Low Lactic Acid and Hypercholesterolemia Reduce 90-day Mortality in Patients Suffering From Septic Shock According to the Sepsis-3 Definition

Dong Wang
The First Affiliated Hospital of Zhengzhou University
Yali Sun
The First Affiliated Hospital of Zhengzhou University
Huan Liu
The First Affiliated Hospital of Zhengzhou University, The First Affiliated Hospital of Zhengzhou University
Xiaojuan Zhang
The First Affiliated Hospital of Zhengzhou University
Xianfei Ding
The First Affiliated Hospital of Zhengzhou University
Shaohua Liu
The First Affiliated Hospital of Zhengzhou University
Bing Han
The First Affiliated Hospital of Zhengzhou University
Haixu Wang
The First Affiliated Hospital of Zhengzhou University
Xiaoguang Duan
The First Affiliated Hospital of Zhengzhou University
Tongwen Sun (suntongwen@163.com)
Zhengzhou University First Affiliated Hospital

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Abstract

Background: Dyslipidemia and lactic acid levels are associated with poor prognosis of septic shock. After the revised definition of sepsis and septic shock (Sepsis-3) in 2016, data on the prognostic value of lactic acid levels and hypocholesterolemia were lacked. This study aimed to evaluate whether lactic acid and cholesterol can be used to predict mortality in ICU patients suffering from septic shock.

Methods: Prospective observational study, 349 patients suffering from septic shock as defined by Sepsis-3. The COX model and the binary logistic regression model evaluate the correlation between lactic acid or total cholesterol and death from septic shock, and are adjusted according to the demographics, chronic diseases, and biomarkers of the participants.

Results: Total cholesterol, total protein, and albumin levels were significantly lower, and lactic acid, acute physiology, and chronic health assessment (APACHE II) were significantly higher in the surviving group compared to those in the non-surviving group. Lactate levels < 4.4 mmol/L and total cholesterol levels < 2.42 mmol/L were associated with mortality after adjusting for confounders (odd ratio, 3.06 [95% CI, 1.78-5.27] and 1.99 [95% CI, 1.15-3.46]). In multivariate analysis, urogenital origin, albumin levels < 25 g/L, age < 60 years, and APACHE II < 20 were independent risk factors for death from septic shock.

Conclusions: In those suffering from septic shock, increased blood lactate levels and decreased total cholesterol levels were associated with higher mortality. Furthermore, it was found that lactic acid and total cholesterol are sensitive markers of mortality in an ICU setting.

Background

Septic shock, which is one of the most serious form of sepsis, has a high mortality rate [1, 2] and an increasing incidence [3, 4]. The hemodynamic management of septic shock aims to correct and prevent insufficient tissue perfusion in order to reduce the risk of multiple organ dysfunction and death [5]. The 2016 “Surviving Sepsis Campaign Guidelines” has identified several indicators of sepsis, such as central venous pressure and central venous oxygen saturation, redundant [7]. Increased serum lactate levels are indicative of insufficient tissue perfusion which can occur as a result of severe sepsis [6]. While serum lactic acid levels are not a direct indication of tissue perfusion, the absence of specific sepsis indicators may increase the clinical importance of this biochemical measurement in patients undergoing early fluid resuscitation [8]. It should be noted that the prognostic value of serum lactate levels in patients with septic shock is poorly understood due to the lack of data.

Cholesterol plays an important role in septic resistance and the prevention of dysfunctional responses to microbial infection [9]. Previous studies have found that high-density lipoproteins (HDL) have multiple protective mechanisms in patients with sepsis, such as binding and neutralizing bacterial toxins, inhibiting the expression of adhesion molecules, stimulating the production of endothelial nitric oxide synthase, and protecting low-density lipid proteins (LDL), which help to remove bacterial toxins from patients with sepsis [11], from peroxidative damage [10]. In the absence of HDLs, these processes can

lead to inflammatory disorders, endothelial damage, organ damage, and death. Lagrost et al. demonstrated that patients who contracted sepsis after cardiac surgery have lower total cholesterol levels [12].

It remains unclear whether a decrease in serum lipoprotein levels reflects the severity of sepsis, as well as whether low levels of serum lipoprotein can be regarded as a risk factor for septic shock. Therefore, using the latest definitions and guidelines for sepsis and septic shock, this study aimed to evaluate the role of lactic acid and cholesterol as predictors of mortality in patients with septic shock.

Materials And Methods

Patients

From a prospective cohort of 759 patients with sepsis, 349 patients who met the septic shock standards, as defined by the Third International Consensus Definitions for Sepsis and Septic Shock, were enrolled in this study. The patients were recruited from the Comprehensive Intensive Care Unit (ICU) of the First Affiliated Hospital of Zhengzhou University. Each day, all of the adult sepsis patients in the ICU were screened to check for septic shock. Exclusion criteria were as follows: under 18 years of age, suffering from human immunodeficiency virus, pregnant or breastfeeding, and < 48 hours spent in the ICU. Eligible patients were then added to the study database.

This study was conducted in the Comprehensive Intensive Care Unit of the First Affiliated Hospital of Zhengzhou University and was approved by the hospital's Ethics Committee. Written informed consent was obtained from all patients or their legal representatives. All methods were performed in accordance with the relevant guidelines and regulations

Data collection

During the patient's first day in the ICU, baseline characteristics, such as sex, age, and Acute Physiology and Chronic Health Evaluation (APACHE II) score were recorded along with the presence of comorbidities, such as hypertension, chronic obstructive pulmonary disease (COPD), diabetes, and cancer. The patient's white blood cell count, procalcitonin levels, creatinine levels, alanine aminotransferase levels, aspartate aminotransferase levels, and lactic acid levels were also noted. The mortality of each patient was recorded and evaluated after 90 days.

Statistical analyses

Continuous variables were expressed as the mean ± standard deviation, and categorical variables were expressed as percentages. For univariate analysis, the subgroups were defined as survivors and non-survivors. The significance of continuous variables were determined using the Mann-Whitney U-test or the Student's *t*-test. Categorical variables were determined using the Pearson chi-square test or the bilateral Fisher's exact test which identified any significant differences between the subgroups. Multivariate analysis was performed using Cox regression models to identify variables that independently predicted

survival. To perform a multivariate analysis, the median continuous variable was halved, while the qualitative variable remained unchanged. In order to estimate the proportional hazard ratio and adjust for related confounding factors, multivariate Cox regression analysis was used to analyze variables whose *P* value was < 0.05 in univariate analysis. In order to approximate the life expectancy of each subgroup, a Kaplan-Meier survival curve was drawn using variables from the Cox analysis. The log-rank test was used to obtain the significant differences in survival rates between subgroups. Finally, a multiple logistic regression model was used to identify variables that were significantly related to death.

This analysis was completed by estimating the “dying” odds ratio and the 95% confidence intervals (CI). Statistically different variables (age, lactate, cholesterol, APACHE II, total protein, albumin, and urogenital origin of infection), which were identified using univariate analysis, were then used in logistic regression models. The Hosmer-Lemeshow goodness-of-fit test was used to evaluate the calibration of the logistic regression model and examine the differences between observed and expected deaths. The positive stepwise selection procedure was assessed using a likelihood ratio test and was used in two regression models (logical model and Cox model) to select variables that were significantly related to death and survival. SPSS 17.0 (SPSS, Inc, IBM, Chicago, IL) and GraphPad Prism 5.0 software (GraphPad Software, La Jolla, CA, USA) were used for statistical analysis. For all tests, $P < 0.05$ was considered statistically significant.

Results

Patients characteristics

A total of 349 patients (mean age, 58.6 ± 15.9 years; range, 20–93 years) participated in this study; 45% of the patients were men and 49.9% suffered from comorbidities. Lung infection was the main source of infection in patients with septic shock (38.7%), followed by blood-borne infection (34.4%). The urogenital tract was found to be the least common source of infection (6.9%). The APACHE II score indicated critically ill patients. The overall 90-day fatality rate was 71.9% (Table 1). All patients demonstrated a decrease in total protein levels, albumin levels, and blood lipids (total cholesterol, triglycerides, HDL, and LDL) and an increase in liver transaminase levels, blood creatinine levels, white blood cell count, and procalcitonin (PCT) following their admission to the ICU (Table 1).

Table 1
Demographic and clinical data of septic shock patients

Characteristic	Value
No. of patients	349
Age (yr)	58.6 ± 15.9[a]
Male (%)	45.0
Disease severity	
Acute Physiology and Chronic Health Evaluation (APACHE II)	20.9 ± 7.8
Lactic acid (mmol/L)	5.9 ± 4.7
Liver values	
AST (U/L)	67.1 ± 55.5
ALT (U/L)	48.6 ± 45.1
ALP (U/L)	99.3 ± 59.4
Total protein (g/L)	52.5 ± 12.0
Albumin (g/L)	25.1 ± 6.9
Lipids	
Total cholesterol (mmol/L)	2.7 ± 1.3
High-density lipoprotein (mmol/L)	0.6 ± 0.4
Low-density lipoprotein (mmol/L)	1.2 ± 0.9
Triglyceride (mmol/L)	1.7 ± 1.6
Kidney values	
Creatinine (µmol/L)	171.3 ± 148.2
Inflammatory values	
Leukocytes (1000/µL)	14.4 ± 9.6
Procalcitonin (ng/dl)	23.3 ± 21.9
Comorbidities (%)	
Heart failure	1.1

[a]Values are mean ± SD unless otherwise indicated.

COPD, chronic obstructive pulmonary disease.

Characteristic	Value
Hypertension	19.8
Coronary heart disease	12.0
Liver disease	4.6
COPD	2.3
Nervous system disease	6.0
Diabetes	16.9
Tumor	13.2
Site of infection (%)	
Lung	38.7
abdomen	26.4
Urogenital	6.9
Primary bacteraemia	34.4
Coagulation	
Platelets (1000/μL)	104.0 ± 90.7
90-day mortality (%)	71.9
[a]Values are mean ± SD unless otherwise indicated.	
COPD, chronic obstructive pulmonary disease.	

Comparison between survival and non-survival patients

Nutritional parameters

The survival and non-survival groups were similar in terms of HDL, LDL, triglycerides, and white blood cells. In the non-surviving group, total cholesterol, high density lipoprotein, low density lipoprotein, total protein, and albumin levels were significantly reduced. It was found that 78.7% of patients with a median total cholesterol level < 2.42 mmol/L, and 65.1% of patients with a median total cholesterol level ≥ 2.42 mmol/L (P = 0.006) died. Compared to the survival group, the total protein and albumin levels of the non-survival group were significantly reduced (P = 0.004, P = 0.001). The fatality rate of patients with a median total protein level < 52.3 g/L was 78.3%. The fatality rate of patients with a median total protein level ≥ 52.3 g/L (P = 0.009) and a median albumin level of < 25 g/L (median value) was 79.3%. Additionally, the fatality rate of patients with a median albumin level ≥ 25 g/L was 64.6% (Table 2).

Table 2
Univariate analysis of nutritional parameters of the septic shock patients

Parameter	Nonsurvivors	Survivors	*P*
Total cholesterol (mmol/L)	2.6 ± 1.3[a]	3.0 ± 1.4	0.015
Total cholesterol < median (2.42 mmol/L)	54.6%	37.8%	0.006
High-density lipoprotein (mmol/L)	0.6 ± 0.4	0.7 ± 0.4	0.007
High-density lipoprotein < median (0.59 mmol/L)	41.8%	53.0%	0.074
Low-density lipoprotein (mmol/L)	1.1 ± 0.8	1.4 ± 1.1	0.005
Low-density lipoprotein < median (1.05 mmol/L)	42.9%	52.6%	0.122
Triglyceride (mmol/L)	1.7 ± 1.6	1.6 ± 1.4	0.970
Triglyceride < median (1.28 mmol/L)	50.0%	49.8%	0.990
Total protein (g/L)	51.4 ± 12.4	55.5 ± 10.3	0.004
Total protein < median (52.3 g/L)	54.6%	38.8%	0.009
Albumin (g/L)	24.4 ± 6.8	27.0 ± 6.9	0.001
Albumin < median (25 g/L)	55.0%	36.7%	0.003
Leukocytes (1000/μL)	13.5 ± 9.6	16.6 ± 9.4	0.007
Leukocytes < median (13.3, 1000/μL)	45.9%	51.4%	0.405
[a]Values are mean ± SD unless otherwise indicated.			

Other variables

In patients suffering from septic shock, older age, APACHE II scores, and blood lactic acid levels were found to be associated with a high mortality. Lactic acid levels were found to be significantly higher in the non-surviving group ($P < 0.001$) compared to the surviving group. The fatality rate of patients with median lactic acid levels ≥ 4.4 mmol/L was 83.6%, while the fatality rate of patients with median lactic acid levels < 4.4 mmol/L was 59.9%. The non-surviving group had significantly higher APACHE II scores ($P < 0.001$) compared to the surviving group. The fatality rate of patients with a median APACHE II value ≥ 20 was 84.1%, while the fatality rate of patients with a median APACHE II value < 20 was 58.7%. ($P < 0.001$).

The age distribution was similar between the two groups. The fatality rate of patients ≥ 60 years old was 77.2%, and the fatality rate of patients < 60 years old was 66.3% ($P = 0.024$). Furthermore, the fatality rate associated with infections originating from the urogenital system was 37.5%, which was lower than the fatality rate associated with infections originating from other regions (74.5%) ($P < 0.001$). The surviving and non-surviving groups were similar in terms of sex, comorbidities, blood creatinine, and PCT (Table 3).

Table 3
Univariate analysis of select possible predictors of mortality in septic shock patients

Parameter	Nonsurvivors	Survivors	*P*
Age (yr)	59.1 ± 16.4[a]	57.3 ± 14.5	0.330
Age < 60 yrs (%)	41.8%	55.4%	0.024
Male sex (%)	54.1%	55.4%	0.905
Comorbid conditions (%)	42.9%	53.0%	0.096
Lactic acid (mmol/L)	6.8 ± 4.7	3.8 ± 3.7	<0.001
Lactic acid < median (4.4 mmol/L)	41.0%	70.4%	<0.001
Creatinine (μmol/L)	167.7 ± 135.2	180.4 ± 177.5	0.396
APACHE II score	22.4 ± 7.9	17.1 ± 6.1	<0.001
APACHE II score < median (20)	39.0%	70.4%	<0.001
Procalcitonin (ng/dl)	22.7 ± 21.2	24.9 ± 23.6	0.408
Procalcitonin < median (20.58 ng/dl)	51.8%	45.9%	0.342
Site of infection (%)			
lung	39.0	37.8	0.903
abdomen	25.1	29.6	0.418
Urogenital	3.6	15.3	<0.001
Primary bacteraemia	37.5	26.5	0.060
[a]Values are mean ± SD unless otherwise indicated.			

Multivariate Cox regression analysis and Kaplan-Meyer survival curves

Variables that were found to be statistically significant during univariate analysis (APACHE II score, total protein, albumin, lactic acid, and total cholesterol urogenital origin and, age) were evaluated using the Cox proportional hazards regression model. Independent predictors of overall patient survival rate were total cholesterol < 2.42 mmol/L, APACHE II < 20, age < 60 years, urogenital source, and lactate < 4.4 mmol/L (Table 4). Figure 1 demonstrates the Kaplan-Meier survival curve grouped according to the median value of total serum cholesterol. Patients with low serum cholesterol had significantly lower survival rates compared to those with high cholesterol levels (log-rank test, $P = 0.002$). Figure 2 demonstrates the Kaplan-Meier survival curve grouped according to median total serum lactate levels.

The survival rate of patients with low lactate levels was significantly higher than that of patients with high lactate levels (log-rank test, $P < 0.001$). Figure 3 demonstrates the relationship between lactic acid and cholesterol ($r^2 = 0.09$, insignificant). Please note that the survival rate of patients in the upper left quadrant (total cholesterol < 2.42 mmol/L and lactate ≥ 4.4 mmol/L) is extremely low.

Table 4
Multivariate Cox proportional hazards regression analysis

Variable[a]	β	SE	Wald	Hazard Ratio (95% CI)	*P*
Total cholesterol < 2.42 mmol/L	0.32	0.13	6.28	1.38 (1.07–1.78)	0.012
Lactic acid < 4.4 mmol/L	0.63	0.13	22.79	1.87 (1.45–2.42)	<0.001
Urogenital	1.09	0.34	10.12	2.96 (1.52–5.78)	0.001
Age < 60 yrs	0.39	0.13	8.50	1.46 (1.13–1.88)	0.004
APACHE II score < 20	0.62	0.13	21.72	1.85 (1.43–2.40)	<0.001
[a]Continuous variables were dichotomized according to their median value. Other variable entered in the model was sepsis. Other variables entered in the model are total protein and albumin.					
β, regression coefficient; CI, confidence interval; SE, standard error.					

Multivariate analysis for independent factors associated with death

Multivariate analysis was used to evaluate APACHE II, albumin, lactic acid, and total cholesterol (divided into two parts according to the median), age and urogenital source of infection. All of the aforementioned factors are independent and significantly correlated with mortality (Table 5). The APACHE II odds ratio was 3.43 (95% CI 1.98–5.95, $P < 0.001$); the albumin odds ratio, 1.73 (95% CI 1.00-2.99, $P = 0.049$); the lactate odds ratio, 3.06 (95% CI 1.78–5.27, $P < 0.001$); the total cholesterol odds ratio, 1.99 (95% CI 1.15–3.46, $P = 0.014$); the odds ratio associated with age, 0.74 (95% CI 1.02–2.98, $P = 0.042$); and the odds ratio associated with urogenital origin was 5.36 (95 % CI 2.06–13.97, $P = 0.001$). The Hosmer-Lemeshow goodness-of-fit test confirms that the model was well calibrated ($P = .094$).

Table 5
Multivariable logistic regression model for mortality in septic shock patients

Variable[a]	β	SE	Wald	Hazard Ratio (95% CI)	*P*
Total cholesterol < 2.42 mmol/L	0.69	0.28	6.03	1.99 (1.15–3.46)	0.014
Lactic acid < 4.4 mmol/L	1.12	0.28	16.30	3.06 (1.78–5.27)	<0.001
Urogenital	1.68	0.49	11.79	5.36 (2.06–13.97)	0.001
Age < 60 yrs	0.56	0.27	4.14	1.74 (1.02–2.98)	0.042
APACHE II score, 20	1.23	0.28	19.34	3.43 (1.98–5.95)	<0.001
Albumin < 25 g/L	0.55	0.28	3.88	1.73 (1.00-2.99)	0.049
[a]Continuous variables were dichotomized according to their median value.					

Discussion

This study evaluated whether serum lactic acid and cholesterol could predict mortality in patients with septic shock. The study cohort consisted of patients suffering from septic shock, as defined by the International Consensus on Sepsis-3. This study found that initial lactate levels are associated with 90-day mortality in patients with septic shock. This finding is consistent with other recent data [8, 13]. Based on the latest definition of septic shock, previous studies which evaluated the effect of cholesterol on the prognosis of patients with septic shock are limited and inconsistent. This study found that higher serum total cholesterol levels are beneficial to patients suffering from septic shock.

It is generally believed that low serum lipid levels are beneficial as the risk of cardiovascular disease is reduced. However, in recent years, studies have shown that low serum lipid levels are significantly correlated with patient mortality [14, 15]. In the early stages of a critical illness, the concentration and composition of lipids and lipoproteins in ICU patients change profoundly [16, 17]. Studies have shown that infection or inflammatory response syndrome can cause a significant decrease in total cholesterol levels along with LDL and HDL levels [18, 19]. This study found that the content of total cholesterol and the concentrations of LDLs and HDLs were significantly lower than the normal values in patients who met the definition of septic shock, according to Sepsis-3 [7]. In patients with sepsis and septic shock, rapid changes in serum lipid levels are closely related to clinical prognosis [20, 21]. Furthermore, HDL and LDL play an important role in removing bacterial toxins. In vitro studies have shown that lipopolysaccharides of gram-negative bacteria combine with HDL (60%) and LDL (25%). Therefore, low HDL and LDL concentrations increase the risk of a poor prognosis in sepsis patients due to the body's inability to remove bacterial toxins from the bloodstream [9].

Interestingly, this study did not demonstrate that a low HDL concentration is associated with a poor 90-day prognosis in patients with septic shock. Contrary to the results of a previous meta-analysis, lower HDL levels are associated with higher mortality in adult patients suffering from sepsis [22]. Such results

are not entirely surprising; a randomized controlled study demonstrated that raised HDL levels have no benefit in protecting patients with myocardial infarction [23]. At the same time, studies have shown that under some chronic inflammatory conditions, such as metabolic syndrome and rheumatoid arthritis, and acute some acute inflammatory conditions, such as sepsis and myocardial infarction, HDL function is dysfunctional and pro-inflammatory [24–28]. Current evidence suggests that HDL function may be more important than quantity. Daniel et al. found that hypocholesterolemia is an independent risk factor for death in critically ill patients [29]. Sérgio et al. also proved that total cholesterol concentrations ≤ 2.48 mmol/L are an independent risk factor for a poor prognosis in patients with acute kidney injuries [30]. The results of this study indicate that a reduction in total cholesterol levels is significantly associated with an increase in mortality in patients with septic shock. To the best of our knowledge, this study is the first to suggest that a total cholesterol level < 2.42 mmol/L is an independent risk factor for 90-day mortality in patients with septic shock.

Lactic acid levels in patients who died as a result of septic shock were significantly increased. Blood lactic acid levels were therefore determined as a predictor of mortality in patients with septic shock. Blood lactic acid levels ≥ 4.4 mmol/L were associated with a higher mortality rate in patients suffering from septic shock [13]. Studies have shown that septic shock, as defined by Sepsis-3, reduces the sample size by 50% and increases the 28-day mortality rate compared to the previous definition [31]. Therefore, the prognostic value of blood lactic acid levels in patients with septic shock, as defined by Sepsis-3, will be of great significance to clinicians in lactic acid-led resuscitation [8]. Previous research found that early, goal-directed therapy can reduce the mortality of adults with severe sepsis and septic shock, and lactate-guided therapy is more effective than early target-oriented therapy [32]. In fact, in the current study, when used alongside cholesterol to predict prognosis, patients with a lactate level above the median and a cholesterol level below the median accounted for only 10% of surviving patients.

In this study, serum albumin levels of non-surviving patients with septic shock were significantly reduced. Serum albumin levels below 25 g/L were found to be associated with a higher mortality rate in patients suffering from septic shock. Previous studies have shown that serum albumin levels are related to the prognosis of critical illness, and the relationship between hypoproteinemia, inflammation, and malnutrition is indissoluble [33, 34]. Furthermore, it is known that serum albumin levels can be reduced by stress. Clinical studies have shown that albumin replacement does not improve the 28-day and 90-day survival rates in patients with severe sepsis compared to crystalloids alone [35]. Therefore, serum albumin may not be an indicator that accurately reflects the prognosis of patients with septic shock.

A survey of sepsis severity demonstrated that patients with septic shock had an APACHE II score of ≥ 20. Furthermore, deaths in patients over 60 years of age were significantly higher than in those under the age of 60 with an APACHE II score of < 20. These findings are consistent with previous research [36, 37]; however, this study further quantified the severity of the disease and the risk of death in patients suffering from septic shock. Previous studies have demonstrated that the majority of sepsis cases originate from primary lung infections [38, 39]. Furthermore, that patients are more likely to develop septic shock if their infection originated from the urogenital tract, abdomen, or blood [40]. The mortality rate of those

suffering from a primary bloodstream infection is higher than that of patients whose primary infections did not originate from the blood [41]. This study shows that the 90-day prognosis of patients with septic shock originating from a urogenital tract infection is better than that of patients with infections which originated from other regions.

Conclusions

High serum lactate levels and hypocholesterolemia at the time of admission to the ICU have been associated with higher mortality in patients with septic shock. The combined use of these prognostic factors may facilitate the early prediction of mortality in patients suffering from septic shock.

Abbreviations

HDL, High-density lipoproteins; LDL, Low-density lipid proteins; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; COPD, Chronic obstructive pulmonary disease; CI, confidence intervals

Declarations

Ethics approval and consent to participate

The study was approved by the Scientific and Clinical Ethics Committee of the First Affiliated Hospital of Zhengzhou University, and all patients signed written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interests

The authors declare that they have no competing interests.

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Author contributions

DW and YLS participated in the research design and coordination and helped to draft the manuscript. HL, XJZ and XGD contributed the clinical sample collection. SHL, BH, HXW, XFD and TWS performed the data analysis. All authors read and approved the final manuscript.

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References

1. Annane D, Aegerter P, Jars-Guincestre MC, et al. Current epidemiology of septic shock: the CUB-Réa Network. *Am J Respir Crit Care Med* 2003;168(2):165-172.
2. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006;34(2):344-353.
3. Kaukonen KM, Bailey M, Suzuki S, et al. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. *JAMA* 2014;311(13):1308-1316.
4. Lagu T, Rothberg MB, Shieh MS, et al. Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. *Crit Care Med* 2012;40(3):754-761.
5. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345(19):1368-1377.
6. Sterling SA, Puskarich MA, Shapiro NI, et al. Characteristics and outcomes of patients with vasoplegic versus tissue dysoxic septic shock. *Shock* 2013;40(1):11-14.
7. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* 2017;43(3):304-377.
8. Ryoo SM, Lee J, Lee YS, et al. Lactate Level Versus Lactate Clearance for Predicting Mortality in Patients With Septic Shock Defined by Sepsis-3. *Crit Care Med* 2018;46(6):e489-e495.
9. Guirgis FW, Donnelly JP, Dodani S, et al. Cholesterol levels and long-term rates of community-acquired sepsis. *Crit Care* 2016;20(1):408.
10. Murch O, Collin M, Hinds CJ, et al. Lipoproteins in inflammation and sepsis. I. Basic science. *Intensive Care Med* 2007;33(1):13-24.
11. Feingold KR, Grunfeld C. Lipoproteins: are they important components of host defense? *Hepatology* 1997;26(6):1685-1686.
12. Lagrost L, Girard C, Grosjean S, et al. Low preoperative cholesterol level is a risk factor of sepsis and poor clinical outcome in patients undergoing cardiac surgery with cardiopulmonary bypass. *Crit Care Med* 2014;42(5):1065-1073.

13. Chambers KA, Park AY, Banuelos RC, et al. Outcomes of severe sepsis and septic shock patients after stratification by initial lactate value. *World J Emerg Med* 2018;9(2):113-117.
14. Schatz IJ, Masaki K, Yano K, et al. Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study. *Lancet* 2001;358(9279):351-355.
15. Lee SH, Park MS, Park BH, et al. Prognostic Implications of Serum Lipid Metabolism over Time during Sepsis. *Biomed Res Int* 2015;2015:789298.
16. Barlage S, Fröhlich D, Böttcher A, et al. ApoE-containing high density lipoproteins and phospholipid transfer protein activity increase in patients with a systemic inflammatory response. *J Lipid Res* 2001;42(2):281-290.
17. Lekkou A, Mouzaki A, Siagris D, et al. Serum lipid profile, cytokine production, and clinical outcome in patients with severe sepsis. *J Crit Care* 2014;29(5):723-727.
18. Gordon BR, Parker TS, Levine DM, et al. Relationship of hypolipidemia to cytokine concentrations and outcomes in critically ill surgical patients. *Crit Care Med* 2001;29(8):1563-1568.
19. Ngaosuwan K, Houngngam N, Limpisook P, et al. Apolipoprotein A-V is not a major determinant of triglyceride levels during human sepsis. *J Crit Care* 2015;30(4):727-731.
20. Chien JY, Jerng JS, Yu CJ, et al. Low serum level of high-density lipoprotein cholesterol is a poor prognostic factor for severe sepsis. *Crit Care Med* 2005;33(8):1688-1693.
21. Chien YF, Chen CY, Hsu CL, et al. Decreased serum level of lipoprotein cholesterol is a poor prognostic factor for patients with severe community-acquired pneumonia that required intensive care unit admission. *J Crit Care* 2015;30(3):506-510.
22. Liu SH, Liang HY, Li HY, et al. Effect of low high-density lipoprotein levels on mortality of septic patients: A systematic review and meta-analysis of cohort studies. *World J Emerg Med* 2020;11(2):109-116.
23. AIM-HIGH Investigators, Boden WE, Probstfield JL, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011;365(24):2255-2267.
24. Dodani S, Kaur R, Reddy S, et al. Can dysfunctional HDL explain high coronary artery disease risk in South Asians? *Int J Cardiol* 2008;129(1):125-132.
25. Van Lenten BJ, Hama SY, de Beer FC, et al. Anti-inflammatory HDL becomes pro-inflammatory during the acute phase response. Loss of protective effect of HDL against LDL oxidation in aortic wall cell cocultures. *J Clin Invest* 1995;96(6):2758-2767.
26. Dodani S, Dong L, Guirgis FW, et al. Carotid intima media thickness and low high-density lipoprotein (HDL) in South Asian immigrants: could dysfunctional HDL be the missing link? *Arch Med Sci* 2014;10(5):870-879.
27. Navab M, Reddy ST, Van Lenten BJ, et al. The role of dysfunctional HDL in atherosclerosis. *J Lipid Res* 2009;50 Suppl(Suppl):S145-S149.
28. Navab M, Hama SY, Hough GP, et al. A cell-free assay for detecting HDL that is dysfunctional in preventing the formation of or inactivating oxidized phospholipids. *J Lipid Res* 2001;42(8):1308-

1317.

29. Bonville DA, Parker TS, Levine DM, et al. The relationships of hypocholesterolemia to cytokine concentrations and mortality in critically ill patients with systemic inflammatory response syndrome. *Surg Infect (Larchmt)* 2004;5(1):39-49.
30. Guimarães SM, Lima EQ, Cipullo JP, et al. Low insulin-like growth factor-1 and hypocholesterolemia as mortality predictors in acute kidney injury in the intensive care unit. *Crit Care Med* 2008;36(12):3165-3170.
31. Sterling SA, Puskarich MA, Glass AF, et al. The Impact of the Sepsis-3 Septic Shock Definition on Previously Defined Septic Shock Patients. *Crit Care Med* 2017;45(9):1436-1442.
32. Ding XF, Yang ZY, Xu ZT, et al. Early goal-directed and lactate-guided therapy in adult patients with severe sepsis and septic shock: a meta-analysis of randomized controlled trials. *J Transl Med* 2018;16(1):331.
33. Al-Subaie N, Reynolds T, Myers A, et al. C-reactive protein as a predictor of outcome after discharge from the intensive care: a prospective observational study. *Br J Anaesth* 2010;105(3):318-325.
34. Vincent JL, Dubois MJ, Navickis RJ, et al. Hypoalbuminemia in acute illness: is there a rationale for intervention? A meta-analysis of cohort studies and controlled trials. *Ann Surg* 2003;237(3):319-334.
35. Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med* 2014;370(15):1412-1421.
36. Banta JE, Joshi KP, Beeson L, et al. Patient and hospital characteristics associated with inpatient severe sepsis mortality in California, 2005-2010. *Crit Care Med* 2012;40(11):2960-2966.
37. Phua J, Koh Y, Du B, et al. Management of severe sepsis in patients admitted to Asian intensive care units: prospective cohort study. *BMJ* 2011;342:d3245.
38. Harrison DA, Welch CA, Eddleston JM. The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: secondary analysis of a high quality clinical database, the ICNARC Case Mix Programme Database. *Crit Care* 2006;10(2):R42.
39. Ore T. Trends and disparities in sepsis hospitalisations in Victoria, Australia. *Aust Health Rev* 2016;40(5):511-518.
40. Bossink AW, Groeneveld AB, Koffeman GI, et al. Prediction of shock in febrile medical patients with a clinical infection. *Crit Care Med* 2001;29(1):25-31.
41. Hugonnet S, Sax H, Eggimann P, et al. Nosocomial bloodstream infection and clinical sepsis. *Emerg Infect Dis* 2004;10(1):76-81.

Figures

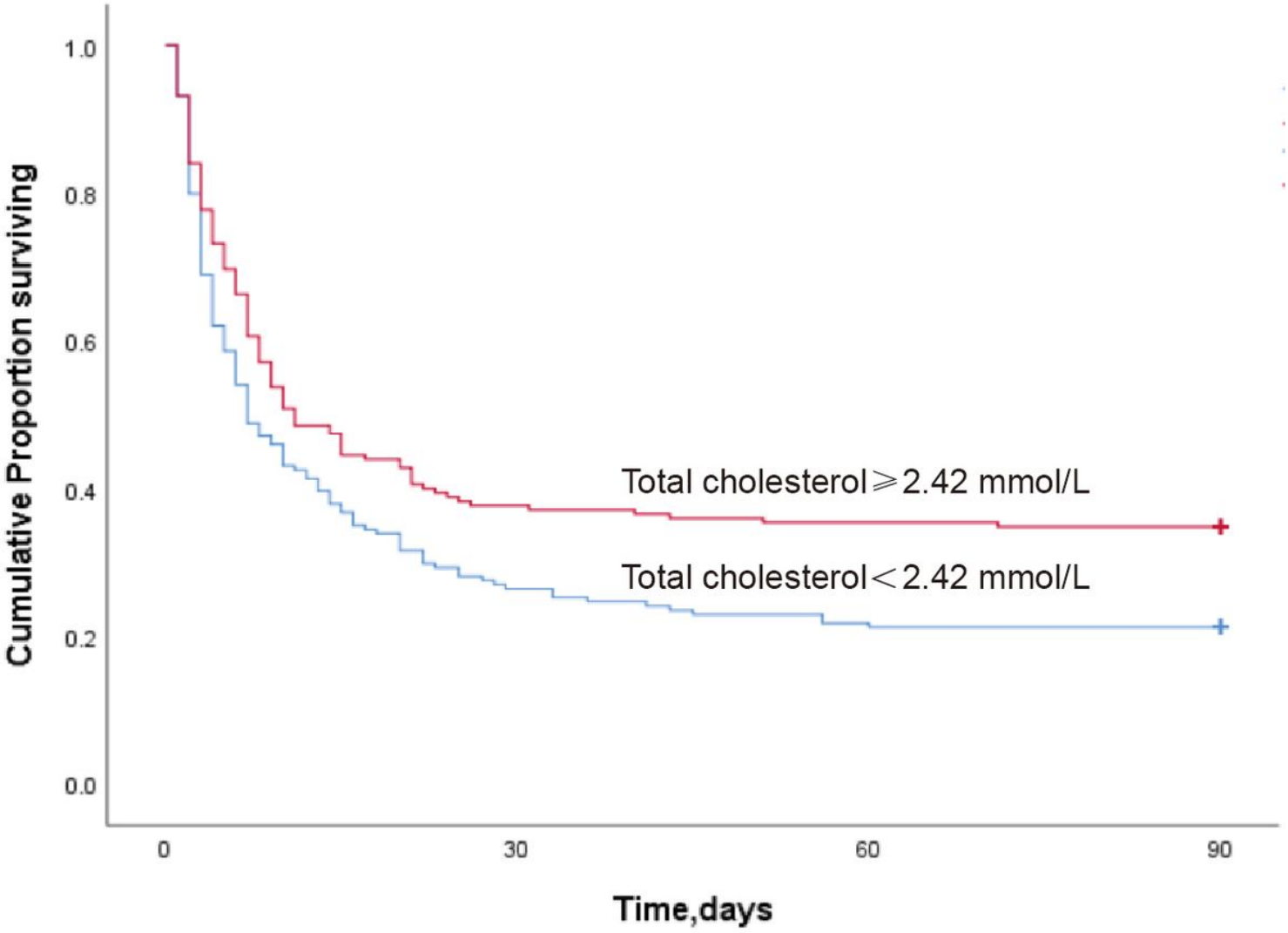

Figure 1

Kaplan-Meier survival curves according to the median value of total cholesterol serum levels in patients with septic shock. Patients with low cholesterol levels had a significantly lower survival rate than did those with high cholesterol levels (log-rank test, p = 0.007).

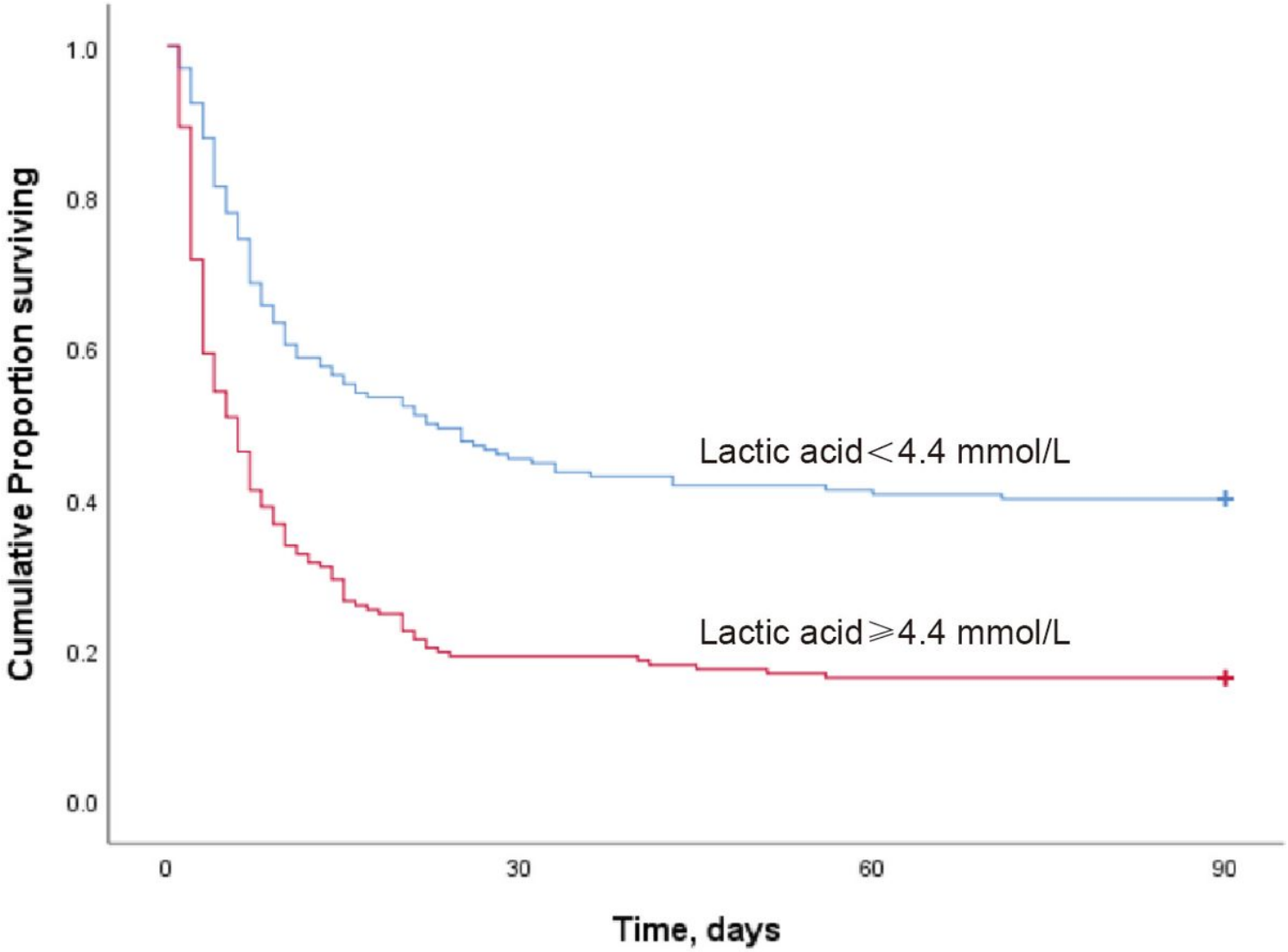

Figure 2

Kaplan-Meier survival curves according to the median value of serum lactic acid levels in patients with septic shock. Patients with high lactic acid levels have a significantly lower survival rate than did those with low lactic acid levels (log rank test, $p < 0.001$).

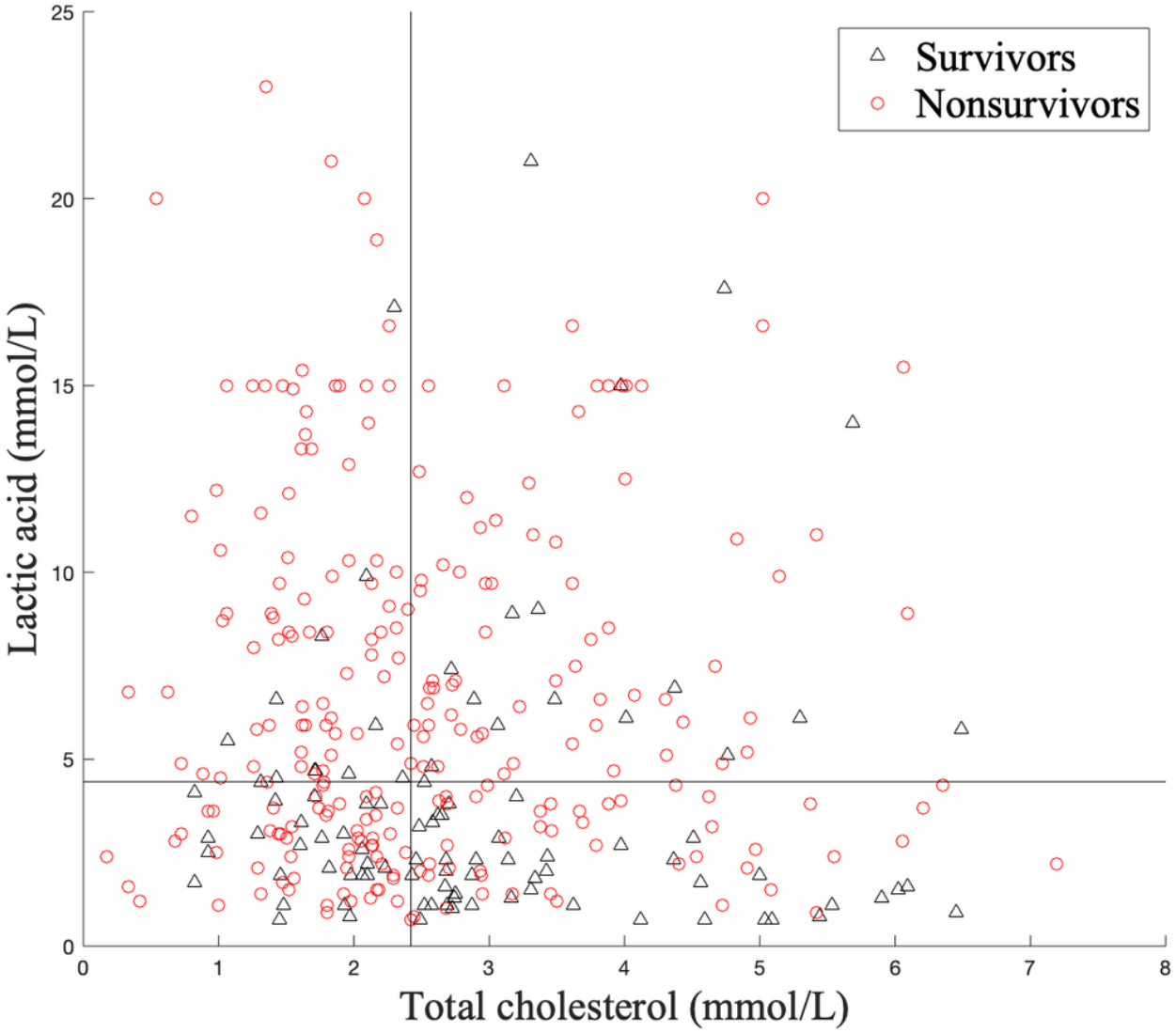

Figure 3

Regression plot showing the association between lactic acid and cholesterol (r2 =0.09, insignificant). Note that patients in the higher left quadrant (total cholesterol < median value and lactic acid > median value) had an extremely high mortality.