/Unknown	22 (9.1%)	19 (7.9%)	19 (7.9%)	
Admission weight (kg)	80.4 ± 24.2	85.2 ± 28.2	91.0 ± 30.8	< 0.001
Period				0.285
2014	104 (43.2%)	121 (50.2%)	110 (45.5%)	
2015	137 (56.8%)	120 (49.8%)	132 (54.5%)	
Vital signs				
Temperature (°C)	36.6 ± 1.1	36.7 ± 1.2	36.6 ± 1.3	0.759
Respiratory rate (bpm)	30.4 ± 14.6	30.1 ± 14.8	30.5 ± 14.4	0.936
Heart rate (/min)	109.5 ± 29.1	111.1 ± 28.7	115.7 ± 25.6	0.043

Data are expressed as the mean ± SD, median (interquartile range), or percentage; BP Blood pressure; GCS Glasgow Coma Scale; HDLc High-density lipoprotein cholesterol; LDLc Low-density lipoprotein cholesterol; MAP Mean Arterial Pressure; SOFA Sequential Organ Failure Assessment; UTI Urinary Tract Infection. Among the 724 patients, the amount of missing values for the covariates were: 11 (1.5%) for admission weight, 45 (6.2%) for temperature, 9 (1.2%) for respiratory rate, 5 (0.7%) for heart rate, 5 (0.7%) for MAP, 2 (0.3%) for triglycerides, 178 (24.6%) for LDLc, 7 (1.0%) for SOFA score, and 16 (2.2%) for GCS score.

	nonHDLc/HDL ratio			
MAP (mmHg)	79.7 ± 44.9	87.3 ± 47.6	77.2 ± 41.8	0.038
Laboratory data				
Total cholesterol (mg/dL)	105.5 ± 35.7	118.6 ± 41.7	123.0 ± 50.8	< 0.001
Triglycerides (mg/dL)	79 (60–107)	112 (79–158)	154 (121–216)	< 0.001
HDLc (mg/dL)	42.6 ± 14.8	30.0 ± 11.2	19.2 ± 9.2	< 0.001
LDLc (mg/dL)	46.0 ± 23.5	64.1 ± 29.6	70.2 ± 39.7	< 0.001
nonHDLc/HDL ratio	1.6 (1.2–1.9)	3.0 (2.6–3.3)	5.4 (4.5–6.6)	< 0.001
Site of infection				
Sepsis, pulmonary	112 (46.5%)	101 (41.9%)	99 (40.9%)	< 0.001
Sepsis, renal/UTI (including bladder)	55 (22.8%)	46 (19.1%)	62 (25.6%)	
Sepsis, GI	26 (10.8%)	21 (8.7%)	24 (9.9%)	
Sepsis, unknown	22 (9.1%)	29 (12.0%)	22 (9.1%)	
Sepsis, cutaneous/soft tissue	18 (7.5%)	25 (10.4%)	15 (6.2%)	
Sepsis, other	8 (3.3%)	19 (7.9%)	20 (8.3%)	
Severity of illness				
SOFA score	3.0 (1.0–5.0)	3.0 (1.0–4.0)	3.0 (1.0–5.0)	0.626
GCS score	11.8 ± 3.7	11.8 ± 3.8	12.2 ± 3.6	0.398
28-day Mortality				0.107
No	224 (92.9%)	233 (96.7%)	224 (92.6%)	
Yes	17 (7.1%)	8 (3.3%)	18 (7.4%)	

Data are expressed as the mean ± SD, median (interquartile range), or percentage; BP Blood pressure; GCS Glasgow Coma Scale; HDLc High-density lipoprotein cholesterol; LDLc Low-density lipoprotein cholesterol; MAP Mean Arterial Pressure; SOFA Sequential Organ Failure Assessment; UTI Urinary Tract Infection. Among the 724 patients, the amount of missing values for the covariates were: 11 (1.5%) for admission weight, 45 (6.2%) for temperature, 9 (1.2%) for respiratory rate, 5 (0.7%) for heart rate, 5 (0.7%) for MAP, 2 (0.3%) for triglycerides, 178 (24.6%) for LDLc, 7 (1.0%) for SOFA score, and 16 (2.2%) for GCS score.

28-Day Mortality

Within 28 days after admission to the ICU, 43 patients (5.94%) died in the ICU. The 28-day mortality rate from the lowest tertile (0.28–2.24) to the highest (3.84-10) nonHDLc/HDLc ratio was 17 (7.1%), 8 (3.3%), and 18 (7.4%), respectively (Table 1).

Unadjusted association between baseline variables and 28-day mortality

Table 2 shows the univariate logistic models. The analysis showed that compared with the low temperature group (30–36.38°C), the high temperature group (36.4–36.72°C) had a lower risk of mortality (OR = 0.28, 95% CI, 0.11–0.72, *P* = 0.0082). And compared with the low SOFA score group (all = 0), the middle and high group (range 1–3 and 4–15) had a higher risk of mortality (OR = 9.28, 95% CI, 1.21–70.97, *P* = 0.0318; OR = 14.61, 95% CI, 1.97–108.56, *P* = 0.0088).

Table 2
The unadjusted association between baseline variables and 28-day mortality (n = 724)

Exposure	Statistics	Odds ratio (95% CI)	*P* value
nonHDLc/HDL ratio	3.43 ± 2.01	1.10 (0.96, 1.27)	0.1682
nonHDLc/HDL ratio Tertile			
Low	241 (33.29%)	Reference	
Middle	241 (33.29%)	0.45 (0.19, 1.07)	0.0707
High	242 (33.43%)	1.06 (0.53, 2.11)	0.8707
Age (years) Tertile			
18–61	240 (33.15%)	Reference	
62–74	238 (32.87%)	1.88 (0.85, 4.17)	0.1189
75–89	246 (33.98%)	1.49 (0.66, 3.39)	0.3380
Source of infection			
Sepsis, pulmonary	312 (43.09%)	Reference	
Sepsis, renal/UTI (including bladder)	163 (22.51%)	0.56 (0.24, 1.34)	0.1958
Sepsis, GI	71 (9.81%)	1.16 (0.45, 2.96)	0.7566
Sepsis, unknown	73 (10.08%)	1.13 (0.44, 2.87)	0.8050
Sepsis, cutaneous/soft tissue	58 (8.01%)	0.22 (0.03, 1.67)	0.1428
Sepsis, other	47 (6.49%)	__§	0.9866
Gender			
Male	390 (53.87%)	Reference	
Female	334 (46.13%)	0.54 (0.28, 1.05)	0.0691
Ethnicity			
Caucasian	518 (71.55%)	Reference	
African American	90 (12.43%)	0.73 (0.25, 2.12)	0.5641
Hispanic	42 (5.80%)	0.79 (0.18, 3.40)	0.7468
Asian	11 (1.52%)	1.57 (0.19, 12.67)	0.6715

Data are expressed as the mean ± SD, or percentage; BP Blood pressure; GCS Glasgow Coma Scale; HDLc High-density lipoprotein cholesterol; LDLc Low-density lipoprotein cholesterol; MAP Mean Arterial Pressure; SOFA Sequential Organ Failure Assessment; UTI Urinary Tract Infection.

__§The model failed because of the small sample size.

Exposure	Statistics	Odds ratio (95% CI)	*P* value
Native American	3 (0.41%)	__§	0.9878
Other/Unknown	60 (8.29%)	1.43 (0.53, 3.82)	0.4782
Hospital discharge year			
2014	335 (46.27%)	Reference	
2015	389 (53.73%)	0.99 (0.53, 1.84)	0.9739
Admission weight, kg Tertile			
27.21–70.2	237 (33.24%)	Reference	
70.3–90.9	235 (32.96%)	1.15 (0.56, 2.37)	0.6960
91–227	241 (33.80%)	0.71 (0.32, 1.57)	0.3969
Temperature (°C) Tertile			
30–36.38	220 (32.40%)	Reference	
36.4–36.72	217 (31.96%)	0.28 (0.11, 0.72)	0.0082
36.8–41.8	242 (35.64%)	0.71 (0.36, 1.40)	0.3226
Respiratory rate (bpm) Tertile			
4–27	227 (31.75%)	Reference	
28–36	248 (34.69%)	1.50 (0.66, 3.37)	0.3301
37–60	240 (33.57%)	1.65 (0.74, 3.69)	0.2193
Heart rate (bpm) Tertile			
26–103	224 (31.15%)	Reference	
104–122	245 (34.08%)	1.20 (0.52, 2.79)	0.6736
123–201	250 (34.77%)	1.86 (0.85, 4.07)	0.1193
MAP (mmHg) Tertile			
40–51	238 (33.10%)	Reference	
52–71	240 (33.38%)	1.13 (0.55, 2.33)	0.7328
72–199	241 (33.52%)	0.71 (0.32, 1.58)	0.4031

Data are expressed as the mean ± SD, or percentage; BP Blood pressure; GCS Glasgow Coma Scale; HDLc High-density lipoprotein cholesterol; LDLc Low-density lipoprotein cholesterol; MAP Mean Arterial Pressure; SOFA Sequential Organ Failure Assessment; UTI Urinary Tract Infection.

__§The model failed because of the small sample size.

Exposure	Statistics	Odds ratio (95% CI)	*P* value
SOFA score Tertile			
0–0	152 (21.20%)	Reference	
1–3	259 (36.12%)	9.28 (1.21, 70.97)	0.0318
4–15	306 (42.68%)	14.61 (1.97, 108.56)	0.0088
GCS score group			
3–10	216 (30.51%)	Reference	
11–14	207 (29.24%)	0.62 (0.28, 1.34)	0.2229
15–15	285 (40.25%)	0.53 (0.25, 1.10)	0.0871
Data are expressed as the mean ± SD, or percentage; BP Blood pressure; GCS Glasgow Coma Scale; HDLc High-density lipoprotein cholesterol; LDLc Low-density lipoprotein cholesterol; MAP Mean Arterial Pressure; SOFA Sequential Organ Failure Assessment; UTI Urinary Tract Infection.			
*S*The model failed because of the small sample size.			

Identification of non-linear relationship

We observed a nonlinear dose-response relationship between the nonHDLc/HDLc ratio and mortality (Fig. 2 and Table 3). The probability of mortality increased when the nonHDLc/HDLc ratio higher than the turning point (≥ 3.41) with a adjusted odds ratio (OR) of1.34 (95% CI: 1.07–1.67, *P* = 0.010) for every 1 increment of nonHDLc/HDLc ratio. As the nonHDLc/HDLc ratio increased per SD, when the nonHDLc/HDLc ratio was ≥ 3.41, the OR for mortality was 1.79 (95% CI: 1.15–2.80, *P* = 0.010). (Table 3).

Using the generalized additive model, the J shaped association between the nonHDLc/HDLc ratio and 30-day mortality was detected (Table 3). The linear regression model and a two-piece-wise linear regression model were compared, and the *P* value of the log-likelihood ratio test is < 0.037. This result indicates that the two-piece-wise linear regression model should be used to fit the model.

The trend of sensitivity analysis was consistent with the main analysis. In the supplementary analysis, we also analyzed 14-day mortality rate, and the result were generally similar to our main results (Figure S1 and Table S1). Dummy variables were used to indicate missing covariate values. Similar results were obtained after considering the impact of missing data (Table S2).

Discussion

This retrospective cohort study found that higher nonHDLc/HDLc ratio was associated with a higher risk of 30-day mortality in patients with sepsis in the eICU-CRD database from 208 distinct ICUs across the United States between 2014 and 2015. The major finding was that the association between the nonHDLc/HDLc ratio and the risk of all cause mortality was J shaped, with high levels associated with an

increased risk of all cause mortality. To our knowledge, this is the first study to report the association between the nonHDLc/HDLc ratio and 28-day mortality in septic patients.

Most studies investigating the relationship between levels of LDLc and the risk of death found no association[18–20] or an inverse association[21–23]. A prospective population-based cohort study with 5 years of follow-up and a validation cohort of African Americans with 4.25-year follow-up show that neither HDLc nor LDLc is associated with mortality[18]. One data from 1948 to 1980 on 5209 men and women enrolled in the Framingham Heart Study found that the negative results in the oldest age group for all-cause morality appeared to be due to a negative relationship with LDL-C levels rather than the protective effect of high HDLc levels[19]. You et al.[24] included 356 patients with intracranial hemorrhage (mean follow-up = 0.22 years) found that the LDLc/HDLc ratio was negatively correlated with all-cause mortality. Liu et al.[25] recruited 3250 stroke patients and found a negative relationship between the LDLc/HDLc ratio and all-cause mortality.

Through observational studies have established that HDLc is inversely associated with both cardiovascular disease and mortality across a wide range of concentrations[26]. A study by Bowe et al.[27] included 1,764,986 men who were US veterans (mean follow-up = 9.1 years) and found a U-shaped relationship between HDL cholesterol and risk of all-cause mortality. A study by Madsen et al.[28] included 116,508 individuals from the general population, the association between HDL cholesterol and all-cause mortality was U shaped, with both extreme high and low HDL cholesterol levels associated with high mortality. No previous study has examined HDLc or LDLc levels associated with the lowest risk of mortality in patients with sepsis. To our knowledge, although the relationship between blood lipids levels and mortality has been concerned, the association between nonHDLc/HDLc ratio and 30-day mortality are still unclear, which prompted us to conduct the current study.

We used non-HDL cholesterol rather than LDL cholesterol because our database measures TC and HDL cholesterol and can be calculated by subtracting non-HDL cholesterol from it. Of the 724 patients included, 178 did not have LDL measurements. In addition, the most commonly used estimation method, the Friedewald equation, can be inaccurate[29]. That non-HDL and LDL cholesterol were correlated in studies with data on both variables (r = 0.93)[4]. In our study, the correlation coefficient between non-HDL and LDL cholesterol was 0.92 (95%CI: 0.91–0.94), showing a high correlation. Non-HDL cholesterol predicts CHD risk at least as well as LDL cholesterol[30] because it includes cholesterol in LDL, lipoprotein(a), intermediate-density lipoprotein, very-low-density lipoprotein and lipoprotein remnants, and is thus a simple measure of cholesterol content within all atherogenic lipoproteins.

In addition, a recent study in a Chinese Hypertension Registry study of 6,941 hypertensive patients aged 65 years or older who were not treated with lipid-lowering drugs, during a median follow-up of 1.72 years, 157 all-cause deaths occurred, a U-shaped relationship between the LDLc/HDLc ratio and all-cause mortality was found[8]. This is similar to our result that the mortality rate associated with non-HDLc / HDLc ratios is not liner.

A possible explanation for our findings was that the association between low levels of nonHDLc and an increased risk of all-cause mortality could be explained by reverse causation. Debilitation and illness are hypothesized to cause a decrease in levels of cholesterol[31, 32]. Nonetheless, cholesterol-related risks are more complex and involve the interplay of several factors such as cholesterol particle concentration, reverse cholesterol transport, and triglyceride-rich lipoproteins, to mention a few[33]. The J shaped association between nonHDLc/HDLc ratios and mortality may resemble the obesity paradox, which is largely explained by methodological issues, including reverse causation[34].

The current retrospective cohort study is based on the eICU-CRD database and may be important for understanding nonHDLc/HDLc ratios in septic patients (ie, when the focus is not limited to myocardial infarction or atherosclerotic cardiovascular disease). We investigated thresholds for nonHDLc/HDLc ratio levels that significantly increased the risk of death in patients with sepsis.

Study limitations

One limitation of this study is inherent to the observational nature of the study design, which lends itself subject to limitations that should be considered including confounding by indication. Our findings are hypothesis-generating and do not imply causality. In our analysis, we adjusted for possible confounding factors, including age (years), gender, weight, heart rate, SOFA score, and site of infection. Despite this adjustment, some unmeasured confounding may remain. Additional limitations of our study include missing data for some variables. Nonetheless, we used contemporary methods to deal with missing data to minimize bias.

Another limitation is related to the fact that the diagnosis was based on the ICD-9 coding which the responsible physician found relevant, and we did not have information concerning causes of death. Since we are examining mortality over a short period after the date of visit to the ICU, we did not find it beneficial to distinguish between cardiovascular and non-cardiovascular death.

Furthermore, lack of information on interventions during the initial stabilization may have influenced nonHDLc/HDLc ratio levels and survival. It is noteworthy that the potential resulting from interventions would bias toward to the null, and thus result in an underestimation of the association between nonHDLc/HDLc ratio level and mortality.

Finally, we acknowledge that the participants were patients referred to the emergency department for some reason, limiting the generalization of findings to other populations.

Conclusion

Data from the eICU-CRD database was used to identify 724 patients with sepsis. This study identifies a nonlinear dose-response relationship between nonHDLc/HDLc ratios and 28-day mortality. The probability of mortality rose rapidly when the nonHDLc/HDLc ratio higher than the turning point (may at

3.41). This retrospective cohort study showed that higher nonHDLc/HDLc ratios were associated with higher risk of 28-day mortality in patients with sepsis.

Abbreviations

ANOVA: One-way analysis of variance; BP: Blood pressure; GAM: Generalized additive model; GCS: Glasgow Coma Scale; HDLc: High-density lipoprotein-cholesterol; HR: Heart rate; ICD: International Classification of Diseases; ICU: Intensive Care Unit ; IQR: Interquartile ranges; LDL:Low-density lipoprotein; MAP: Mean Arterial Pressure; nonHDLc: Non-high-density lipoprotein-cholesterol; OR: Odds ratio; SOFA: Sequential Organ Failure Assessment; UTI: Urinary Tract Infection; 95% CIs: 95% confidence intervals.

Declarations

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Authors' contributions

XLC performed statistical analysis. LC cleaned the data. CL conceived and designed the research. XLC and LC drafted the manuscript. CL made critical revision of the manuscript for key intellectual content.

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Availability of data and materials

Data were fully available at https://eicu-crd.mit.edu/.

Ethics approval and consent to participate

Data was extracted from the eICU Collaborative Research Database (eICU-CRD)[9] ain accordance with the data usage agreement (our record ID: 40859994) by the PhysioNet review committee. The utilized database is released under the Health Insurance Portability and Accountability Act (HIPAA) safe harbor provision. This was a retrospective analysis based on an anonymous database for researchers and did not require ethical approval from the local ethics committee.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Marshall JC. Why have clinical trials in sepsis failed? Trends Mol Med. 2014;20(4):195–203.
2. Lewington S, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet. 2007;370(9602):1829–39.
3. Di Angelantonio E, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA. 2009;302(18):1993–2000.
4. National trends in. total cholesterol obscure heterogeneous changes in HDL and non-HDL cholesterol and total-to-HDL cholesterol ratio: a pooled analysis of 458 population-based studies in Asian and Western countries. Int J Epidemiol. 2020;49(1):173–92.
5. Eliasson B, et al. LDL-cholesterol versus non-HDL-to-HDL-cholesterol ratio and risk for coronary heart disease in type 2 diabetes. Eur J Prev Cardiol. 2014;21(11):1420–8.
6. Wang D, et al. Higher non-HDL-cholesterol to HDL-cholesterol ratio linked with increased nonalcoholic steatohepatitis. Lipids Health Dis. 2018;17(1):67.
7. Zuo PY, et al. Non-HDL-cholesterol to HDL-cholesterol ratio as an independent risk factor for the development of chronic kidney disease. Nutrition, Metabolism and Cardiovascular Diseases; 2015.
8. Yu Y, et al., A U-shaped association between the LDL-cholesterol to HDL-cholesterol ratio and all-cause mortality in elderly hypertensive patients: a prospective cohort study. Lipids in Health and Disease, 2020. 19(1).
9. Pollard TJ, et al., The eICU Collaborative Research Database, a freely available multi-center database for critical care research. Scientific Data, 2018. 5(1).
10. Serpa NA, et al. Mechanical power of ventilation is associated with mortality in critically ill patients: an analysis of patients in two observational cohorts. Intensive Care Med. 2018;44(11):1914–22.
11. van den Boom W, et al. The Search for Optimal Oxygen Saturation Targets in Critically Ill Patients: Observational Data From Large ICU Databases. Chest. 2020;157(3):566–73.
12. Davidson S, et al. Vital-sign circadian rhythms in patients prior to discharge from an ICU: a retrospective observational analysis of routinely recorded physiological data. Crit Care. 2020;24(1):181.

13. Singer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801–10.
14. Zimmerman JE, et al. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. Crit Care Med. 2006;34(5):1297–310.
15. Jaddoe VW, et al. First trimester fetal growth restriction and cardiovascular risk factors in school age children: population based cohort study. BMJ. 2014;348:g14.
16. Yu X, Cao L, Yu X. Elevated cord serum manganese level is associated with a neonatal high ponderal index. Environ Res. 2013;121:79–83.
17. Yu X, et al. Threshold effects of moderately excessive fluoride exposure on children's health: A potential association between dental fluorosis and loss of excellent intelligence. Environ Int. 2018;118:116–24.
18. Fried LP, et al. Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study. JAMA. 1998;279(8):585–92.
19. Kronmal RA, et al. Total serum cholesterol levels and mortality risk as a function of age. A report based on the Framingham data. Arch Intern Med. 1993;153(9):1065–73.
20. Psaty BM, et al. The association between lipid levels and the risks of incident myocardial infarction, stroke, and total mortality: The Cardiovascular Health Study. J Am Geriatr Soc. 2004;52(10):1639–47.
21. Akerblom JL, et al. Relation of plasma lipids to all-cause mortality in Caucasian, African-American and Hispanic elders. Age Ageing. 2008;37(2):207–13.
22. Schupf N, et al. Relationship between plasma lipids and all-cause mortality in nondemented elderly. J Am Geriatr Soc. 2005;53(2):219–26.
23. Bathum L, et al. Association of lipoprotein levels with mortality in subjects aged 50 + without previous diabetes or cardiovascular disease: a population-based register study. Scand J Prim Health Care. 2013;31(3):172–80.
24. You S, et al. LDL-C/HDL-C ratio and risk of all-cause mortality in patients with intracerebral hemorrhage. Neurol Res. 2016;38(10):903–8.
25. Liu L, et al. Association of LDL-C/HDL-C Ratio With Stroke Outcomes Within 1 Year After Onset: A Hospital-Based Follow-Up Study. Front Neurol. 2020;11:408.
26. Di Angelantonio E, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA. 2009;302(18):1993–2000.
27. Bowe B, et al. High Density Lipoprotein Cholesterol and the Risk of All-Cause Mortality among U.S. Veterans. Clin J Am Soc Nephrol. 2016;11(10):1784–93.
28. Madsen CM, Varbo A, Nordestgaard BG. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies. Eur Heart J. 2017;38(32):2478–86.

29. Martin SS, et al. Friedewald-estimated versus directly measured low-density lipoprotein cholesterol and treatment implications. J Am Coll Cardiol. 2013;62(8):732–9.
30. Arsenault BJ, et al. Beyond low-density lipoprotein cholesterol: respective contributions of non-high-density lipoprotein cholesterol levels, triglycerides, and the total cholesterol/high-density lipoprotein cholesterol ratio to coronary heart disease risk in apparently healthy men and women. J Am Coll Cardiol. 2009;55(1):35–41.
31. Jacobs D, et al., Report of the Conference on Low Blood Cholesterol: Mortality Associations. Circulation, 1992. 86(3): p. 1046-60.
32. Ranieri P, et al. Serum cholesterol levels as a measure of frailty in elderly patients. Exp Aging Res. 1998;24(2):169–79.
33. Sanin V, Pfetsch V, Koenig W. Dyslipidemias and Cardiovascular Prevention: Tailoring Treatment According to Lipid Phenotype. Curr Cardiol Rep. 2017;19(7):61.
34. Greenberg JA. Correcting biases in estimates of mortality attributable to obesity. Obesity (Silver Spring). 2006;14(11):2071–9.

Figures

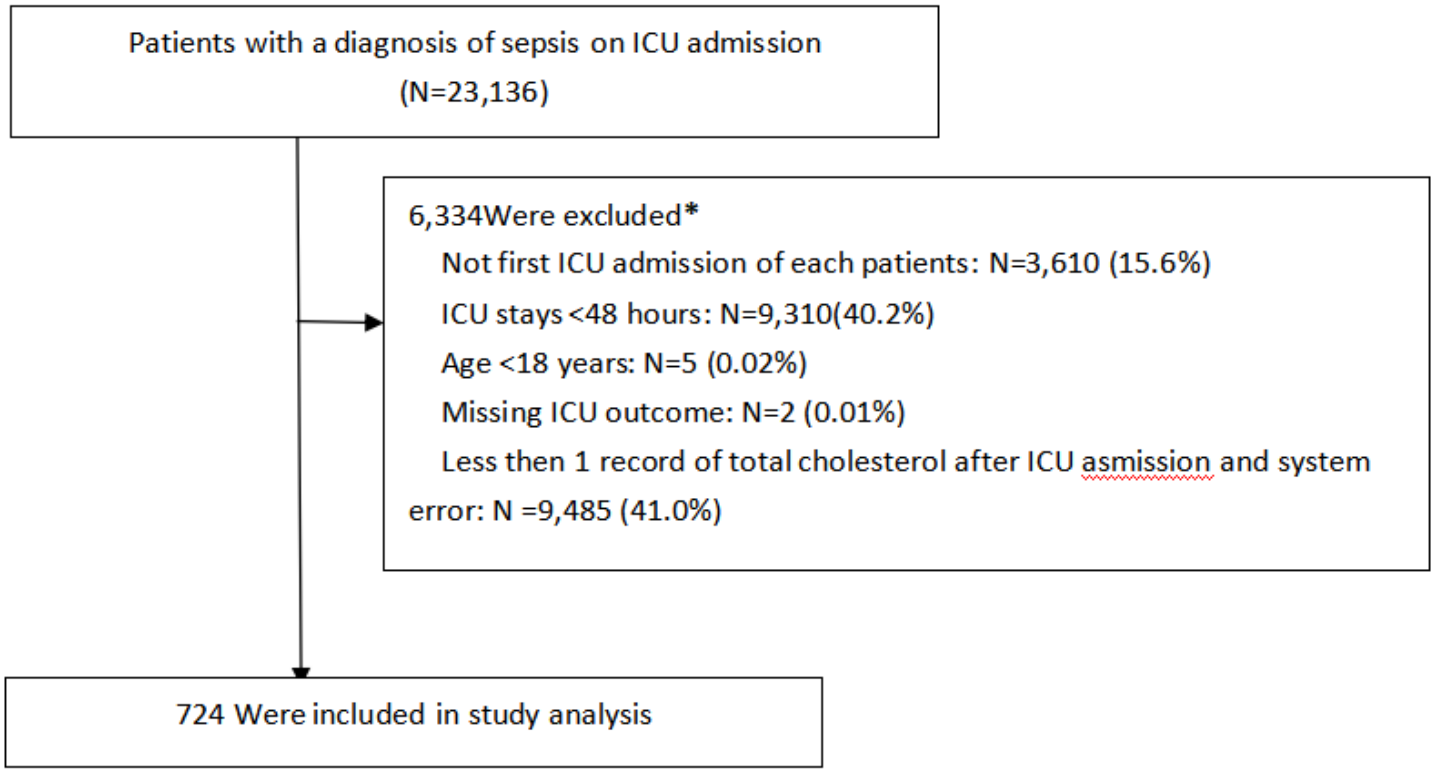

Figure 1

Study population Briefly, all patients diagnosed with sepsis on admission to the ICU were included. Sepsis was defined as suspected or documented infection plus an acute increase in SOFA score greater than 2

points[13]. Recorded on the Acute Physiology and Chronic Health Evaluation (APACHE) IV dataset[14]. The following exclusion criteria were used: (1) Not first ICU admission; (2) ICU stay <48 hours; (3) 18 years old; (4) Missing ICU outcome; (5) Missing total cholesterol after ICU asmission and system error. The study flowchart was presented in Figure 1.

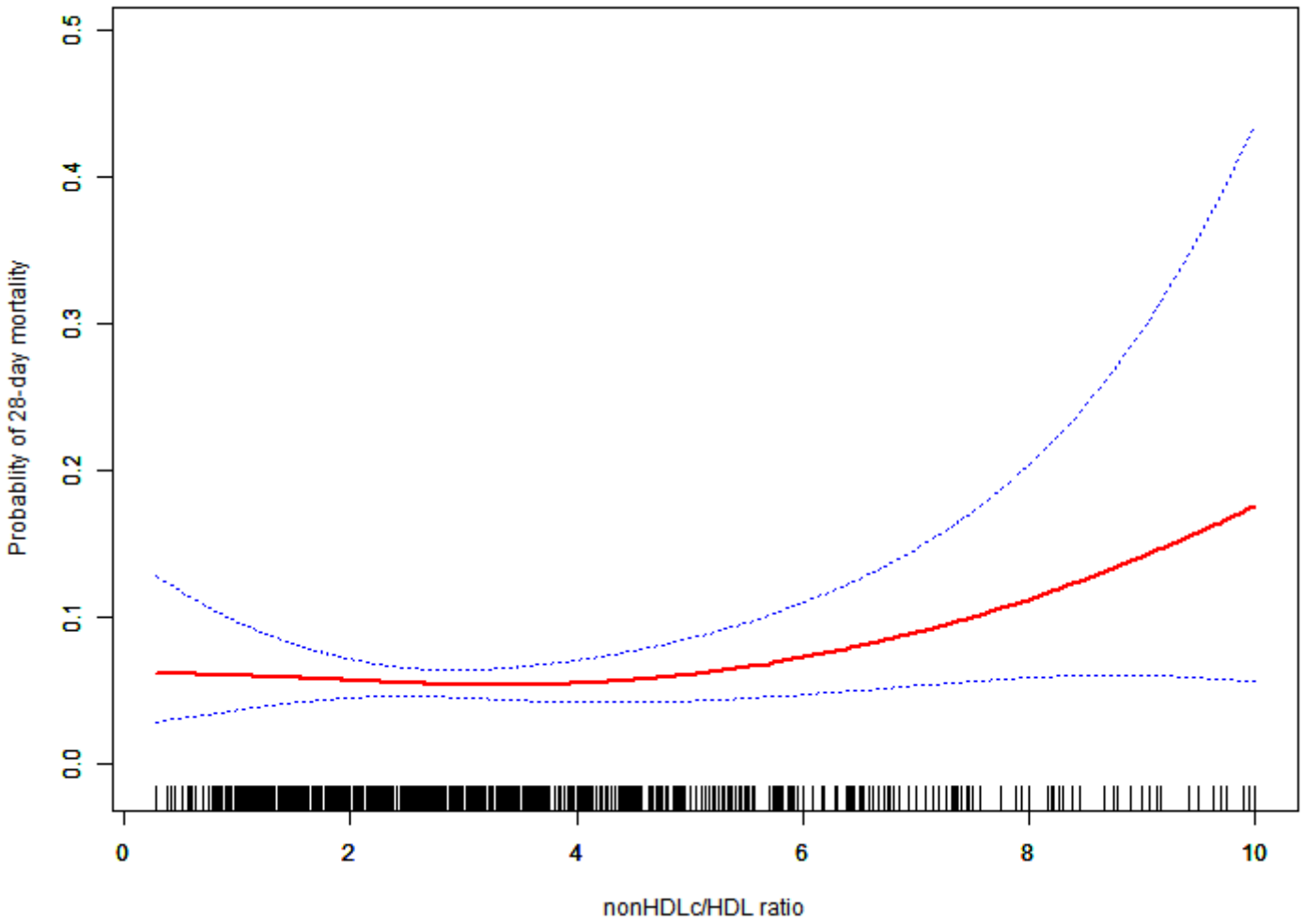

Figure 2

Identification of non-linear relationship We observed a nonlinear dose-response relationship between the nonHDLc/HDLc ratio and mortality (Figure 2 and Table 3). The probability of mortality increased when the nonHDLc/HDLc ratio higher than the turning point (≥3.41) with a adjusted odds ratio (OR) of1.34 (95% CI: 1.07–1.67, P=0.010) for every 1 increment of nonHDLc/HDLc ratio. As the nonHDLc/HDLc ratio increased per SD, when the nonHDLc/HDLc ratio was ≥3.41, the OR for mortality was 1.79 (95% CI: 1.15–2.80, P=0.010). (Table 3).

Supplementary Files

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