

# Association between the nonHDLc/HDLc ratio and 30-day mortality for patients with sepsis: a retrospective observational cohort study based on a large multicentre critical care database

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## Research

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# Abstract

**Background:** Dyslipidemia contributes to the development and progression of cardiovascular disease. The objective of this study was to investigate the association between the non-high-density lipoprotein-cholesterol-to-high-density lipoprotein-cholesterol (non-HDL-c/HDL-c) ratio and mortality for patients with sepsis.

**Methods:** Using data from the eICU Collaborative Research Database (eICU-CRD) with high granularity data for over 200,000 admissions to ICUs monitored by eICU Programs across the United States. We identified 1680 patients with sepsis. All-cause mortality within 30-days after the date of visit to the ICU. We estimated the risk of mortality using multivariable logistic-regression model.

**Result:** There were 115 deaths (6.85%). The probability of mortality decreased when the nonHDLc/HDLc ratio lower than the turning point ( $<3.58$ ) with a adjusted odds ratio (OR) of 0.75 (95% CI: 0.61–0.94,  $P=0.011$ ) for every 1 increment of nonHDLc/HDLc ratio. With the per-SD increase in the nonHDLc/HDLc ratio, the OR for mortality was 0.36 (95% CI: 0.16–0.79,  $P=0.011$ ) when nonHDLc/HDLc ratio was  $<3.58$ , while the OR was 1.56 (95% CI: 1.29–1.88,  $P<0.001$ ) when nonHDLc/HDLc ratio was  $\geq 3.58$ .

**Conclusion:** Higher nonHDLc/HDLc ratio, even at a low level, was associated with a higher risk of 30-day mortality for patients with sepsis. The probability of mortality rose rapidly when the nonHDLc/HDLc ratio higher than the turning point (may at 3.58).

## Background

Sepsis is a frequent and lethal syndrome. The systemic inflammatory response is biologically complex, redundant, and activated by both infectious and noninfectious triggers. Its manipulation can cause both benefit and harm[1]. Closer scrutiny of phenotypes and subphenotypes of patients that display strong survival signals in sepsis may enable us to understand novel mechanisms to improve treatment.

High-density lipoprotein (HDL) and non-HDL or low-density lipoprotein (LDL) cholesterol have opposite associations with coronary heart disease (CHD)[2, 3] and can respond differently to changes in diet and treatment. The nonHDLc/HDLc ratio, available from the standard lipid profile at no extra cost and highly correlated with levels of LDL particle number[4], has been shown to be a strong cardiovascular risk marker by several studies[5, 6]. We previously showed that nonHDLc/HDLc ratio is an independent risk factor for the development of chronic kidney disease(CKD)[7].

A recent clinical research revealed that mortality in relation to the LDL-C/HDL-C ratio ranges was U-shaped in patients with hypertension, during a median follow-up of 1.72 year[8]. However, evidence is lacking to guide the emergency management of patients with sepsis.

Exploring the threshold the nonHDLc/HDLc ratio where risk of death significantly increases is a high priority in patients with sepsis. We used the eICU-CRD, a large multicentre critical care database to

investigate association between the nonHDLc/HDLc ratio and 30-day mortality. In our observational study, we hypothesized that in patients with sepsis even high and low the nonHDLc/HDLc ratio is associated with a higher risk of all-cause mortality within 30-days after the date of visit to the ICU.

## Methods

### Data Source

We extracted data from eICU-CRD database, which is publicly and freely accessible to researchers, according to data usage agreement by the review board of PhysioNet (our record ID: 40859994). The eICU-CRD covers 200 859 ICU admissions of 139 367 patients in 208 US hospitals between 2014 and 2015. All data were stored automatically and retrieved electronically through the Philips Healthcare eICU programme. It includes records of demographics, physiological indices from 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 data were deidentified by the eICU programme and anonymous to researchers before analysis[9]. As this research was a retrospective cohort study based on data from eICU-CRD, no ethical approval was required from our local ethics committee.

### Study population

Briefly, all patients with sepsis admitted to ICU from eICU database were included. The following exclusion criteria were applied: (i)  $\geq 89$  or  $\leq 18$  years old; (ii) missing total cholesterol. In total, 1680 patients with sepsis were included. The study flowchart was presented in *Fig. 1*.

### Variables

All subject data within the first 24 hours after admission were collected from eICU-CRD. The physiological variables, including heart rate (HR) and current blood pressure (BP), were obtained from the table apacheApsVar. The baseline characteristics such as age, gender, ethnicity weight and height were collected from the tables of patient and apachePatientResult. The laboratory indices, for total cholesterol, triglycerides, HDLc, LDLc and serum creatinine were extracted from the table lab. The comorbidities, for chronic obstructive pulmonary disease (COPD) and pneumonia were extracted from the table diagnosis.

### Outcomes

The outcome of the study was all-cause mortality within 30 days after the date of visit to the ICU. In supplementary analyses, we also analyzed 60-days mortality.

### Statistical analysis

Continuous variables are described as means  $\pm$  SD or medians (interquartile ranges) and categorical data are 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 relationships between the nonHDLc/HDLc ratio and 30-day mortality (Fig. 1). We applied logistic-regression model to estimate the association between the nonHDLc/HDLc ratio and 30-day mortality. The results were presented as odds ratios (ORs) with their 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 associations with the outcomes of interest or a change in effect estimate of more than 10%. [10] Adjusted for the following potential confounders: age, sex, ethnicity, serum creatinine, systolic blood pressure, pneumonia and chronic obstructive pulmonary disease.

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 of 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 conducted log likelihood ratio test comparing one-line linear regression model with two-piece-wise linear model. As described in previous analyses [11, 12].

Table 3  
Threshold effect analysis of nonHDLc/HDLc ratio and 30-day mortality

Threshold	Per-unit increase		Per-SD increase	
	OR (95%CI)	Pvalue	OR (95%CI)	Pvalue
NonHDLc/HDLc ratio < 3.58	0.75 (0.61, 0.94)	0.011	0.36 (0.16, 0.79)	0.011
NonHDLc/HDLc ratio ≥ 3.58	1.13 (1.07, 1.19)	< 0.001	1.56 (1.29, 1.88)	< 0.001
Adjusted for age, sex, ethnicity, serum creatinine, systolic blood pressure, pneumonia and chronic obstructive pulmonary disease; CI, confidence interval; OR, odds ratio.				

To examine the robustness of our results, we conducted stratified analyses according to covariates. Dummy variables were used to indicate missing covariate values. The two-sided alpha level was set at 0.05. All the statistical analysis was performed using the EmpowerStats ([www.empowerstats.com](http://www.empowerstats.com), X&Y solutions, Inc. Boston MA) and R software version 3.6.1 (<http://www.r-project.org>).

## Results

### Baseline characteristics

A total of 1680 patients with sepsis were included in the study. The median age of all patients was 67 years (IQR 57–77 years). 816 patients (48.6%) were female. Table 1 compares the demographic, vital signs, laboratory and comorbidity of patients by tertiles of the nonHDLc/HDLc ratio. Compared with subjects in the lowest tertile of the nonHDLc/HDLc ratio, those in the highest tertile were younger, had higher body mass index (BMI) and heart rate (all  $P < 0.05$ ).

Table 1

Baseline characteristics and 30-day mortality according to the tertiles of nonHDLc/HDL ratio (n = 1680)

Parameters	nonHDLc/HDL ratio			P value
	Tertile 1 0.23–2.17, n = 559	Tertile 2 2.18–3.92, n = 561	Tertile 3 3.93–20, n = 560	
Demographics				
Age (yr)	68.9 ± 13.8	66.7 ± 14.2	61.4 ± 15.1	< 0.001
Sex				0.936
Female	270 (48.3%)	276 (49.2%)	270 (48.2%)	
Male	289 (51.7%)	285 (50.8%)	290 (51.8%)	
Ethnicity				0.765
Caucasian	396 (70.8%)	391 (69.7%)	399 (71.2%)	
African-American	60 (10.7%)	73 (13.0%)	61 (10.9%)	
Asian	72 (12.9%)	63 (11.2%)	62 (11.1%)	
Other/Unknown	31 (5.5%)	34 (6.1%)	38 (6.8%)	
Body mass index (kg/m <sup>2</sup> )	27.5 ± 7.8	28.9 ± 8.4	30.5 ± 6.9	< 0.001
Height (cm)	167.9 ± 11.1	168.0 ± 12.0	168.5 ± 13.3	0.723
Weight (kg)	81.7 ± 29.9	85.9 ± 27.6	91.7 ± 31.9	0.003
Vital signs				
Systolic BP (mmHg)	113.3 ± 23.7	114.7 ± 26.9	113.4 ± 25.6	0.630
Diastolic BP (mmHg)	62.5 ± 16.7	65.3 ± 19.1	62.8 ± 16.4	0.086
Heart rate (/min)	93.1 ± 19.4	94.9 ± 20.3	98.4 ± 21.4	< 0.001
Laboratory data				
Total cholesterol (mg/dL)	109.8 ± 36.0	124.0 ± 42.2	133.2 ± 58.4	< 0.001
Triglycerides (mg/dL)	78 (59–103)	112 (83–153)	174 (127–249)	< 0.001
HDLc (mg/dL)	46.2 ± 15.8	31.7 ± 11.2	17.9 ± 9.6	< 0.001

Data are expressed as the mean ± SD, median (interquartile range), or percentage; HDLc High-density lipoprotein cholesterol; BP Blood pressure; LDLc Low-density lipoprotein cholesterol; COPD, Chronic obstructive pulmonary disease. Among the 1680 visits, the amount of missing values for the covariates were: 1089 (64.8%) for body mass index, 237 (14.1%) for systolic BP and diastolic BP, 286 (17.0%) for heart rate, 11 (0.7%) for triglycerides, 468 (27.9%) for LDLc, and 3 (0.2%) for serum creatinine.

	nonHDLc/HDL ratio			
LDLc (mg/dL)	43 (30–63)	63 (45–89)	65 (45–91)	< 0.001
Serum creatinine (mg/dL)	1.3 (0.9–2.1)	1.4 (0.9–2.4)	1.5 (1.0-2.6)	< 0.001
Comorbidity				
COPD				< 0.001
No	489 (87.5%)	505 (90.0%)	530 (94.6%)	
Yes	70 (12.5%)	56 (10.0%)	30 (5.4%)	
Pneumonia				0.329
No	369 (66.0%)	353 (62.9%)	379 (67.7%)	
Yes	190 (34.0%)	208 (37.1%)	181 (32.3%)	
30-day Mortality				0.213
No	515 (92.1%)	531 (94.7%)	519 (92.7%)	
Yes	44 (7.9%)	30 (5.3%)	41 (7.3%)	
Data are expressed as the mean ± SD, median (interquartile range), or percentage; HDLc High-density lipoprotein cholesterol; BP Blood pressure; LDLc Low-density lipoprotein cholesterol; COPD, Chronic obstructive pulmonary disease. Among the 1680 visits, the amount of missing values for the covariates were: 1089 (64.8%) for body mass index, 237 (14.1%) for systolic BP and diastolic BP, 286 (17.0%) for heart rate, 11 (0.7%) for triglycerides, 468 (27.9%) for LDLc, and 3 (0.2%) for serum creatinine.				

## 30-Day Mortality

There were 115 (6.85%) patients died within 30 days after the date of visit to the Emergency department. The 30-day mortality in the lowest tertiles of nonHDLc/HDLc ratio (0.23–2.17) to the highest (3.93-20) were 44 (7.9%), 30 (5.3%) and 40 (7.3%) respectively (Table 1).

## Unadjusted association between baseline variables and 30-day mortality

Table 2 shows the univariate logistic models. The analysis indicated that higher age (OR = 1.01, 95% CI, 1.00–1.03, P = 0.043), higher heart rate (OR = 1.01, 95% CI, 1.00–1.02, P = 0.014) and higher total cholesterol (OR = 0.99, 95% CI, 0.99–1.00, P = 0.001) were significant associated with the risk of 30-day mortality.

Table 2  
The unadjusted association between baseline variables and 30-day mortality (n = 1680)

Parameters	Statistics	Odds ratio (95% CI)	P value
Age (yr)	65.7 ± 14.7	1.01 (1.00, 1.03)	0.0433
Sex			
Female	816 (48.57%)	Reference	
Male	864 (51.43%)	1.03 (0.71, 1.51)	0.8684
Ethnicity			
Caucasian	1186 (70.60%)	Reference	
African American	194 (11.55%)	1.13 (0.64, 2.00)	0.6797
Asian	197 (11.73%)	1.11 (0.63, 1.97)	0.7217
Other/Unknown	103 (6.13%)	0.40 (0.13, 1.30)	0.1289
Body mass index (kg/m <sup>2</sup> )	28.94 ± 7.79	0.97 (0.93, 1.01)	0.1178
Systolic BP (mmHg)	113.8 ± 25.4	0.99 (0.99, 1.00)	0.1787
Diastolic BP (mmHg)	63.5 ± 17.5	0.99 (0.98, 1.01)	0.3686
Heart rate (/min)	95.44 ± 20.49	1.01 (1.00, 1.02)	0.0141
Total cholesterol (mg/dL)	122.32 ± 47.43	0.99 (0.99, 1.00)	0.0013
Triglycerides (mg/dL)	114.0 (78.0-171.0)	1.00 (1.00, 1.00)	0.8253
HDLc (mg/dL)	31.93 ± 16.98	0.99 (0.98, 1.00)	0.0929
LDLc (mg/dL)	57.0 (38.0-80.2)	1.00 (0.99, 1.00)	0.2383
Serum creatinine (mg/dL)	1.4 (1.0-2.3)	1.07 (0.98, 1.17)	0.1346
COPD			
No	1524 (90.71%)	Reference	
Yes	156 (9.29%)	1.15 (0.62, 2.14)	0.6603
Pneumonia			
No	1101 (65.54%)	Reference	
Yes	579 (34.46%)	1.29 (0.88, 1.90)	0.1966

Data are expressed as the mean ± SD, median (interquartile range), or percentage; HDLc High-density lipoprotein cholesterol; BP Blood pressure; LDLc Low-density lipoprotein cholesterol; COPD, Chronic obstructive pulmonary disease.

## Identification of non-linear relationship

We observed a nonlinear dose-response relationship between nonHDLc/HDLc ratio and mortality (Fig. 2 and Table 3). The probability of mortality increased when nonHDLc/HDLc ratio higher than the turning point ( $\geq 3.58$ ) with a adjusted OR of 1.13 (95% CI: 1.07–1.19,  $P < 0.001$ ) for every 1 increment of nonHDLc/HDLc ratio. Moreover, the probability of mortality decreased when nonHDLc/HDLc ratio lower than the turning point ( $< 3.58$ ) with a adjusted OR of 0.75 (95% CI: 0.61–0.94,  $P = 0.011$ ) for every 1 increment of nonHDLc/HDLc ratio. With the per-SD increase in the nonHDLc/HDLc ratio, the OR for mortality was 0.36 (95% CI: 0.16–0.79,  $P = 0.011$ ) when nonHDLc/HDLc ratio was  $< 3.58$ , while the OR was 1.56 (95% CI: 1.29–1.88,  $P < 0.001$ ) when nonHDLc/HDLc ratio was  $\geq 3.58$  (Table 3).

Using the generalized additive model, the non-linear association between 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 for the log-likelihood ratio test is  $< 0.001$ . This result demonstrates that the two-piece-wise linear regression model should be used to fit the model.

As shown in Table 4, stratified analyses were conducted with stratification by age, sex, ethnicity, serum creatinine, COPD, pneumonia, systolic BP, diastolic BP and heart rate. These analyses both show the same trend as the main analysis. We performed sensitivity analyses to test the robustness of our results. Dummy variables were used to indicate missing covariate values. Similar results were obtained after considering the impact of missing data, data not shown.



Table 4  
Association between nonHDLc/HDLc ratio and 30-day mortality by subgroup analysis

Y = Probability of Mortality	nonHDLc/HDL ratio			
	N	Tertile 2 2.18–3.92	Tertile 1 0.23–2.17	Tertile 3 3.93-20
Age (yr) group				
≤ 65	766	Ref.	1.49 (0.56, 3.94) 0.419	2.16 (0.94, 4.93) 0.068
≥65	914	Ref.	1.39 (0.79, 2.42) 0.249	1.18 (0.62, 2.23) 0.611
Sex				
Female	816	Ref.	1.54 (0.78, 3.04) 0.210	1.24 (0.61, 2.52) 0.546
Male	864	Ref.	1.48 (0.75, 2.92) 0.254	1.55 (0.79, 3.04) 0.200
Ethnicity				
Caucasian	1186	Ref.	1.29 (0.75, 2.22) 0.362	0.98 (0.55, 1.74) 0.941
Other/Unknown	494	Ref.	2.62 (0.90, 7.62) 0.076	3.64 (1.30, 10.19) 0.013
Serum creatinine (mg/dL)				
0.2–1.39	818	Ref.	1.69 (0.79, 3.62) 0.176	1.39 (0.61, 3.17) 0.428
1.4–18.6	859	Ref.	1.43 (0.77, 2.67) 0.258	1.33 (0.73, 2.44) 0.356
COPD				
No	1295	Ref.	1.43 (0.81, 2.53) 0.220	1.58 (0.91, 2.75) 0.101
Yes	156	Ref.	3.98 (0.82, 19.25) 0.085	0.93 (0.08, 10.71) 0.954
Pneumonia				
No	872	Ref.	1.85 (0.90, 3.82) 0.094	1.45 (0.68, 3.06) 0.334
Yes	579	Ref.	1.50 (0.69, 3.26) 0.304	1.80 (0.84, 3.85) 0.127
Systolic BP (mmHg)				
<140	1219	Ref.	1.17 (0.67, 2.05) 0.581	1.35 (0.78, 2.32) 0.285
≥140	224	Ref.	6.08 (1.29, 28.72) 0.022	2.47 (0.44, 13.91) 0.305
Diastolic BP (mmHg)				

Y = Probability of Mortality	nonHDLc/HDL ratio			
	N	Tertile 2 2.18–3.92	Tertile 1 0.23–2.17	Tertile 3 3.93-20
<90	1338	Ref.	1.46 (0.85, 2.49) 0.167	1.38 (0.80, 2.37) 0.243
≥90	105	Ref.	2.22 (0.35, 14.15) 0.397	2.58 (0.40, 16.50) 0.316
Heart rate (/min)		Ref.		
<100	816	Ref.	1.23 (0.61, 2.51) 0.561	1.05 (0.49, 2.25) 0.9001
≥100	578	Ref.	1.81 (0.85, 3.84) 0.124	1.65 (0.79, 3.45) 0.184

## Discussion

This study showed that higher nonHDLc/HDLc ratio, even at a low level, was associated with a higher risk of 30-day mortality among patients with sepsis in ICU. The major finding was that the probability of mortality decreased when the nonHDLc/HDLc ratio lower than the turning point (< 3.58) with a adjusted OR of 0.75 (95% CI: 0.61–0.94,  $P=0.011$ ) for every 1 increment of nonHDLc/HDLc ratio. To our knowledge, this is the first study to report the relation between the nonHDLc/HDLc ratio and 30-day mortality in adult ICU patients with sepsis.

Most studies investigating the relation between levels of LDL-C and the risk of all cause mortality have found no association[13–15] or an inverse association[16–18]. You et al.[19] included 356 patients with intracranial hemorrhage (mean follow-up = 0.22 years) and found that the LDL-C/HDL-C ratio was negatively correlated with all-cause mortality, they suggested that the LDL-C/HDL-C ratio should be controlled above 2.96. Liu et al.[20] recruited 3250 stroke patients (mean follow-up = 1.00 years) and found a negative relationship between the LDL-C/HDL-C ratio and all-cause mortality. The findings of the above studies suggest that the relationship between the LDL-C/HDL-C ratio and all-cause mortality may be negative, and the proposed optimal range of the LDL-C/HDL-C ratio has been inconsistent. These conflicting results can be attributed to differences in the study populations, follow-up durations, and end-point events. Consequently, the relationship between the nonHDLc/HDLc ratio and all-cause mortality are still unclear, which prompted us to conduct the current study.

We used non-HDL cholesterol rather than LDL cholesterol because in our database had measured TC and HDL cholesterol, from which non-HDL cholesterol can be calculated by subtraction. LDL cholesterol was directly measured in only 72% of patients. Further, the most commonly used estimation method, i.e. the Friedewald equation, can be inaccurate[21]. That non-HDL and LDL cholesterol were correlated in studies with data on both variables ( $r = 0.93$ )[4]. Non-HDL cholesterol predicts CHD risk at least as well as LDL

cholesterol[22] 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.

Also, a recent study in a Chinese Hypertension Registry study of 6941 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 LDL-C/HDL-C ratio and all-cause mortality was found. The optimal range of the LDL-C/HDL-C ratio was 1.67–2.10[8], similar to our results that mortality in relation to the nonHDLc/HDLc ratio was U-shaped.

Possible explanations for our findings. The association between low levels of nonHDLc and an increased risk of all cause mortality could be explained by reverse causation. Debilitation and illness have been hypothesised to cause a decrease in levels of cholesterol[23, 24]. Nonetheless, cholesterol-related risk is more complex, and involves the interplay of several factors such as cholesterol particle concentration, reverse cholesterol transport and triglyceride-rich lipoproteins, to mention a few[25]. The U shaped association between the nonHDLc/HDLc ratio and mortality might be similar to the obesity paradox, which is largely explained by methodological issues, including reverse causation[26].

The current study is based on a ICU data, could be important for understanding what is a “normal and healthy” the nonHDLc/HDLc ratio in patients with sepsis (that is, when the focus is not limited to myocardial infarction and atherosclerotic cardiovascular disease). Explored the threshold the nonHDLc/HDLc ratio level where risk of death significantly increases is a high priority 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 likely confounders, including age, sex, ethnicity, serum creatinine, systolic blood pressure, pneumonia and COPD. Despite this adjustment, it is still possible that some amount of unmeasured confounding remains. 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 relates to the fact that the diagnoses were 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, we lacked information about interventions during the initial stabilization, which may have influenced the 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 the nonHDLc/HDLc ratio level and mortality.

Finally, we also acknowledge that as our participants were patients referred for any reason to the emergency department, which limits the generalizability of the findings to other population.

## Conclusion

Using data from a retrospective cohort study, we identified 1680 patients with sepsis referred for any reason to the ICU. This study identifies a nonlinear dose-response relationship between the nonHDLc/HDLc ratio and 30-day mortality. The probability of mortality rose rapidly when the nonHDLc/HDLc ratio higher than the turning point (may at 3.58).

## Abbreviations

ANOVA: One-way analysis of variance; BMI: Body mass index; BP: Blood pressure; CHD: coronary heart disease; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; GAM: Generalized additive model; HDL-c: High-density lipoprotein-cholesterol; HR: Heart rate; ICD: International Classification of Diseases; ICU: Intensive Care Unit ; IQR: Interquartile ranges; LDL:Low-density lipoprotein; non-HDL-c: Non-high-density lipoprotein-cholesterol; OR: Odds ratio; 95% CIs: 95% confidence intervals

## Declarations

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The author is very grateful to the data providers of the study.

### Authors' contributions

X.L.C. performed statistical analysis. L.C. cleaned the data. Z.X.Y. conceived and designed the research. X.L.C. and L.C. drafted the manuscript. Z.X.Y. made critical revision of the manuscript for key intellectual content.

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### Availability of data and materials

The data are available on the eICU-CRD website at <https://eicu-crd.mit.edu/https://eicu-crd.mit.edu/>.

### Ethics approval and consent to participate

All data were deidentified by the eICU programme and anonymous to researchers before analysis[9]. As this research was a retrospective cohort study based on data from eICU-CRD, no ethical approval was required from our local ethics committee.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

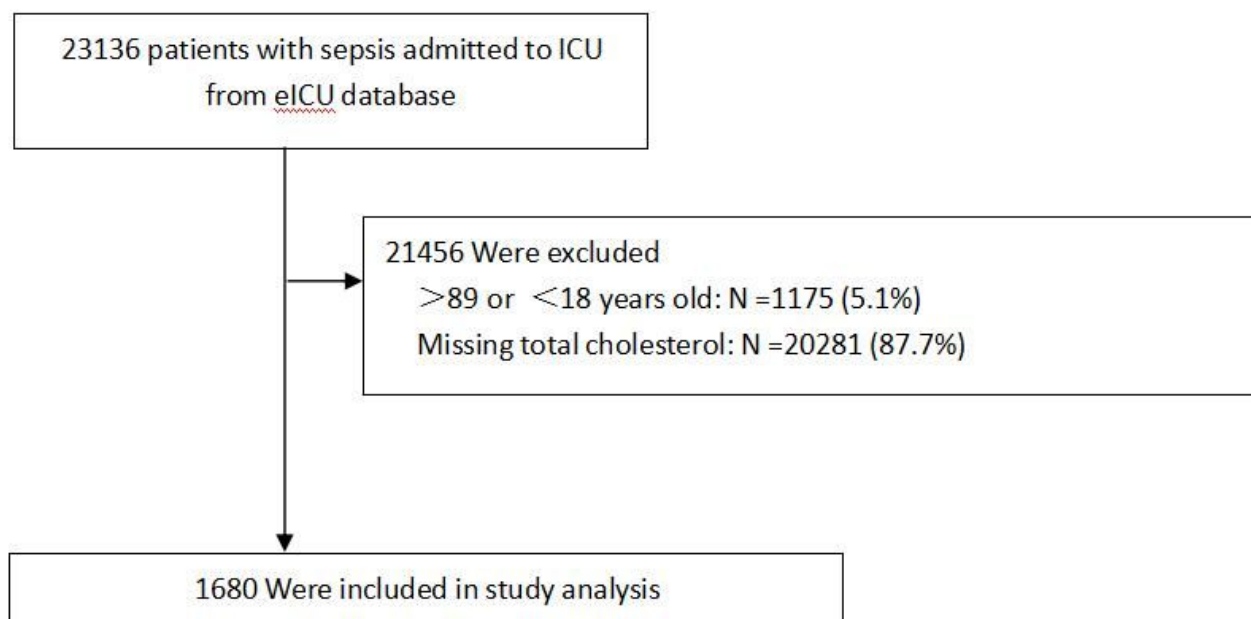
## References

1. Marshall JC. Why have clinical trials in sepsis failed? *Trends Mol Med*. 2014;20(4):195–203.
2. Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R, Collins R. 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, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, Wood AM, Lewington S, Sattar N, Packard CJ, 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, Gudbjörnsdóttir S, Zethelius B, Eeg-Olofsson K, Cederholm J. 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, Wang L, Wang Z, Chen S, Ni Y, Jiang D. Higher non-HDL-cholesterol to HDL-cholesterol ratio linked with increased nonalcoholic steatohepatitis. *Lipids Health Dis*. 2018;17(1):67.
7. Zuo PY, Chen XL, Liu YW, Zhang R, He XX, Liu CY. Non-HDL-cholesterol to HDL-cholesterol ratio as an independent risk factor for the development of chronic kidney disease. *Metabolism: Nutrition*; 2015.
8. Yu Y, Li M, Huang X, Zhou W, Wang T, Zhu L, Ding C, Tao Y, Bao H, Cheng X. 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 Health Dis* 2020, 19(1).
9. Pollard TJ, Johnson AEW, Raffa JD, Celi LA, Mark RG, Badawi O. The eICU Collaborative Research Database, a freely available multi-center database for critical care research. *Sci Data* 2018, 5(1).
10. Jaddoe VW, de Jonge LL, Hofman A, Franco OH, Steegers EA, Gaillard R. First trimester fetal growth restriction and cardiovascular risk factors in school age children: population based cohort study. *BMJ*. 2014;348:g14.

11. 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.
12. Yu X, Chen J, Li Y, Liu H, Hou C, Zeng Q, Cui Y, Zhao L, Li P, Zhou Z, 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.
13. Fried LP, Kronmal RA, Newman AB, Bild DE, Mittelmark MB, Polak JF, Robbins JA, Gardin JM. Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study. *JAMA.* 1998;279(8):585–92.
14. Kronmal RA, Cain KC, Ye Z, Omenn GS. 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.
15. Psaty BM, Anderson M, Kronmal RA, Tracy RP, Orchard T, Fried LP, Lumley T, Robbins J, Burke G, Newman AB, 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.
16. Akerblom JL, Costa R, Luchsinger JA, Manly JJ, Tang MX, Lee JH, Mayeux R, Schupf N. Relation of plasma lipids to all-cause mortality in Caucasian, African-American and Hispanic elders. *Age Ageing.* 2008;37(2):207–13.
17. Schupf N, Costa R, Luchsinger J, Tang MX, Lee JH, Mayeux R. Relationship between plasma lipids and all-cause mortality in nondemented elderly. *J Am Geriatr Soc.* 2005;53(2):219–26.
18. Bathum L, Depont CR, Engers PL, Lyngsie PP, Larsen J, Nexøe J. 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.
19. You S, Zhong C, Xu J, Han Q, Zhang X, Liu H, Zhang Y, Shi J, Huang Z, Xiao G, 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.
20. Liu L, Yin P, Lu C, Li J, Zang Z, Liu Y, Liu S, Wei Y. 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.
21. Martin SS, Blaha MJ, Elshazly MB, Brinton EA, Toth PP, McEvoy JW, Joshi PH, Kulkarni KR, Mize PD, Kwiterovich PO, et al. Friedewald-estimated versus directly measured low-density lipoprotein cholesterol and treatment implications. *J Am Coll Cardiol.* 2013;62(8):732–9.
22. Arsenault BJ, Rana JS, Stroes ES, Després JP, Shah PK, Kastelein JJ, Wareham NJ, Boekholdt SM, Khaw KT. 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.
23. Jacobs D, Blackburn H, Higgins M, Reed D, Iso H, McMillan G, Neaton J, Nelson J, Potter J, Rifkind B, et al: Report of the Conference on Low Blood Cholesterol: Mortality Associations. *Circulation* 1992, 86(3):1046–1060.

24. Ranieri P, Rozzini R, Franzoni S, Barbisoni P, Trabucchi M. Serum cholesterol levels as a measure of frailty in elderly patients. *Exp Aging Res.* 1998;24(2):169–79.
25. Sanin V, Pfetsch V, Koenig W. Dyslipidemias and Cardiovascular Prevention: Tailoring Treatment According to Lipid Phenotype. *Curr Cardiol Rep.* 2017;19(7):61.
26. Greenberg JA. Correcting biases in estimates of mortality attributable to obesity. *Obesity (Silver Spring).* 2006;14(11):2071–9.

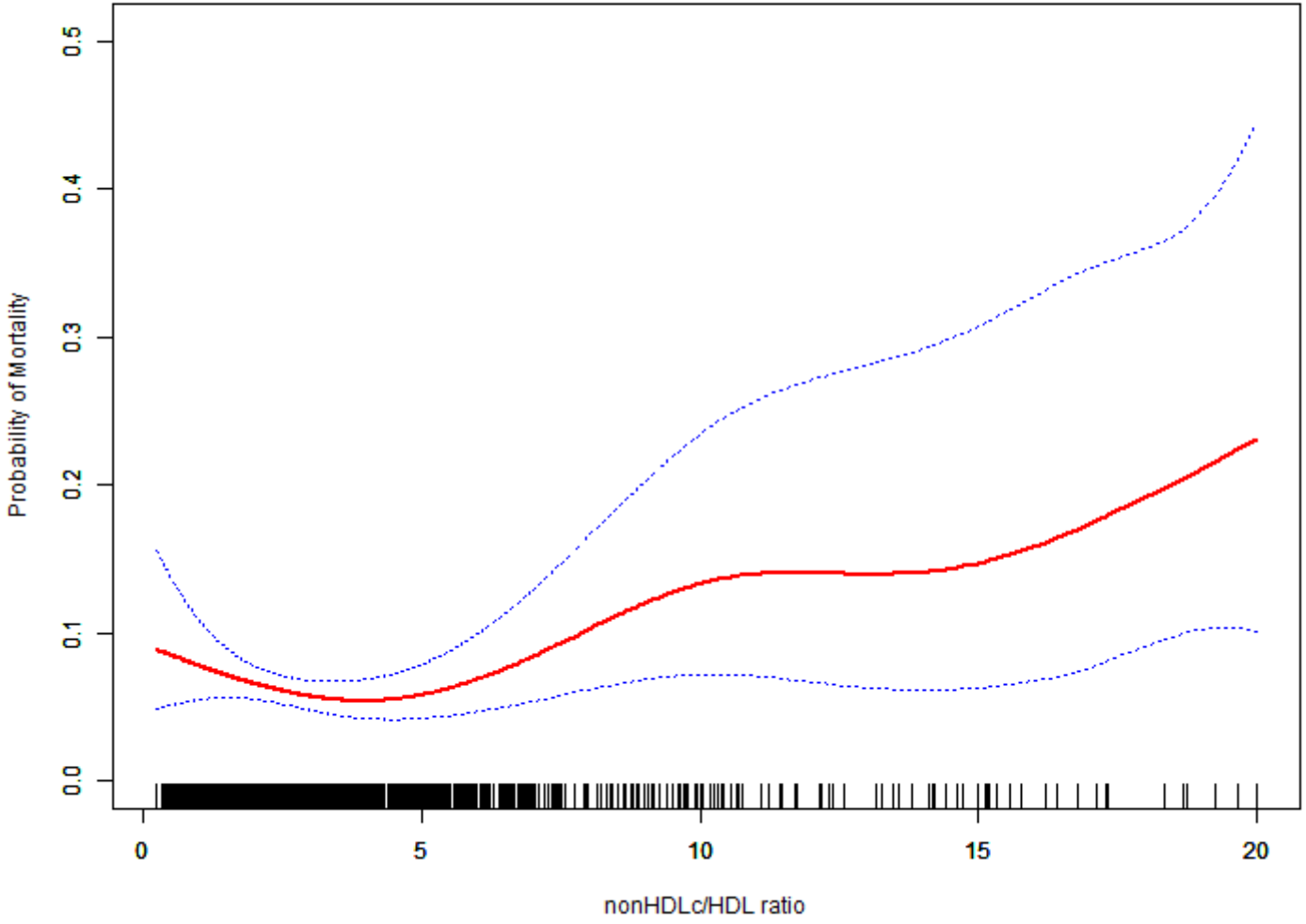
## Figures



**Figure 1** Study flowchart. ICU, intensive care unit.

### Figure 1

Study flow chart



**Figure 2**

Associations between nonHDLc/HDL ratio and 30-day mortality in all patients with sepsis. A threshold, nonlinear association between nonHDLc/HDL ratio and 30-day mortality was found in a generalized additive model (GAM) . Solid red line represents the smooth curve fit between variables. Blue bands represent the 95% of confidence interval from the fit. Adjusted for age, sex, ethnicity, serum creatinine, systolic blood pressure, pneumonia and chronic obstructive pulmonary disease.