

Are Lipoprotein Levels and Ratios Able to Predict Mortality due to Sepsis?

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ABSTRACT

Objective: To compare lipoprotein levels, and non-HDL to high-density lipoprotein (HDL) ratios of survivors and non-survivors of sepsis, and to determine the predictivity levels of specified parameters in mortality.

Study Design: Descriptive study.

Place and Duration of Study: Department of Internal Medicine, Kirikkale University, School of Medicine, Training and Research Hospital, Kirikkale, Turkey, from December 2017 to December 2018.

Methodology: The study subjects included 37 non-survivors and 32 survivors of sepsis with similar ages, comorbidities, and disease activities. The total lipoprotein levels, and non-HDL to HDL ratios of the participants were compared retrospectively.

Results: HDL and non-HDL to HDL ratios were found to be different between the two groups. The cut-off levels of these values were determined as 32 and 3.4, respectively. The cut-off levels found in the study suggest that the low HDL levels and high non-HDL to HDL ratios significantly increase the mortality risk for patients (OR=1.8 and 3.45, respectively).

Conclusion: Non-HDL to HDL ratio may be used as a useful tool for predicting sepsis mortality. These values may also be included as a part of scoring systems. Further investigations are needed to clarify the role of lipoproteins in sepsis.

Key Words: Sepsis, Lipoproteins, Non-HDL to HDL ratio.

How to cite this article: Karahan I, Cifci A. Are lipoprotein levels and ratios able to predict mortality due to sepsis? *J Coll Physicians Surg Pak* 2020; **30**(3):272-275.

INTRODUCTION

Sepsis is a serious, life-threatening organ dysfunction caused by a dysregulated host response to infection. In the literature, increasing rates of in-hospital mortality due to sepsis, greater than %10, have been reported.¹

Recently, the definitions for sepsis and septic shock have been reviewed and revised (Sepsis-3 definition). Sepsis is defined as 'an organ dysfunction characterised by sequential organ failure assessment (SOFA) score of more than two points, with the exaggerated host response to infection'. The SOFA score includes variables pertinent to respiratory, cardiovascular, liver, coagulation, renal, and neurological parameters.²

Lipoproteins are macromolecular complexes carrying lipid molecules. They provide lipid exchange to the liver and peripheral tissues. Lipoproteins are classified according to their relative densities as chylomicrons, low-density lipoprotein (LDL), very-low density lipoprotein

(VLDL), intermediate density lipoprotein (IDL), and high-density lipoprotein (HDL).³ Lipoprotein values are frequently altered in critically ill patients. Reduction in HDL and LDL, and increase in triacylglycerol are well known in sepsis.⁴

A recent trial has shown that non-HDL to HDL ratio is a good predictor for coronary heart disease.⁵ Other studies have found that impairment of this ratio is associated with non-alcoholic steatohepatitis, chronic kidney disease, and heart failure.⁶⁻⁸

The aim of the present study was to show the predictability of lipoprotein levels and ratios in sepsis mortality.

METHODOLOGY

The present retrospective study included an evaluation of the cases of 69 adult patients that were admitted to Department of Internal Medicine, Kirikkale University, School of Medicine, with sepsis from December 2017 to December 2018. Thirty-seven patients died, while 32 patients were cured and discharged from hospital. Discharged patients were called 'survivors' albeit dead patients were called 'non-survivors'. Medical records and time of death of the patients, and SOFA scores were first noted. Then, lipid parameters and ratios of the groups were compared following the calculation of LDL,

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Received: September 28, 2019; Revised: January 18, 2020;

Accepted: January 27, 2020

HDL, triglyceride, non-HDL to HDL ratios using the Friedewald formula [LDL = Total Cholesterol-(HDL + VLDL), VLDL = Triglyceride/5]. Besides, correlations between days of death after admission and lipid parameters of the patients were evaluated. Finally, it was attempted to calculate the risk of mortality based on the cut-off levels of HDL and non-HDL.

IBM SPSS 25 was utilised for all statistical analyses. Normally distributed values were given as mean \pm standard deviation while non-normally distributed values were given as median (minimum-maximum). The Mann-Whitney-U test was performed for the between-group comparison. The ROC analysis was used to detect the cut-off levels of significant values while Fisher's exact test was used for group distributions and odds ratio was calculated based on the cut-off levels between the groups. The correlations were determined using Spearman's correlation analysis. The significance level was accepted as $p < 0.05$.

RESULTS

There were 34 female and 35 male subjects; and the mean age was 71.20 ± 9.35 years. The age, Charlson comorbidity scores, and SOFA scores on admission were similar by group comparisons (Table I). LDL and triglyceride levels did not show a significant difference between survivor and non-survivor groups. By ROC analysis, the cut-off levels of HDL and non-HDL to HDL ratio were found to be 32 (95% CI 0.68-4.99) and 3.4, (95% CI 1.27-9.36), respectively. HDL level was significantly lower, and non-HDL/HDL ratio was significantly higher in the non-survivor group ($p < 0.001$ for both parameters, Table I).

Table I: Patient characteristics and laboratory values by group comparisons.

	Survivor (n=32)	Non-survivor (n=37)	p value
Age (years)	73.34 \pm 7.71	73.11 \pm 10.63	0.636
Female / male ratio (n)	15/17	19/18	0.711
Charlson comorbidities score	5 (1-8)	6 (1-9)	0.25
Time of death after admission, day	NA	9 (2-50)	
SOFA score	5 (3-7)	5 (4-8)	0.68
CRP on admission (mg/dl)	158 (5-562)	145 (4-507)	0.583
HDL (mg/dl)	33 (11-62)	19 (4-60)	0.002
LDL (mg/dl)	80 (33-181)	75 (6-181)	0.393
Triglyceride (mg/dl)	114 (55-315)	142 (61-427)	0.396
Non-HDL to HDL ratio	3.15 (1.16-10.23)	4.47 (1.02-23.68)	0.009

The odds ratios were 1.85 and 3.45 for HDL and non-HDL/HDL, respectively. There was no correlation between time of death after admission, and HDL and non-HDL/HDL ($r = -0.22$, $p = 0.18$; $r = 0.08$, $p = 0.60$, respectively).

DISCUSSION

The present study revealed that HDL levels were lower in the non-survivor group than the survivor group, while no such relationship was found between LDL and

triglyceride levels. The non-HDL to HDL ratio was different between the groups. These findings suggest that this ratio may be more predictive than HDL alone. Moreover, these parameters did not have a relationship with the time of death.

HDLs comprise various lipoproteins that are produced initially in the liver. The major function of HDL is to transport and recycle cholesterol in the liver. The mechanisms of HDL against sepsis can be clearance of bacterial toxins, prevention of the release of inflammatory cytokines, modulation of innate cellular immunity, and transportation of cholesterol molecules to the adrenal gland for steroid biosynthesis. The capacity of HDL to provide the clearance of bacterial toxins results from its own main apolipoprotein, Apo-AI. Bacteria can produce lipoteichoic acid (LTA) and lipopolysaccharide (LPS) both in gram-negative and gram-positive bacterial infections. They are bound to their own receptors, resulting in the increase of key inflammatory cytokines. HDL binds both LTA and LPS, and neutralises these products. Afterwards, LTA and LPS bound to HDL are removed by hepatic cells, and so the inflammatory process is suppressed.⁹⁻¹¹

It has been confirmed in animal models that the binding of HDL molecules to LPS and such neutralisation have positive effects on sepsis survival. HDL may modulate macrophage function and reduce the thrombotic process by reducing the expression of endothelial adhesion molecules. Therefore, tissue factor expression may be suppressed, the activity of cyclooxygenase-2 may be promoted, and the synthesis of prostacyclin may increase.¹²

Two trials have confirmed a relationship between low levels of HDL and an increased sepsis mortality with more complications by defining the cut-off points for HDL concentrations in critical care patients,^{13,14} which supports the present findings. Gordon *et al.*,¹⁵ have shown surgical patients with low lipoprotein levels have a high sepsis-related mortality rate. The beneficial effects of lipoproteins may be related to their capability to neutralise almost all the toxic bacterial products in sepsis. The mentioned study demonstrated that serum concentrations of proinflammatory cytokines such as TNF- α interleukin-6 are higher in patients with low HDL levels, which reflects the overactive status of inflammatory response, and causes multiple organ damage and mortality.¹⁵

Van Leeuwen *et al.*,¹⁶ showed HDL cholesterol concentrations declined rapidly in the early phase of severe sepsis, but discrimination between survivors and non-survivors by initial HDL cholesterol concentrations could not be achieved. Moreover, their study had certain limitations, such as small sample size.

The mechanism of the rapid decline in cholesterol levels was unclear. Few studies have uncovered whether the

sharp drop in cholesterol levels is related to organ failure and mortality. In this sense, many possible explanations have been claimed. One posits that HDL and LDL are connected to reverse cholesterol transport and toxin clearance. HDL transports cholesterol molecules to the adrenal glands for steroid hormone production, and it removes from circulation. This is a process mediated by the scavenger receptor BI (SR-BI). Mice over-expressing SR-BI demonstrated the effective clearance of HDL from blood.^{17,18} The other possible mechanisms explaining the acute HDL reductions may be the reduced expression of the hepatic ABCA1 transporter, lipolysis by activation of phospholipase A2, and increased HDL clearance by increased serum amyloid A.¹⁹

A recent study has reported that levels of both HDL and LDL are dysregulated during sepsis. However, lipoprotein particles become oxidised during inflammation, so they can become pro-inflammatory and dysfunctional, resulting in dysfunctional HDL. This process can lead to a propagation of inflammation and tissue damage in sepsis patients.²⁰

LDL has a protective role against sepsis, thanks to its ability to neutralise bacterial toxins and provide substrate for steroid biosynthesis. What is interesting about this process is the crucial role of the LDL receptor (LDL-R) on hepatocytes. LDL-R knockout mice, which have reduced ability to remove LDL from blood, demonstrate endotoxin clearance deficiency.²¹ Recently, a study has established a connection between the proprotein convertase subtilisin/kexin type 9 (PCSK9) molecule and microbial products. PCSK9 binds and degrades the LDL-R, and therefore LDL levels increase in blood. It has been shown that a high level of PCSK9 is related to reduced bacterial endotoxin clearance in cultured human liver cells of sepsis patients.²² However, the present study did not detect any LDL difference between the groups.

In addition, hypertriglyceridemia (>150 mg/dl) has been shown to be a predictive factor for sepsis mortality. A decrease in lipoprotein lipase activity was reported in animal models and bacteremic subjects. Hypertriglyceridemia in early sepsis can be explained with this mechanism. In the present study, there was no difference between the survivor and non-survivor groups.²³

The present study may be the first one investigating the non-HDL to HDL ratio in sepsis. While this ratio has been studied in various diseases, there is no corresponding detailed data related to an infectious disease. Non-HDL include LDL, VLDL and IDL and low LDL and high triglyceride levels are expected in sepsis. No subjects of the present study had abnormal LDL and triglyceride values as expected. Also, the present study revealed that the non-HDL to HDL ratio was more predictable than HDL cut-off levels.

This study has several limitations, such as retrospective design and small sample size. Moreover, the detailed inflammatory markers, other lipoprotein levels, and nutritional parameters were not evaluated.

CONCLUSION

Lipoprotein measurement is an economical and easily-performed test. Lipoprotein levels, and especially the non-HDL to HDL ratio, may be used as a favourable tool for predicting sepsis mortality. Perhaps these values may be incorporated as a part of scoring systems. Further investigations are needed to clarify the role of lipoproteins in sepsis.

ETHICAL APPROVAL:

Kirikkale University's Ethical Committee approval was obtained for this study.

PATIENTS' CONSENT:

Informed consents were obtained from all participants or their family on admission.

CONFLICT OF INTEREST:

Authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

IK: Conception and design of the work; acquisition, analysis, interpretation of data.

AC: Provided ideas on the status, and reviewed the paper, advices and final approval.

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