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## Study of serum cholesterol levels as a prognostic marker in patients with sepsis

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### Abstract

**Introduction:** Sepsis affects persons of all ages and is one of the leading cause of morbidity and mortality in patients admitted to an intensive care unit (ICU). Several studies suggests that serum cholesterol may be a useful prognostic marker of sepsis.

**Material and methods:** This was a prospective study conducted in the Department of Medicine, Muzaffarnagar Medical College, Muzaffarnagar, U.P. with 200 ICU patients diagnosed with sepsis by fulfilling all inclusion and exclusion criteria after informed consent and ethical clearance. Serum cholesterol levels were measured on the day 1 and the day 5 of presentation.

**Result:** In the present study, out of 200 subjects, 137 patients had a cholesterol level below 200mg/dl. During the study, 126 patients survived whereas 74 patients expired during the course of treatment. The mean serum cholesterol levels were lower in non-survivor group as compared to survivor group.

**Conclusion:** We can conclude from the results of the present study that monitoring the total cholesterol levels can be used as a prognostic tool in patients with sepsis for predicting the disease outcome.

**Keywords:** Serum Cholesterol, Sepsis

### Introduction

Sepsis affects persons of all ages and is one of the leading cause of morbidity and mortality in patients admitted to an intensive care unit (ICU) [1]. 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 [2]. 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]. Lipoproteins have been implicated to play a role in innate immunity. Authors have associated hypocholesterolemia with inflammatory states [4, 5]. 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 [6]. 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. Patients with severe sepsis have low levels of cholesterol, including high-density lipoprotein (HDL), low-density lipoprotein (LDL), and apolipoprotein A-I (Apo A-I) and high levels of triglycerides (TGs) and free fatty acids (FFAs) [7, 8].

Recent studies suggests that serum cholesterol may be a useful prognostic marker of sepsis given that cholesterol metabolism has been shown to be markedly influenced by a state of widespread inflammation secondary to bacteremia. These changes have been noted to occur early (within hours) in the inflammatory cascade associated with sepsis. Few studies, however, have evaluated the efficacy of serum cholesterol compared to the current gold standards, which have significant limitations in diagnosing sepsis early and accurately identify those at high risk for mortality. Sepsis related organ failure assessment (SOFA) score could be used to characterize patients at entry (and even serve within the entry criteria) or to evaluate the effects of treatment.

**Material and methods**

This was a prospective study conducted in the Department of Medicine, Muzaffarnagar Medical College, Muzaffarnagar, U.P. The present study was undertaken to evaluate serum cholesterol levels as a prognostic marker in patients of sepsis and to assess the relation of age, gender, serum total cholesterol and SOFA score with disease outcome in sepsis patients. ICU patients diagnosed with sepsis were taken in the study. A total of 200 cases were taken during the period of January 2018 to June 2019 and serum cholesterol level was measured on day 1 and day 5 in ICU patients.

**Inclusion criteria**

1. Patients with age greater than 18 years.
2. Patients satisfying the criteria for sepsis [9].
3. SOFA (sepsis-related organ failure assessment) score.

**Exclusion criteria**

Patients with chronic liver disease, thyroid dysfunction, diabetes mellitus, severe anaemia, malignancy, CVA, burns, coronary artery disease, known chronic inflammatory condition like SLE, RA, malabsorption disorders, and patients on statins were excluded from the present study.

**Methodology**

After getting written informed consent from the patients or immediate relatives, a detailed clinical examination was done in all patients. After the diagnosis of sepsis was made in patients with the help of examination and laboratory investigations, blood sample were collected on day of admission and on fifth day to determine serum total cholesterol levels. The increase or decrease in cholesterol value was compared with outcome of the disease. Serum total cholesterol was determined using cholesterol oxidase-peroxidase method.

**Statistical analysis**

Statistical analysis was done using SPSS data 20.0 and Microsoft Office Excel 2010. Variables were compared using chi-square test and Student's t-test. A p-value of <0.05 was considered significant.

**Investigations**

CBC, ESR, Serum Cholesterol, LFT, KFT, Urine, Blood culture, Chest x-ray, USG whole abdomen, HBA1C, Blood Sugar.

**Result**

In the present study, 116 (58%) patients were male and 84 (42%) patients were female (Table-2). The mean SOFA score was 8.59. Mean serum cholesterol at day 1 was 161.85 and at day 5 was 169.23 (Table-1).

**Table 1:** The baseline characteristics of the study participants

Descriptive Statistics	Mean	Std. Deviation
Age (yrs)	55.81	16.40
Temp.(°F)	101.66	1.11
Heart Rate (b/m)	110.13	10.75
Respiratory Rate (br/m)	26.67	3.30
TLC	18404.80	5287.65
GCS	12.27	2.74
Bilirubin (mg/dL)	1.79	1.24
Creatinine(mg/dL)	2.21	1.05
Platelet Count	178620	109629.64
SOFA score	8.59	3.19
Total Cholesterol D1 (mg/dL)	161.85	37.58
Total Cholesterol D5 (mg/dL)	169.23	47.50

Out of 200 patients having sepsis, 137 (68.5%) patients were found with the cholesterol levels below 200 mg/dL whereas 63 (31.5%) patients were found with total cholesterol above 200 mg/dL. It was found that 126 (63%) patients having sepsis had survived the crisis whereas 74 (37%) patients died due to sepsis and its associated complications. In the present study, 79 (62.7%) patients survived with cholesterol level below 200 mg/dL and 58 (78.4%) patients died, whereas 47 (37.3%) patients survived and 16 (21.6%) expired with cholesterol levels above 200 mg/dL (Table 5).

The mean age of survivors was 52.13±16.43 years, whereas the mean age of non-survivors was 62.08±14.40 years which was statistical significant (p<0.001) (Table-4). Mean serum cholesterol at day 1 in survivors was 172.61±33.38mg/dl whereas at day 5 it was 195.51±26.03mg/dl and mean serum cholesterol at day 1 in non-survivors was 143.51±37.42 whereas at day 5 it was 124.49±42.07 and the difference was statistically significant (Table-6).

**Table 2:** Distribution of patients according to gender versus disease outcome

Gender	Results		Total
	Survivors	Non-survivors	
Male	71 (56.3%)	45 (60.8%)	116 (58%)
Female	55 (43.7%)	29 (39.2%)	84 (42%)
Total	126 (100%)	74 (100%)	200 (100%)

Chi Square= 0.381, P value=0.537091(Not Significant)

**Table 3:** Distribution of patients according to age group versus disease outcome

Age	Outcome		Total
	Survivors	Non-survivors	
18-33 years	20 (15.9%)	2 (2.7%)	22 (11%)
34-49 years	27 (21.4%)	12 (16.2%)	39 (19.5%)
50-65 years	51 (40.5%)	26 (35.1%)	77 (38.5%)
>65 years	28 (22.2%)	34 (46%)	62 (31%)
TOTAL	126 (100%)	74 (100%)	200 (100%)

Chi Square= 16.8104. P value=0.000773(Significant)

**Table 4:** Comparison of age and SOFA score among survivors and non-survivors

Parameters	Survivors (n=126)* Mean±SD	Non-survivors (n=74)* Mean±SD	p-value
Age	52.13±16.43	62.08±14.40	P<0.0001
SOFA Score Day 1	6.62±2.00	11.95±1.68	P<0.0001

**Table 5:** Total cholesterol value versus outcome

Total Cholesterol Value Day 1	Results		Total
	Survivors	Non-survivors	
<200 mg/dl	79 (62.7%)	58 (78.4%)	137 (68.5%)
>200 mg/dl	47 (37.3%)	16 (21.6%)	63 (31.5%)
Total	126 (100%)	74 (100%)	200 (100%)

Chi Square= 5.312. P value= 0.021179 (Significant at p < 0.05)

**Table 6:** Mean total cholesterol values at admission and day 5 among survivors and non survivors

Total cholesterol	Survivors (n=126)* Mean+ SD	p-value	Non-survivors (n=74)* Mean+ SD	p-value
Day 1	172.61±33.38	P<0.0001	143.51±37.42	P=0.0042
Day 5	195.51±26.03		124.49±42.07	

## Discussion

In our study it has been observed that non-survivors had low cholesterol levels on day 5 after admission (Table-6). There are many reasons suggested for the hypocholesterolemia seen in critically ill patients, but the one that seems to be pertinent when patients with sepsis are concerned is related to the ability of lipids and lipoproteins to bind to and neutralize bacterial endotoxin (LPS) from gram negative microorganisms as well as lipoteichoic acid from gram positive microorganisms.

### Age distribution and disease outcome

Most of the non survivors are found to be elderly with age >65 years. The mean age of survivors was  $52.13 \pm 16.43$  years, whereas the mean age of non-survivors was  $62.08 \pm 14.40$  years which was statistically significant (p value was <0.001) (Table-3, 4). Findings in our study was similar to the study by Gaddam BK et al, in which age distribution among the survivors and non survivors showed statistical significance in age group 30-59. Most of the non survivors are found to be elderly with age >60 years with 67.6% and survivors are more among the young age group in between 18-29 years with 43.9%<sup>[1]</sup>. This indicates that patients with higher age group had a worse disease outcome in terms of sepsis and sepsis associated complications.

### Gender distribution and disease outcome

In our study, 116 (58%) patients were male with 84 (42%) female patients. The survival rate among males was 56.3% whereas among females it was 43.7% and the mortality rate was 60.8% and 39.2% in males and females respectively but was statistically insignificant (Table-2). In the study by Gaddam BK et al, sex distribution shows most of the males (22:64.7%) have higher mortality rate compared to that of females (12:35%)<sup>[1]</sup>. In a similar study conducted by Monigari N et al, also showed higher mortality rate in male population (70.9%)<sup>[10]</sup>.

### SOFA score and disease outcome

In our study, the mean SOFA score in survivors was  $6.62 \pm 2.00$  whereas mean SOFA score in non-survivors was  $11.95 \pm 1.68$  which was statistical significant (p value was <0.0001) (Table-4). This finding was comparable to the study conducted by Gaddam BK et al, in which among non survivors SOFA score was found to be high both at day of admission and day 5 (median: 8.5 and 15 respectively) when compared to the survived patients (median 2 and 1 respectively). Both the values are found to be statistically significant<sup>[1]</sup>.

### Total Cholesterol versus disease outcome

In this study, out of 200 subjects, 137 (68.5%) patients had their total cholesterol levels below 200 mg/dL whereas 63 (31.5%) patients were found with total cholesterol above 200 mg/dL. During the study, 126 subjects survived whereas 74 subjects expired during the course of treatment. Total 79 (62.7%) patients survived with cholesterol level below 200 mg/dL and 58(78.4%) patients died. Whereas maximum 47(37.3%) patients survived and 16 (21.6%) expired with cholesterol levels above 200 mg/dl (p value= 0.021) (Table-5).

Several studies have demonstrated that hypocholesterolemia in patients with sepsis is a predictor of increased mortality.

Our results are comparable with the results obtained by a number of authors.

Memis D *et al.* demonstrated that cholesterol levels were significantly lower among the nonsurviving patients (day 1,  $92.2 \pm 25.1$  mg/dL; day 2,  $92.1 \pm 21.7$  mg/dL; death/discharge day,  $92.2 \pm 21.7$  mg/dL) than surviving patients (day 1,  $175.1 \pm 38.6$  mg/dL [p < 0.001]; day 2,  $173.0 \pm 39.3$  mg/dL [p < 0.001]; death/discharge day,  $171.8 \pm 39.6$  mg/dL [p = 0.010])<sup>[11]</sup>. Das S *et al.* (2011) observed that mean total cholesterol, HDL-C and LDL-C levels in the non surviving group were significantly less than the surviving group (p=0.000, p=0.008, p=0.04)<sup>[12]</sup>. Similary Biller K et al demonstrated that total cholesterol levels were significantly lower in nonsurviving patients in comparison with surviving patients (p = 0.006)<sup>[13]</sup>.

B Abraham et al concluded that the mean admission cholesterol was  $212.5 \pm 56$  mg/dl, while the mean cholesterol level on day 5 was  $112.3 \pm 34.5$  mg/dl in the sepsis group and  $179.4 \pm 47.6$  mg/dl in the control group<sup>[14]</sup>. A study by Windler E et al, reported a higher mortality with lower cholesterol levels. The mean serum cholesterol levels of patients who died was significantly lower than that of those who survived (163.6mg/dL versus 217.8 mg/dL; p < 0.0001)<sup>[15]</sup>.

In our study, significant difference in cholesterol level was observed between the survivor and non-survivor groups (Table-5, 6). Similar results were obtained by above authors. However in a study conducted by Jeyasuriya A et al the mean cholesterol value among 33 survivors on day 1 was  $120.76(\pm 18.54)$  and day 3 was  $145.30(\pm 55.65)$ , it was statistically significant which is comparable to the present study. Whereas the mean cholesterol value among 22 non-survivors on day 1 was  $131.64(\pm 15.24)$  and day 3 was  $122.09(\pm 26.23)$ , which was statistically not significant. This finding was inconsistent with the present study. This was because in this study ICU patients suffering from various diseases were included hence the disease outcome varied independent of total cholesterol value<sup>[16]</sup>.

Sunayana P et al observed that 81.4% of patients had total cholesterol < 200 mg/dL and 18.6% had total cholesterol > 200 mg/dL. We observed the similar result in present study, 137 (68.5%) patients with total cholesterol levels below 200 mg/dL whereas 63 (31.5%) patients with total cholesterol above 200 mg/dL. In the study by Sunayana P et al, with the total cholesterol of more than 200 mg/dL, 15.4% patients expired compared to 29.8% of patients with total cholesterol below 200 mg/dL. But this difference was not statistically significant (p-value 0.2). The mortality rate in our study was 78.4% and 21.6% in patients with total cholesterol levels below and above 200 mg/dL respectively (p= 0.02) which was inconsistent with the study done by Sunayana P *et al.*<sup>[17]</sup>.

The mechanism that modifies cholesterol level in sepsis is not yet well understood and further studies in larger populations with sequential cholesterol monitoring for a longer period will lead to more timely interventions and enhance patient outcomes.

## Conclusion

Emerging evidence suggests that serum total cholesterol may be a useful and superior prognostic marker of mortality for patients admitted with sepsis secondary to infection compared to its other biochemical indicators. Serum cholesterol monitoring on hospital admission could provide

a very novel, inexpensive tool that has the potential to start early and aggressive therapy in patients most at risk of death, thus decreasing the mortality rate secondary to sepsis. Present study demonstrated reduced total cholesterol levels in patients with sepsis and there was a significant association between low total cholesterol and high mortality. The increasing trend in total cholesterol levels favoured better prognosis and disease outcome and decreasing trend implied worsening of the clinical condition. In inference, it is clear from the results of the present study that monitoring the total cholesterol levels can be used as a prognostic tool in patients with sepsis for predicting the disease outcome.

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