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A prospective study on prognostic value of hypocholestrolemia in sepsis

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Abstract

Background: Sepsis is a major cause of mortality in adult, non-coronary intensive care units (ICUs) and holds significant clinical importance. Multicentre prospective surveys have shown that 1% of hospitalized patients experience bacteraemia, with 0.3% suffering from bacteraemia with severe sepsis. These rates increase eightfold and thirtyfold, respectively, when ICU admissions are considered. Approximately 10% of ICU patients have sepsis, 6% have severe sepsis, and 2-3% experience septic shock.

Aim: This study aimed to assess the dynamic changes in serum cholesterol levels in sepsis patients and evaluate whether these cholesterol levels correlate with prognosis using the Sequential Organ Failure Assessment (SOFA) score.

Materials and methods: A comprehensive analysis was conducted over 18 months on 115 patients with sepsis. SOFA scores and lipid profiles were collected at ICU admission (day 0) and day 3. Patients were categorized into two groups based on their total cholesterol: Group A (<160 mg/dl) and Group B (>160 mg/dl). Statistical analysis was performed to examine differences.

Results: The study found that 56.5% of patients had cholesterol <160 mg/dl (Group A) and 43.5% had >160 mg/dl (Group B). Significant differences in cholesterol and SOFA scores between groups were observed on days 0 and 3 ($p < 0.001$). Mortality was higher in Group B, indicating that hypocholesterolaemia is associated with increased mortality risk.

Conclusion: This study suggests that monitoring cholesterol levels can serve as a prognostic tool in sepsis. An increasing cholesterol trend may indicate a better disease outcome.

Keywords: Total cholesterol; Sofa score; Hypocholesteremia; Sepsis; Prognosis; Mortality

1. Introduction

Cholesterol is integral to several key physiologic processes including physical properties of the cell membrane, maintenance of cell membrane integrity, signaling pathways, immunity, and as a precursor for the synthesis of hormones, Vitamin D, and bile acids [1].

Hypolipidemia is a decrease in plasma lipoprotein caused by primary (genetic) or secondary (acquired) factors. It is usually asymptomatic and diagnosed incidentally on routine lipid screening. The first report of hypocholesterolemia in the medical literature was in 1911 by Chauffard and coworkers, in patients with active tuberculosis. Since then (about 95 years), only few dozens of studies were published in this regard. The terms Hypolipidemia, hypocholesterolemia and hypobetalipoproteinemia are used interchangeably in the literature, and refer to reduced plasma cholesterol[1, 2].

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Sepsis affects persons of all ages and is one of the leading causes of morbidity and mortality in patients admitted to an intensive care unit (ICU). Sepsis is a dysregulated host response to infection that leads to acute organ dysfunction and septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities lead to substantially increased mortality risk. According to a study on epidemiology of severe sepsis in India (2010), the incidence of severe sepsis in India was 16.45% of all admissions. Intensive therapy unit mortality of all admissions was 12.08% and that of severe sepsis was 59.26%. Hospital mortality and 28-day mortality of severe sepsis were 65.2% and 64.6%, respectively[3, 4].

Lipoproteins have been implicated to play a role in innate immunity. Authors have associated hypocholesterolemia with inflammatory states. Lipopolysaccharide (LPS), the major component of the outer membrane of Gram-negative bacteria, plays a key role in the initiation of inflammatory response in sepsis. Lipoprotein plays an important role in LPS binding and neutralization, enzyme incorporation, inhibition of the expression of endothelial cell adhesion and stimulation of the expression of endothelial nitric oxide synthase in vitro. Cholesterol and lipoprotein levels change rapidly over time in patients with proinflammatory conditions, especially in critically ill intensive care unit (ICU) patients with severe infection or sepsis[5, 6].

Most authors use the total serum Total cholesterol (TC) to define this condition. Yet, there is no consensus about the level below which a clinically significant hypocholesterolemia will ensue, and each author used a different cut-off value. Most of the authors use a cut-off value between 120 mg/dl (3.1 mmol/l) and 150m/dl (3.88mmol/l). However, some authors use higher levels up to 190mg/dl (4.9mmol/l) while others use lower values such as 100mg/dl (2.59mmol/l)[7].

Epidemiologic studies have identified a relationship between hypocholesterolemia (<130mg/dL)and increased mortality from all causes and authors in present study have considered total cholesterol less than 160 mg/dL as hypocholesterolemia based on American Heart Association, Hypocholesterolemia occurring with the development of infection was demonstrated during the 15-year period of the Kaiser Permanente study, conducted in 15000 healthy men and women[8,15].

Other authors have associated hypocholesterolemia with inflammatory states. A 30% or greater reduction in lipid and lipoprotein concentrations is known to occur in a variety of inflammatory states. Interleukin-6 and tumor necrosis factor-α have been implicated as potent negative regulators of lipoprotein metabolism in vitro and in vivo. Fraunberger and coworkers demonstrated a relationship between hypocholesterolemia and several disease states, as well as organ dysfunction[9,14].

The association between sepsis and cholesterol leads to the life-threatening organ dysfunction caused by a dysregulated host response to infection. Little mechanistic work has been performed to date to understand the pathophysiological mechanisms underlying hypocholesterolemia, nor clinical implications beyond the association with poor outcomes. Nonetheless, the therapeutic possibilities of lipoprotein administration or modifying the cholesterol pathway in sepsis are generating increasing interest. A recent review article noted that high-density lipoproteins (HDLs) display antioxidant, antiapoptotic, antithrombotic, anti-inflammatory, and anti-infectious properties. Improved organ function and survival were noted in animal models of sepsis infused with reconstituted HDL or an apolipoprotein A1 mimetic (apolipoprotein A1 being the major lipoprotein in HDL). A small pilot study of a cholesterol-sphingomyelin liposome given to patients with pneumococcal pneumonia showed good safety and tolerability and an encouraging reduction in organ dysfunction. A clinical trial with an anti-inflammatory intravenous fish oil emulsion is ongoing[10, 11].

Many subsequent studies have demonstrated an association between the magnitude of decrease in serum cholesterol in sepsis and mortality, in particular the component of cholesterol bound to high-density lipoprotein (HDL-C). The association between outcome and serum levels of cholesterol bound to low-density lipoprotein (LDL-C) or triglyceride (TG) appears less consistent. Many studies have used the cholesterol as a prognostic marker during the severe infection[12,13].

Even though many studies have been done on hypolipidemia and sepsis still the lacunae persists and the complete mechanism is not clear. Hence keeping this in mind the present study has been undertaken to find the association between the hypolipidemia and the sepsis and to find the prognostic value of hypolipidemia[16,17].

Aims and objective

- Aim

To examine the difference and dynamic changes in serum cholesterol levels in patients with sepsis and evaluate whether these Cholesterol levels are associated with prognosis using SOFA score

- Objective

To assess how serum cholesterol levels vary and evolve in sepsis patients and investigate whether these levels are related to prognosis according to the SOFA score.

2. Materials and methods

- STUDY DESIGN: Prospective study

2.1. Source of data

All patients admitted to Medicine Department, AL-AMEEN MEDICAL COLLEGE AND HOSPITAL VIJAYAPUR from SEPTMBER 2022 TO march 2024, with SEPSIS were taken for the study considering the inclusion and exclusion criteria.

2.2. The inclusion criteria

- Age ≥ 18 years
- patients admitted to the ICU/MICU/SICU with sepsis between September 2022 and MARCH 2024

2.3. Exclusion criteria

- age less than 18 years
- pregnancy
- ICU readmission
- need for primary cardiac care.
- Patients with liver disease (hepatitis B, hepatitis C, immune hepatitis, liver cirrhosis, and hepatocellular carcinoma),
- Dyslipidemia

2.4. Method of collection of data

For each patient, data on age, gender, comorbidity, length of ICU/MICU/SICU stay, and mortality were collected. In addition, Sequential Organ Failure Assessment (SOFA) scores and laboratory data, including cholesterol, TG, HDL, LDL were collected on day 0 (ICU admission) and day 3.

2.5. Method of test

2.5.1. Estimation of lipid profile

A total of 115 patients with sepsis admitted to Al Ameen Medical College and Hospital, Bijapur, were included in this study. Patients have their history taken according to a proforma and subjected to clinical examination and investigations like complete blood count, plasma glucose, blood urea, serum creatine, LFT, lipid profile, PT/INR, ECG, Chest X ray, USG abdomen

2.6. Sample size

The anticipated Mean±SD of Total cholesterol (mg/dL) at 0th day and at 3rd day 110±0.11 and 113±12 respectively. (11) The required minimum sample size is 115 to achieve a power of 80% and a level of significance of 5% (two sided) and effect size 0.260, for detecting a true difference in means between 0th day and 3rd day. Sample size was calculated using G*Power software. (t tests - Means: Difference between two dependent means (matched pairs)

2.7. Statistical analysis

The data obtained was entered in a Microsoft Excel sheet, and statistical analysis was Performed using statistical package for the social sciences (Version 20).

Descriptive analysis was performed using Mean ±SD, Median and Inter quartile range, frequency, percentages and diagrams.

For normally distributed continuous variables between paired data was compared using Paired t test for normally distributed variables and for not normally distributed variables Wilcoxon signed rank paired test was used.

For normally distributed continuous variables between survival and non-survival patients was compared using independent t test for not normally distributed variables Mann Whitney U test was used to evaluate the association with prognosis.

To elucidate the associations and comparisons between different parameters, Chi square test was applied.

P less than 0.05 was considered statistically significant. All statistical tests were performed two tailed.

3. Results

Table 1 Distribution of group

GROUP	Frequency	Percent
Total cholesterol <160 mg/dl (GROUP A)	65	56.5
Total cholesterol >160 mg/dl (GROUP B)	50	43.5
Total	115	100.0

INFERENCE: Among total, total cholesterol <160 mg/dl (group A) was 65(56.5%) and total cholesterol >160 mg/dl (group B) was 50(43.5%).

Table 2 Comparison of lipid parameters at day 0 with group a (total cholesterol <160 mg/dl) and group b (total cholesterol >160 mg/dl)

LIPID PARAMETERS	GROUP	Mean	Std. Deviation	Mean diff	pvalue
Total Cholesterol (mg/dl)	GROUP A GROUP B	132.25 191.00	14.472 16.617	-58.754	<0.001***
Triglyceride (mg/dl)	GROUP A GROUP B	139.82 151.92	13.326 4.140	-12.105	<0.001***
LDL (mg/dl)	GROUP A GROUP B	82.95 107.32	11.943 23.150	-24.366	<0.001***
HDL (mg/dl)	GROUP A GROUP B	38.08 43.96	5.348 6.266	-5.883	<0.001***

Test used- independent t test, p<0.001*** very highly significant, p>0.05 insignificant

INFERENCE: Among the study patients, there was a statistically significant difference in relation to total cholesterol distribution between group A (mean=132.25, SD=14.472) and group B (mean=191.00, SD=16.617) with a p value of <0.001 as per unpaired t test.

Table 3 Comparison of lipid parameters at day 3 with group a (total cholesterol <160 mg/dl) and group (total cholesterol >160 mg/dl)

LIPID PARAMETERS	GROUP	Mean	Std. Deviation	Mean diff	pvalue
Total Cholesterol (mg/dl) Day 3	GROUP A GROUP B	128.60 186.52	14.329 16.059	-57.920	<0.001***
Triglyceride (mg/dl) Day 3	GROUP A GROUP B	135.49 148.46	13.096 4.586	-12.968	<0.001***
LDL (mg/dl) Day 3	GROUP A GROUP B	80.31 104.76	12.353 22.388	-24.452	<0.001***
HDL (mg/dl) Day 3	GROUP A GROUP B	35.46 41.52	4.902 6.348	-6.058	<0.001***

Test used- independent t test, p<0.001*** very highly significant, p>0.05 insignificant.

INFERENCE: Among the study patients, there was a statistically significant difference in relation to total cholesterol distribution between group A (mean=128.60, SD=14.329) and group B (mean=186.52, SD=16.059) with a p value of <0.001 as per unpaired t test. The total cholesterol at day 3 was less in group A in comparison to group B.

Table 4 Comparison of sofa score with group a (total cholesterol <160 mg/dl) and group b (total cholesterol >160 mg/dl)

SOFA SCORE	GROUP	Mean	Std. Deviation	Mean diff	pvalue
SOFA	GROUP A GROUP B	1.95 0.68	1.643 0.741	1.274	<0.001***
SOFA At Day 3	GROUP A GROUP B	2.05 0.06	1.856 0.240	1.99	<0.001***

Test used- independent t test, p<0.001*** very highly significant, p>0.05 insignificant

INFERENCE

SOFA: Among the study patients, there was a statistically significant difference in relation to SOFA distribution between group A (mean=1.95, SD=1.643) and group B (mean=6.8, SD=.471) with p value of <0.001 as per unpaired t test. The SOFA was less in group B in comparison to group A.

SOFA AT DAY 3: Among the study patients, there was a statistically highly significant difference in relation to SOFA at day 3 distribution between group A (mean=2.05, SD=1.856) and group B (mean=.06, SD=.240) with p value of <0.001 as per unpaired t test. The SOFA at day 3 was less in group B in comparison to group A.

Table 5 Distribution of patient survival in group a (total cholesterol <160 mg/dl) and group b(total cholesterol >160 mg/dl)

Patient survived	GROUP		Total	Chi value	pvalue
	GROUP A	GROUP B			
Yes	28 24.3%	3 2.6%	31 27.0%	19.973	<0.001***
No	37 32.2%	47 40.9%	84 73.0%		
TOTAL	65 56.5%	50 43.5%	115 100.0%		

Test used- chi square, p<0.001*** significant

INFERENCE: Among total 65(56.5%) from group A, maximum 37(32.2%) patient were not survived. Among total 50(43.5%) from group B, maximum 47(40.9%) patients were not survived. Results were found to be highly significant on comparing group A and group B with patient survived.

4. Discussion

Septicemia is a state of microbial invasion from a portal of entry into the blood stream which causes sign of illness. In response to an infection, body's immune system reacts and protects but sometimes it goes into overdrive, attacking the body itself. This overactive toxic response of the body causes the clinical syndrome of sepsis rather than the direct effects of micro-organisms.

In recent studies, it is shown that cholesterol metabolism is highly influenced by a state of widespread inflammation which is usually secondary to bacteremia. Cholesterol levels are adversely affected by infection or organ dysfunction, but the physiologic significance for these decreased concentrations is not known. The terms Hypolipidemia, hypocholesterolemia and hypobetalipoproteinemia are used interchangeably in the literature, and refer to reduced plasma cholesterol. Most authors use the total serum cholesterol (TC) to define this condition.

Thus, based on this the present prospective study has been conducted in the Medicine Department, AL-AMEEN MEDICAL COLLEGE AND HOSPITAL VIJAYAPUR from SEPTMBER 2022 TO march 2024. The study included all the patients above 18 yrs with some exclusion criteria with the sample size of 115.

For each patient, Sequential Organ Failure Assessment (SOFA) scores and total cholesterol was collected on day 0 (ICU admission) and day 3 and the observations were made and statistical analysis was done.

In the present study we have divided the 115 patients into two groups based on cholesterol levels. We made total cholesterol levels less than 160 (Total cholesterol <160 mg/dl) as GROUP A and total cholesterol levels more than 160 (Total cholesterol >160 mg/dl) as GROUP B.

Most of the authors use a cut-off value between 120mg/dl (3.1 mmol/l) and 150m/dl (3.88mmol/l).2,5 However, some authors use higher levels up to 190mg/dl (4.9mmol/l) while others use lower values such as 100mg/dl (2.59mmol/l).4-8 Epidemiologic studies have identified a relationship between hypocholesterolemia (<130mg/dL)and increased mortality from all causes and we in present study have considered total cholesterol less than 160 mg/dL as hypocholesterolemia based on American Heart Association. Thus, we have taken cut off value as 160mg/dl in our study.

In the present study (table 1) shows the distribution of group. Among total, total cholesterol <160 mg/dl (group A) was 65(56.5%) and total cholesterol >160 mg/dl (group B) was 50(43.5%). This shows group A cases were more compared to group B.

4.1. Total cholesterol and disease outcome:

In this study total cholesterol at day 0, we found that among the study patients, there was a statistically significant difference in relation to total cholesterol distribution between group A (mean=132.25, SD=14.472) and group B (mean=191.00, SD=16.617) with a p value of <0.001 as per unpaired t test. It was clear that total cholesterol was less in group A in comparison to group B.

In this study total cholesterol at day 3, shows among the study patients, there was a statistically significant difference in relation to total cholesterol distribution between group A (mean=128.60, SD=14.329) and group B (mean=186.52, SD=16.059) with a p value of <0.001 as per unpaired t test. It was clear that total cholesterol at day 3 was less in group A in comparison to group B.

There is significant reduction in total cholesterol from day 0 to day 3.

These findings are in consistency with the findings of study conducted by Concepclon Alvarez and Alvarez Ramos (1986),[17] in their study sepsis was found to cause concentrations of total cholesterol, high-density lipoprotein cholesterol, and apoproteins A and B in serum to decrease, whereas triglycerides increase.6 Similarly C. Iribarren and his associates (1998)[18] found inverse relationship between sepsis and cholesterol level which is in consistent with the instant study.7 Giovannini I and his associates (1999)[19] assessed and correlates hypocholesterolemia in moderate to critical surgical illness and observed cholesterol level decreased after surgery, in sepsis, liver failure. They found that

dynamics of the development, clinical relevance, and a fall in level of serum cholesterol was also negatively correlated to clinical outcome and length of stay, which carries additional mortality risk.

As discussed by Das S et al[16] patients showing decreasing trend of total cholesterol levels is a poor prognostic indicator of disease outcome, whereas my study does not confirm the above results. This is because in Das S et al study ICU patients suffering from sepsis disease alone was taken for study, but in my study ICU patients suffering from various disease were included hence the disease outcome varies independent of total cholesterol value.

In this study it has been observed that patients with sepsis in ICU develop extremely low cholesterol levels. Lipoproteins have been known to play an innate immunity and variation in its level have been observed in a variety of inflammatory disorders, but not much is known about lipoprotein metabolism in patients with sepsis. Some authors believe that hypocholesterolemia is a more sensitive marker for the onset of infection than leukocytosis Moreover, hypocholesterolemia was also significantly correlated with the intensity of the acute phase responses during sepsis. A study by Chiarlo et al has shown that hypocholesterolemia gets aggravated by the simultaneous development of hypertriglyceridemia.

4.2. SOFA SCORE WITH GROUP A (Total cholesterol <160 mg/dl) AND GROUP B (Total cholesterol >160 mg/dl)

In this study, we observed that SOFA score at day 0 was among the study patients, there was a statistically significant between group A (mean=1.95, SD=1.643) and group B (mean=6.8, SD=.471) with p value of <0.001 as per unpaired t test. It was clear that SOFA was less in group B in comparison to group A

Among the study patients, there was a statistically highly significant difference in relation to SOFA at day 3 distribution between group A (mean=2.05, SD=1.856) and group B (mean=.06, SD=.240) with p value of <0.001 as per unpaired t test. It was clear that SOFA at day 3 was less in group B in comparison to group A.

A significant increase in day 0 SOFA score is associated with hypocholesterolemia among patients admitted in ICU with sepsis, elevated day 1 SOFA score levels were more common when patients admitted in ICU with sepsis present with hypocholesterolemia

A significant increase in day 3 SOFA score is associated with hypocholesterolemia among patients admitted in ICU with sepsis, elevated day3 SOFA score levels more common when patients admitted in ICU with sepsis present with hypocholesterolemia SOFA Score Day 0 and 3 ≥ 2 and hypocholesterolemia are significant and strong independent risk factors for predicting death in patients admitted in ICU with sepsis.

4.3. Distribution of patient survival in group A (Total cholesterol <160 mg/dl) and group B (Total cholesterol >160 mg/dl)

In the present study we observed that among total 65(56.5%) from group A, maximum 37(32.2%) patient were not survived. Among total 50(43.5%) from group B, maximum 47(40.9%) patients were not survived. There is a significant death with the increase in the SOFA score. This indicates that hypocholesteremia increases the risk of mortality.

As a matter of fact, the contribution of hypocholesterolemia to mortality might be modest compared to increase in severity of illness but nevertheless these simple measurements represent a potential therapeutic target in sepsis. The mechanism that modifies cholesterol level in sepsis is not yet well understood and further studies in populations with sequential cholesterol monitoring for a longer period will lead to more timely interventions and enhance patient outcomes.

5. Conclusion

It is clear from present study that monitoring the total cholesterol level can be used as prognostic tool in ICU patients. The increasing trend in total cholesterol level indicates better prognosis of disease outcome. Similarly, the increasing trend in HDL and LDL levels also can be used as prognostic tool to determine the survival rate of patient. However, from the observations of the present study we would like to suggest that, new therapies directed at increasing serum cholesterol level may have significant options in better management of sepsis.

Compliance with ethical standards

Acknowledgement

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

The study was approved by the Institutional Ethical Committee.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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