Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1507962
J Health Sci Med. 2024;7(6):615-620

The relationship between lipid levels and clinical outcomes in sepsis patients in the intensive care unit: a retrospective study

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Cite this article as: Kollu K, Kızılarslanoğlu MC. The relationship between lipid levels and clinical outcomes in sepsis patients in the intensive care unit: a retrospective study. *J Health Sci Med.* 2024;7(6):615-620.

Received: 01.07.2024 ◆ **Accepted**: 01.10.2024 ◆ **Published**: 27.10.2024

ABSTRACT

Aims: This study aimed to investigate the relationship between serum cholesterol levels (HDL-C, LDL-C, and triglycerides) and clinical outcomes in sepsis patients in an intensive care unit (ICU).

Methods: This retrospective study included patients aged >18 years diagnosed with sepsis who were admitted to the Internal Medicine ICUs of Konya City Hospital between June 15, 2021, and March 6, 2024. All data were obtained from routine blood tests of the patients in the ICU.

Results: The study included 477 patients (median age, 73 years; females, 45.9%). The median levels of APACHE-II and SOFA scores were 27 (range, 5-55) and 7 (range, 2-19) points, respectively. The survived patients were younger and had lower median APACHE and SOFA scores compared to the non-survived patients ($p<0.05$ for all). The survived patients had higher levels of platelets, albumin, and HbA1c ($p=0.001$, $p<0.001$, and $p=0.022$, respectively), but significantly lower levels of HDL-C, triglycerides, and C-reactive protein (CRP) compared to the non-survived patients ($p=0.026$, $p=0.011$, $p=0.034$, respectively). In multivariable regression analyses to document independently related parameters, it was found that age (HR: 1.030), SOFA score (HR: 1.891), HDL-C (HR: 1.054), and triglyceride (HR: 1.007) levels were positively and independently related, while acute pancreatitis (HR: 0.057) and albumin levels (HR: 0.428) were inversely related to in-hospital mortality in the study population (all had p-value <0.05).

Conclusion: The findings highlight the potential utility of lipid biomarkers in risk assessment and prognostication in critically ill patients, emphasizing the need for further prospective research to elucidate underlying mechanisms and optimize therapeutic strategies for sepsis management in intensive care settings.

Keywords: Sepsis, lipid levels, intensive care unit, lipid metabolism, prognosis, critically ill

INTRODUCTION

Variations in serum total cholesterol (TC) concentrations, deviations from the expected normal range of high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), are recognized features associated with chronic inflammatory conditions.[1] It has been demonstrated that in immunity and host defense, cholesterol metabolism is directly regulated by interferon cytokine response, and additionally, it has been shown that metabolites both upregulate and downregulate the pathway directing immune effector functions and anti-infective activity.[2] In terms of lipoprotein levels, it has been observed that HDL-C neutralizes infections or supports the clearance of toxins both in gram-negative bacteria (lipopolysaccharide) and Gram-positive bacteria (lipoteichoic acid) infections.[3] It has been noted that there is a positive correlation between sepsis and its severity with clinically significant cytokines, including tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and interleukin 10 (IL-10).[4,5] In patients with sepsis and septic shock, these cytokines exhibit a reverse correlation with serum cholesterol levels.[6,7]

There are numerous clinical observational studies, primarily focusing on sepsis, which report a reverse relationship between serum cholesterol levels and mortality rates in critically ill adults.[8,9] Despite limitations in population size and scope, these studies consistently report associations between low cholesterol levels (HDL-C, LDL-C, triglycerides, and TC) and mortality in sepsis.[10,11]

The current study aimed to investigate the relationship between serum cholesterol levels (HDL-C, LDL-C, triglycerides) and clinical outcomes in patients with sepsis hospitalized in intensive care unit (ICU).

METHODS

The study was approved by KTO-Karatay University Medical Faculty Ethics Committee for Non-drug and Non-medical Device Trials (Date: 07.03.2024, Decision No: 2024/042). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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The present retrospective study included patients aged ≥18 years diagnosed with sepsis who were admitted to the Internal Medicine ICUs (from emergency department or wards in the hospital) of Konya City Hospital between June 15, 2021, and March 6, 2024. Patients with hypothyroidism, those receiving lipid-lowering medications, with trauma, immune-deficiency, and applied cardiopulmonary resuscitation before ICU admissions were excluded from the study. A total of 477 patients were included in the study. All data were obtained from routine blood tests of the patients, and the initial day blood results of the patients in the ICU were scanned and recorded. Acute Physiology and Chronic Health Evaluation (APACHE)-II scores indicating mortality and Sequential Organ Failure Assessment (SOFA) scores used as diagnostic criteria for sepsis were calculated using the worst clinical and laboratory findings of the patients at the end of the 24th hour of ICU admission. The APACHE-II scores of the patients who died within the first 24 hours of ICU admission were also calculated by the worst clinical and laboratory findings of them (n=14). The Sepsis-3 criteria were used to diagnose sepsis in this study.[12] Additional blood samples were not taken from the patients for this study. General demographic properties, co-morbidities, and ICU and hospital admission and discharged dates of the patients were recorded. Length of hospital and ICU stays were calculated using the mentioned dates. The patients were divided into two groups according to the hospital last status (survived or non-survived). Primary end-point was accepted as in-hospital mortality in this study.

Statistical Analysis

The data were analyzed using the IBM SPSS Statistics for Windows, Version 22.0. (IBM Corp, Armonk, NY, USA). Descriptive statistical methods were used to express categorical variables as numbers and percentages. Whether numerical parameters exhibited a normal distribution was determined using the Kolmogorov-Smirnov test, histogram, and coefficient of variation. Numerical parameters exhibiting a normal distribution were presented as mean ± standard deviation, while non-normally distributed numerical parameters were expressed as median (minimum-maximum). For comparisons of medians between groups, the Mann-Whitney U test was used for two independent groups, while student's t-test was used for comparing means between two independent groups. Spearman's correlation test was applied for correlation analyses. Binary logistic regression analysis was used to find out independently associated factors for in-hospital mortality. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 477 patients with sepsis were enrolled in the study. Demographic and clinical characteristics of the patients are summarized in Table 1, 2; respectively. Among the patients, 45.9% were female, and the median age of the overall cohort was 73 years (range: 18-97 years). Of the patients included in the study, 47.6% survived. The most prevalent comorbidities included hypertension (47.4%), acute kidney failure (45.1%), and diabetes mellitus (40.5%), respectively. The median APACHE score was 27 (range: 5-55), and the median SOFA score was 7 (range: 2-19).

Table 1. Demographic data of the patients

	n=477
Sex, n (%)	
Female	219 (45.9)
Age, Median (minimum-maximum)	73 (18-97)
Hospital end state, n (%)	
Death	250 (52.4)
Comorbidities, n (%)	
Hypertension	226 (47.4)
Acute kidney failure	215 (45.1)
Diabetes mellitus	193 (40.5)
Malignancy	136 (28.5)
Coronary artery disease	136 (28.5)
Congestive heart failure	90 (18.9)
Chronic obstructive pulmonary disease	86 (18.0)
Chronic kidney disease	82 (17.2)
Dementia	78 (16.4)
Hematological disease	43 (9.0)
Asthma	33 (6.9)
Gastrointestinal bleeding	19 (4.0)
Acute pancreatitis	15 (3.1)

Table 2. Clinical data of the patients

	n=477
Clinical scores, median (minimum-maximum)	
APACHE-II	27 (5-55)
SOFA	7 (2-19)
Laboratory parameters, median (minimum-maximum)	
WBC, 103/µL	11575 (50-172240)
Hb, g/dL	10.5 (3.4-20.9)
PLT, 103/µL	191 (3-1714)
Glucose, mg/dl	142.5 (58-996)
CRE, mg/dl	1.42 (0.2-8.05)
ALT, IU/L	21 (5-5787)
Total cholesterol, mg/dl	119 (27.2-307.2)
LDL-C, mg/dl	61 (3.87-218)
HDL-C, mg/dl	28 (3-88)
Triglyceride, mg/dl	140 (34-722)
Albumin, g/dl	2.8 (1.4-5.2)
CRP, mg/L	119.18 (0.6-550)
TSH, mU/L	1.39 (0.01-5.94)
HbA1c, %	6.40 (4.40-18.80)
Length of stay (days), median (minimum-maximum)	
Hospital	16 (0-745)
Intensive care unit	7 (0-126)

APACHE: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment; WBC: white-blood-cell count; Hb: hemoglobin; PLT: platelet count; CRE: creatinine; ALT: alanine transaminase; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CRP: C-reactive protein; TSH: thyroid-stimulating hormone

Table 3, 4 present a comparison of demographic, clinical, and laboratory parameters between the survived and non-survived patients, respectively. The survived patients were significantly younger compared to the non-survived patients (p=0.001), and their median APACHE-II and SOFA scores were significantly lower (p<0.001, for both). Additionally, the survived patients exhibited significantly higher levels of platelets (PLT), albumin, and HbA1c (p=0.001, p<0.001, and p=0.022, respectively) while their levels of HDL, triglycerides, and C-reactive protein (CRP) were significantly lower than those of the non-survived patients (p=0.026, p=0.011, p=0.034 respectively). Furthermore, the length of stay in the ICU was significantly shorter in the survived patients than in the non-survived patients (p=0.019).

Table 3. Comparison of demographic data between the survived and non-survived patients

	Survived (n=227)	Non-survived (n=250)	p
Sex, n (%)			
Female	107 (47.1)	112 (44.8)	0.609
Age, median (minimum-maximum)	69 (18-97)	75 (21-95)	0.001
Comorbidities, n (%)			
Diabetes mellitus	98 (43.2)	95 (38.0)	0.250
Hypertension	112 (49.3)	114 (45.6)	0.414
Dementia	38 (16.7)	40 (16.0)	0.827
Chronic kidney disease	36 (15.9)	46 (18.4)	0.463
Acute kidney failure	96 (42.3)	119 (47.6)	0.244
Gastrointestinal bleeding	9 (4.0)	10 (4.0)	0.984
Acute Pancreatitis	11 (4.9)	4 (1.6)	0.042
Chronic obstructive pulmonary disease	39 (17.2)	47 (18.8)	0.646
Asthma	17 (7.5)	16 (6.4)	0.640
Coronary artery disease	66 (29.1)	70 (28.0)	0.795
Congestive heart failure	47 (20.7)	43 (17.2)	0.329
Malignancy	52 (22.9)	84 (33.6)	0.010
Hematological disease	25 (11.0)	18 (7.2)	0.146

Table 5 illustrates the correlation of TC, HDL-C, LDL-C, and triglyceride levels with various clinical parameters. According to the data, TC showed positive correlations with hemoglobin (Hb), blood glucose (GLU), LDL-C, HDL-C, triglycerides, albumin, and HbA1c, while exhibiting a negative correlation with CRP. LDL-C was positively correlated with Hb, PLT, GLU, TC, HDL-C, albumin, and HbA1c, but negatively correlated with SOFA score, and creatinine (CRE), and CRP levels. HDL-C demonstrated positive correlations with Hb, PLT, TC, LDL, and albumin levels, while negatively correlated with SOFA score, and CRE, triglycerides, and CRP levels. Triglyceride levels showed positive correlations with APACHE and SOFA scores, and GLU, CRE, TC, CRP, and HbA1c levels, but were negatively correlated with age and HDL and albumin levels. The significant correlation results had rho coefficient levels lower than 0.30, which indicated weak correlations. No correlation was found between lipid parameters and the duration of hospital or ICU stay.

Table 4. Clinical and laboratory parameters between the survived and non-survived patients

	Survived (n=227)	Non-survived (n=250)	p
Clinical scores, median (minimum-maximum)			
APACHE-II	24 (5-53)	29 (12-55)	<0.001
SOFA	5 (2-15)	9 (2-19)	<0.001
Laboratory parameters, median (minimum-maximum)			
WBC, 103/µL	11055 (110-90460)	12035 (50-172240)	0.433
Hb, g/dL	10.8 (3.4-18.2)	10.3 (5.6-20.9)	0.093
PLT, 103/µL	212.5 (8-613)	160.5 (3-1714)	0.001
Glucose, mg/dl	147 (64-996)	139.5 (58-755)	0.210
CRE, mg/dL	1.35 (0.21-7.35)	1.46 (0.2-8.05)	0.070
ALT, IU/L	20 (5-1470)	22 (5-5787)	0.066
Total cholesterol, mg/dl	115.2 (27.8-307.2)	123.1 (27.2-265.4)	0.131
LDL, mg/dl	60 (3.87-218)	61 (3.87-167)	0.872
HDL, mg/dl	25 (6-64)	30 (3-88)	0.026
Triglyceride, mg/dl	134 (34-722)	149 (46-718)	0.011
Albumin, g/dl	2.9 (1.4-5.2)	2.6 (1.4-4.2)	<0.001
CRP, mg/L	110.97 (0.6-458)	127.73 (1.21-550)	0.034
TSH, mU/L	1.39 (0.01-5.53)	1.37 (0.01-5.94)	0.913
HbA1c, %	6.6 (4.7-18.8)	6 (4.4-11.1)	0.022
Length of Stay (days), median (minimum-maximum)			
Hospital	14 (0-670)	17 (0-745)	0.601
Intensive care unit	6 (0-108)	7 (0-126)	0.019

APACHE: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment; WBC: white-blood-cell count; Hb: hemoglobin; PLT: platelet count; KRE: creatinine; ALT: alanine transaminase; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CRP: C-reactive protein; TSH: thyroid-stimulating hormone

In multivariable regression analyses to document independently related parameters with hospital mortality (Table 6), it was found that age (HR: 1.030), SOFA score (HR: 1.891), HDL-C (HR: 1.054), and triglyceride (HR: 1.007) levels were positively and independently related to in-hospital mortality, while acute pancreatitis (HR: 0.057) and albumin levels (HR: 0.428) were inversely related to in-hospital mortality in the study population.

DISCUSSION

Sepsis constitutes a leading cause of mortality in critical care units globally and consumes substantial healthcare resources. According to the current study results, older age, higher APACHE and SOFA scores, as well as elevated CRP and triglyceride levels, were identified as risk factors for mortality in sepsis patients, consistent with previous findings.[1,4,5,7,9] Notably, the HDL-C levels of survivors were lower compared to those of non-survivors in this study, contrary to some previous research indicating lower HDL-C levels as a risk factor for sepsis-related mortality.[9-11,13] Conversely, one study proposed that low serum HDL levels may serve as a poor prognostic indicator for severe sepsis, suggesting an association between day 1/2 HDL-C levels and survival.[14] Another study reported that lipoprotein concentrations lack discriminatory ability between survivors and non-survivors,[15] and a separate

Table 5. Correlation analysis between study parameters and lipid levels

	Total cholesterol		LDL-C		HDL-C		Triglyceride	
	rho	p	rho	p	rho	p	rho	p
Age	-0.019	0.671	0.023	0.623	0.082	0.073	-0.153	0.001
Clinical scores								
APACHE-II	-0.029	0.533	-0.080	0.091	-0.088	0.064	0.166	<0.001
SOFA	-0.071	0.121	-0.116	0.011	-0.124	0.007	0.155	0.001
Laboratory parameters								
WBC, 103/µL	-0.067	0.196	-0.050	0.333	-0.056	0.281	-0.037	0.471
Hb, g/dl	0.268	<0.001	0.272	<0.001	0.219	<0.001	0.000	0.993
PLT, 103/µL	0.065	0.211	0.103	0.047	0.106	0.040	-0.095	0.064
Glucose, mg/dl	0.138	0.003	0.121	0.008	0.043	0.353	0.140	0.002
CRE, mg/dl	-0.089	0.053	-0.142	0.002	-0.149	0.001	0.121	0.008
ALT, IU/L	0.025	0.590	0.048	0.297	-0.053	0.248	0.064	0.164
Total cholesterol, mg/dl	1.000		0.897	<0.001	0.671	<0.001	0.289	<0.001
LDL-C, mg/dl	0.897	<0.001	1.000		0.643	<0.001	-0.005	0.910
HDL-C, mg/dl	0.671	<0.001	0.643	<0.001	1.000		-0.210	<0.001
Triglyceride, mg/dl	0.289	<0.001	-0.005	0.910	-0.210	<0.001	1.000	
Albumin, g/dl	0.284	<0.001	0.293	<0.001	0.348	<0.001	-0.112	0.014
CRP, mg/L	-0.148	0.001	-0.212	<0.001	-0.224	<0.001	0.163	<0.001
TSH, mU/L	-0.053	0.249	-0.020	0.663	-0.072	0.114	-0.019	0.685
HbA1c, %	0.175	0.030	0.180	0.025	-0.050	0.535	0.177	0.028
Length of stay								
Hospital	0.072	0.114	0.054	0.242	0.046	0.314	0.045	0.326
Intensive care unit	-0.019	0.684	-0.020	0.663	-0.002	0.964	-0.038	0.405

APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, WBC: White-blood-cell count, Hb: Hemoglobin, PLT: Platelet count, CRE: Creatinine, ALT: Alanine transaminase, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, CRP: C-reactive protein, TSH: Thyroid-stimulating hormone

Table 6. Multivariable binary logistic regression analyses results that show the independently related factors for hospital mortality

Parameters	HR	95% CI	p-value
Age, years	1.030	1.006-1.054	0.015
Acute pancreatitis	0.057	0.005-0.687	0.024
SOFA score	1.891	1.645-2.173	<0.001
HDL-C level	1.054	1.026-1.083	<0.001
Triglyceride level	1.007	1.003-1.011	<0.001
Albumin level	0.428	0.237-0.774	0.005

HR: Hazard ratio, CI: Confidence interval, SOFA: Sequential Organ Failure Assessment, HDL-C: High-density lipoprotein cholesterol

The significantly related parameters (p<0.05) with hospital mortality in univariable analyses were included in multivariable analyses (age, acute pancreatitis, malignancy, APACHE-II, SOFA scores, platelet, HDL-C, triglyceride, albumin, C-reactive protein, and length of ICU stay). HbA1c level was not added to the regression model due to significantly correlation between triglyceride levels and high missing data (HbA1c level was measured in 154 patients). Binary logistic regression analysis was done using backward method. The last step (step-6) was shown in the table. The Omnibus test p-value was <0.001, Nagelkerke R square was 0.670, and the Hosmer and Lemeshow test p-value was 0.118 for this step.

study found no significant relationship between HDL-C and hospital mortality.[16] In another study conducted by Aydemir et al.,[17] low HDL and LDL levels may be useful in predicting mortality. The etiology of the reported low HDL-C levels on the first day of severe sepsis remains unclear, with possible influences from baseline HDL-C levels preceding sepsis, heightened endotoxin production during severe infection, or suppression of production by pro-inflammatory cytokines.[14] Due to lack of data in this subject, further studies are needed and warranted to clarify causality between mentioned parameters. Additionally, variations in comorbidities, age, CRP, and APACHE II values within the patient population may have affected the current HDL-C profiles.[9] A previous retrospective cohort study in sepsis patients suggests that intra-sepsis HDL-C levels are more critical than baseline values and may be related to the different types of HDL present during inflammation.[16] Additionally, a prospective cohort study analyzing dysfunctional HDL in sepsis patients demonstrated a significant association between dysfunctional HDL levels and in-hospital mortality, as well as between early cholesterol levels and the severity of organ failure and sepsis-related death.[18] Therefore, the functionality of HDL particles is as crucial as their quantity or size.[13] These findings may also explain the current study's observation of higher HDL-C levels in non-survivors. Future studies are needed to explore other potential mechanisms.

Previous studies have extensively investigated changes in serum cholesterol levels in sepsis patients, primarily examining associations with illness severity and mortality.[10,11,13,16,18,19] In the present study, we conducted a comprehensive analysis to elucidate correlations between serum cholesterol levels (HDL-C, LDL-C, Triglycerides) and various clinical parameters, including blood counts and medical scores in sepsis patients, potentially contributing to future research endeavors. In a prior study, researchers analyzed correlations

at different time points and compared them between survivors and non-survivors,[9] revealing dynamic relationships influenced by patient population and time points. Another study reported correlations between APACHE III scores and CRP levels on days 4-7 in sepsis patients.[20] Additionally, several studies investigating cytokine levels and clinical parameters such as albumin, CRP, and APACHE scores,[5,21] as well as cholesterol and cytokine concentrations,[6] and cholesterol and monocyte/platelet activation,[8] have contributed to the understanding of sepsis pathophysiology.

In the current study, no correlation was found between lipid parameters and the duration of hospital or ICU stay. To our knowledge, no other studies have investigated the correlation between lipid profiles and the length of hospital or ICU stay in sepsis patients. In addition, we found that low HbA1c level might be related to in-hospital mortality in the study population. This finding supports the knowledge that intensive glycemic control (targeting HbA1c level <6%) especially in older and critically ill patients might be dangerous.[22]

Limitations

The biological mechanisms underlying lipid levels in sepsis remain incompletely understood, leading to limited and conflicting data regarding sepsis's impact on cholesterol synthesis.[23] Further research is warranted to expand our comprehension of these mechanisms and the role of cholesterol in sepsis.

This study has several limitations. Firstly, its retrospective nature precludes additional tests and interventions. Additionally, the lack of serum cholesterol levels at different time points during hospitalization due to the retrospective setup limits our insights. Although the population size is considerable, data were collected from a single institution, limiting the generalizability of the findings. Moreover, the heterogeneous patient group regarding infection types, comorbidities, and ages directly influences mortality rates and laboratory parameters.

CONCLUSION

This study sheds light on the significant role of serum cholesterol levels, particularly HDL-C, LDL-C, and triglycerides, in the clinical outcomes of sepsis patients. The observed associations between cholesterol levels and mortality rates underscore the prognostic relevance of lipid metabolism in sepsis. The current findings highlight the potential utility of lipid biomarkers in risk assessment and prognostication in critically ill patients, emphasizing the need for further prospective research to elucidate underlying mechanisms and optimize therapeutic strategies for sepsis management in intensive care settings.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of KTO-Karatay University Medical Faculty Ethics Committee for Non-drug and Non-medical Device Trials (Date: 07.03.2024, Decision No: 2024/042).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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