

## IMPACT OF HDL ON SEPSIS AND ITS ROLE AS A PROGNOSTIC MARKER IN SEPSIS

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### Abstract

**Background:** Sepsis is the second leading cause of mortality in the ICU. Recently HDL cholesterol was found to have a significant association between mortality and its levels. Hence, this study assessed the association between sepsis and HDL levels. **Materials and Methods:** This cross-sectional study was conducted from April 2020- April 2021 on 100 patients aged 18 years of age diagnosed with sepsis. One hundred patients who fulfil inclusion/exclusion criteria will be studied. Blood samples from each patient will be taken for HDL, creatinine, bilirubin levels, platelet count, peripheral smear, appropriate culture, and sensitivity; the source of infection is identified at the time of admission and day five after admission. The severity of sepsis was assessed using SOFA/qSOFA scores. **Result:** In the present study, 100 patients ageing 18 years or more having sepsis were enrolled for the study. Most patients were female (52%), in the age group of 51 to 60 years (42%). Maximum patients (32%) were reported with a platelet count of 50-90 lack. Of all patients, 37% required ventilation and 34% mortality was reported in our study. SOFA and qSOFA were found significantly correlate with HDL levels from admission to day 5. Mortality was correlated with HDL, with the 31 mg/dl cut-off. The sensitivity and specificity of HDL to diagnose mortality was 95.50% and 94.10%, respectively, at day 5. **Conclusion:** There was a strong link between sepsis and serum HDL levels in the patients. Patients with severe sepsis and significant organ failure had low HDL levels.

## INTRODUCTION

Public health is seriously affected by sepsis.<sup>[1]</sup> All ages are affected by sepsis, which may be the tenth most common cause of death in the United States. It is the leading cause of morbidity and mortality for patients referred to intensive care units (ICUs). By 2020, it is anticipated that there will be at least 1,110,000 cases of sepsis yearly, a rise of 1.5% from the current level.<sup>[2]</sup> In India, 16.45% of the 5478 hospitalisations were for severe sepsis. The population's median age was 58.17 years, and 57.71% of men made up that demographic.<sup>[3]</sup> A dysregulated host response to infection results in sepsis, characterised by life-threatening organ failure.<sup>[4]</sup> The Sequential Organ Failure Assessment (SOFA) score, which measures organ failure, must have increased by two or more points in a short period to meet the clinical criteria for sepsis. Sepsis still has a significant death rate despite advancements in aggressive care, which rises with sepsis severity from

20.8% in patients with sepsis to as high as 48.8% in those with septic shock.

Empiric antibiotic treatment, intensive volume replacement, and strict insulin control are some effective therapeutic approaches to address sepsis. The requirement for an "early prognostic marker" to identify people at the highest risk for death to maximize therapy choices is crucial to minimize the ICU mortality attributable to sepsis since severe sepsis has a poor prognosis for recovery.

Recent data indicate that since extensive inflammation brought on by bacteremia has been demonstrated to impact cholesterol metabolism significantly, high-density lipoprotein cholesterol (HDL-C) may be a helpful predictive marker of sepsis.<sup>[5]</sup> Additional research has shown that, regardless of comorbidities, individuals with severe sepsis who are identified in the intensive care unit had a measurable drop in circulating levels of lipoproteins and an increase in triglycerides.<sup>[6]</sup> These alterations have been shown to happen quickly (within hours)

during the sepsis-related inflammatory cascade. Clinical outcome was also inversely linked with a decrease in serum cholesterol.<sup>[7]</sup>

A low HDL-C cholesterol level is strongly linked to increased mortality and poor clinical outcomes on the first day of severe sepsis. This study aimed to examine the relationship between HDL-C and clinical outcomes in sepsis patients. Because it is readily available, affordable, and has a wide range of normal HDL-C values (40-60 mg/dl) compared to other biomarkers, HDL-C value can be utilized as a biomarker of septicemia. The HDL-C level might fall from 40 mg/dl to as low as 15 mg/dl in sepsis.

Hence the present study was carried out to study the impact of HDL on sepsis and its role as a prognostic marker in sepsis.

## MATERIALS AND METHODS

This cross-sectional study was conducted at the Department of General Medicine, Kanyakumari Government Medical College, Tamil Nadu, from April 2020- April 2021. A total of 100 patients aged eight years of age diagnosed with sepsis were enrolled on this study. The written consent and Institutional ethical committee approval were taken before the start of the study.

Inclusion criteria: Patients of both genders ageing 18 years or above. Patients meet the criteria for sepsis.

Sepsis-3 criteria: Suspicious/ known infection/ Increase of  $\geq 2$  SOFA were included in the study.

Exclusion criteria: Patient's refusal, patients with chronic liver disease, chronic infection, HIV, SLE,

and Rheumatoid arthritis. Patients with malabsorption disorders and on treatment with statins. Patients with a history of coronary artery disease and familial hyperlipidemia. Patients who refused to participate in the study were excluded.

One hundred patients who fulfil inclusion/exclusion criteria will be studied. Blood samples from each patient will be taken for HDL, creatinine, bilirubin levels, platelet count, peripheral smear, appropriate culture, and sensitivity; the source of infection is identified at the time of admission and day five after admission. Investigation results will be compared with normal reference values. The severity of sepsis will be assessed using SOFA/qSOFA scores.

Data are presented as percentages and the number of cases. Correlation between continuable variables was analyzed using the Pearson correlation test. ROC curves were used to predict the cut-off value. Significance was defined by P values less than 0.05 using a two-tailed test. Data analysis was performed using IBM-SPSS version 21.0.

## RESULTS

In the present study, 100 patients ageing 18 years or more having sepsis were enrolled for the study. Most patients were female (52%), in the age group of 51 to 60 years (42%). Maximum patients (32%) were reported with a platelet count of 50-99 lack. Of all patients, 37% required ventilation and 34% mortality was reported in our study [Table 1].

**Table 1: Observation of demographic parameters of patients**

Particulars		Observation N (%)
Gender	Male	48 (48%)
	Female	52 (52%)
Age Group	<40	15 (15%)
	41-50	24 (24%)
	51-60	42 (42%)
	>61	19 (19%)
Platelet count (Lakh)	>150	5 (5%)
	100-149	16 (16%)
	50-99	32 (32%)
	20-49	24 (24%)
Ventilation requirement	<20	23 (23%)
	No	63 (63%)
Mortality	Yes	37 (37%)
	No	34 (34%)
		66 (66%)

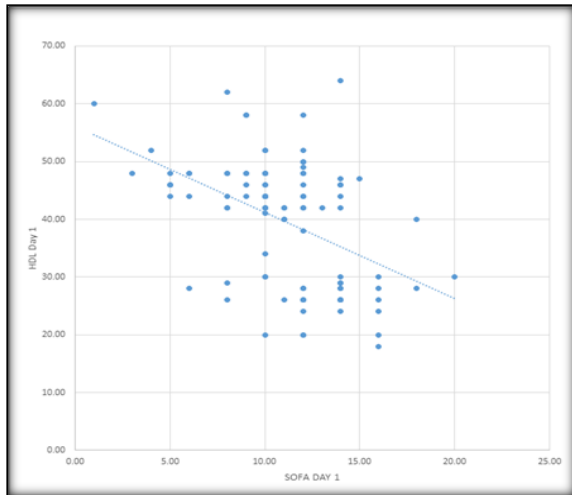
SOFA score was correlated along with HDL levels, and it was found that there was a statistically significant relationship among the patients with a Pearson correlation coefficient of -0.467 and p-value of <0.0001 on admission and Pearson correlation coefficient of -0.853 and p-value of <0.0001 on day 5 (Table 2, Fig 1, 2).

Similarly, the qSOFA score was also correlated with HDL levels. The Pearson correlation coefficient of -0.376 and p-value of <0.0001 at the time of admission and Pearson correlation coefficient of -0.778 and p-value of <0.0001 on day five were recorded, which was statistically significant [Figure 3, 4].

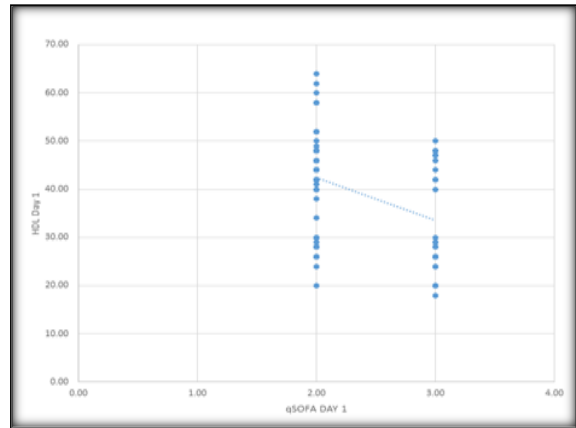
**Table 2: Correlation between SOFA and qSOFA score with HDL**

HDL Day 1	Pearson Correlation	SOFA	qSOFA
	P value	-0.467	-0.376
		<0.0001	<0.0001

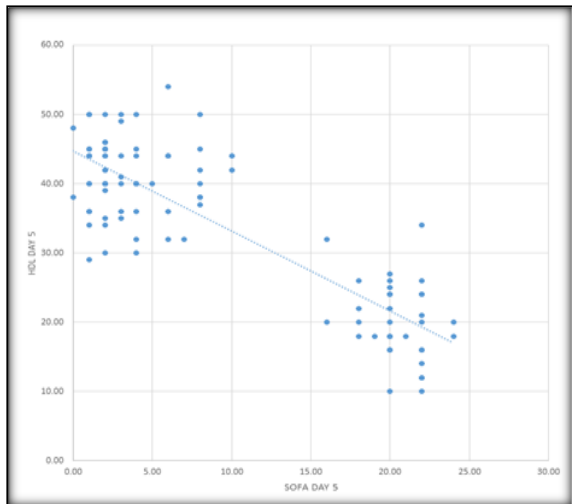
HDL DAY 5	Pearson Correlation	-0.853	-0.778
	P value	<0.0001	<0.0001



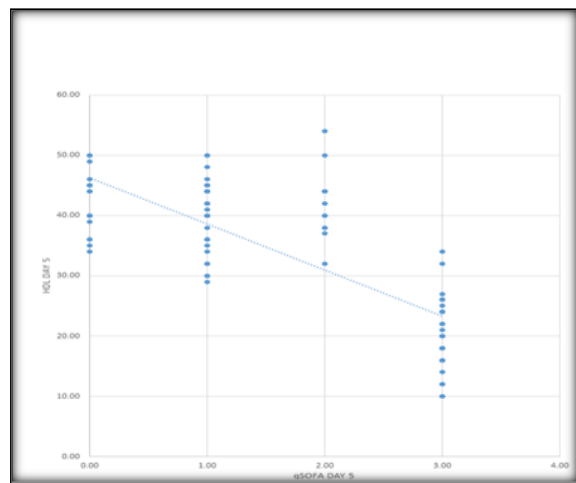
**Figure 1: Correlation between SOFA with HDL on Day 1**



**Figure 3: Correlation between qSOFA with HDL on Day 1**



**Figure 2: Correlation between SOFA with HDL on Day 5**

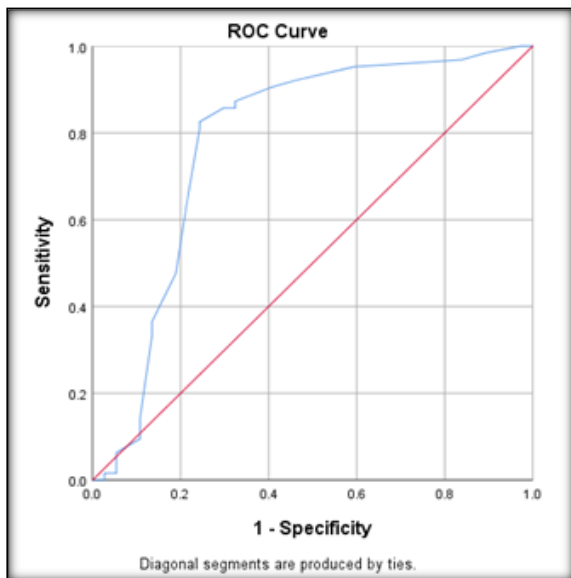


**Figure 4: Correlation between qSOFA with HDL on Day 5**

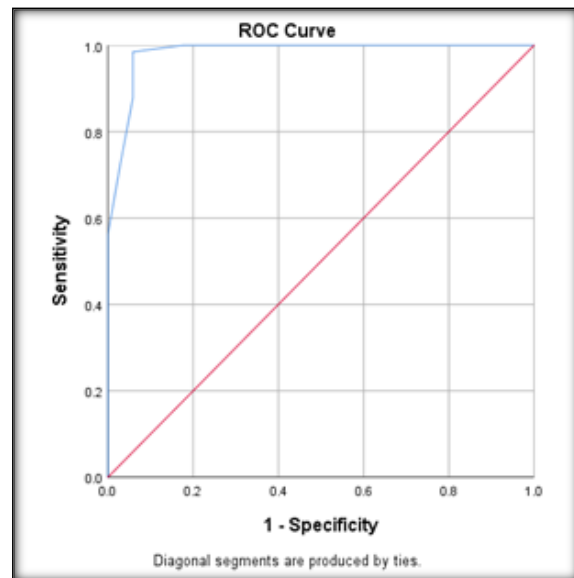
ROC analysis was carried out on day one and day 5 to find the cut-off value of HDL that indicates the ventilation requirement. ROC analysis was carried out on day one and day 5 to find the cut-off value of HDL that indicates the ventilation requirement. On day one, the area under the curve was 0.779, which was significant statistically ( $p < 0.05$ ).

For the 40.5 mg/dl cut-off, the HDL sensitivity and specificity to ventilation requirement were 82.50% and 75.70%. On day 5, the area under the curve was 0.76, which was statistically significant. For the cut-off at 26.5 mg/dl, HDL's sensitivity and specificity to ventilation requirement were 90.50% and 67.60%, respectively [Figure 5, 6].

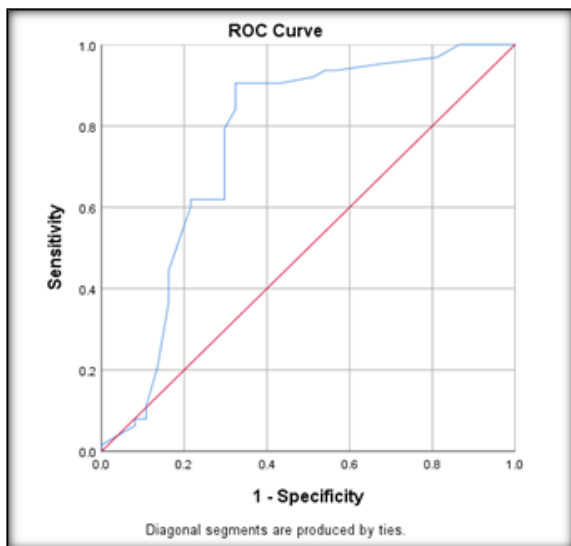
ROC analysis was carried out to determine the cut-off value of HDL that indicates the mortality of patients admitted. On day 1, the area under the curve was 0.983 and statistically significant ( $p < 0.0001$ ). For the cut-off at 32 mg/dl, HDL's sensitivity and specificity to diagnose mortality were 98.50% and 94.10%, respectively. On day 5, the area under the curve was 0.995, which was found to be statistically significant ( $p < 0.0001$ ). For the cut-off at 31 mg/dl, the sensitivity and specificity of HDL to diagnose mortality were 95.50% and 94.10%, respectively, at day 5 [Figure 7, 8].



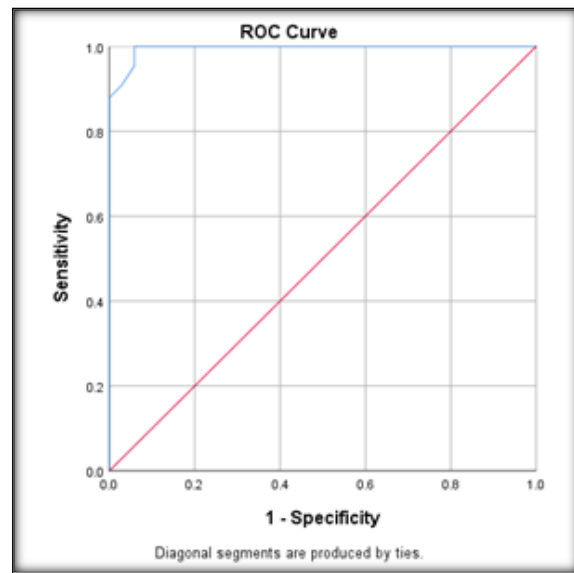
**Figure 5:** Area under the curve based on ROC analysis for ventilation and HDL value of study patients on Day 1



**Figure 7:** Area under the curve based on ROC analysis for mortality and HDL value of study patients on Day 1



**Figure 6:** Area under the curve based on ROC analysis for ventilation and HDL value of study patients on Day 5



**Figure 8:** Area under the curve based on ROC analysis for mortality and HDL value of study patients on Day 1

## DISCUSSION

Sepsis is a life-threatening infection that affects millions of individuals throughout the world. Organ malfunction, vascular leakage, and hypotension result from an imbalanced systemic inflammatory response to infection in the more severe types. This study aimed to determine the clinical effect of severe sepsis and the diagnostic characteristics of clinical and biochemical indicators in patients with suspected or confirmed acute illness.<sup>8</sup> There is a need to develop more sensitive biomarkers for the early detection of sepsis. This cross-sectional study was conducted in IMCU and Medicine wards of Kanyakumari Government Medical College, India, a rural tertiary care hospital. The present study compared age distribution, gender distribution,

mechanical ventilation requirement, HDL levels, SOFA score, and mortality.

In developing countries like India, sepsis remains the primary cause of mortality and morbidity. Early recognition and prompt treatment will prevent adverse outcomes. SOFA and APACHE II scores help in the prognostication of the disease. Serum HDL is a widely used general investigation available in most centres. The concept of decreasing HDL levels in sepsis was used in this study and has been evaluated.<sup>[9]</sup> Among the 100 patients in this study, male patients 48 and female 52, and the survival rate was 66%. In a similar study by Sunayana et al., among 70 patients, 42 were male, 28 were female, and the survival rate was 72.8%.<sup>[10]</sup> A study conducted by Naresh et al. had 111 patients, of which

67 (60.4%) were males and 44 (39.6%) were female, with a survival rate of 54%.<sup>[11]</sup>

In this study, 100 patients were taken into consideration with sepsis. Most of the patients are from the age group between 51-60 years (42%). This can be attributed to the additional risk factors for sepsis in the elderly compared to the young group with good immunity and health. In an observational study using hospital discharge data, Martin et al. determined that incident rates of sepsis in older adults aged 65 increased 20.4% faster than in those aged less than 65 years (mean increase 11.5% vs 9.5% per year,  $P < 0.001$ ).<sup>12</sup> In a similar study done by Naresh et al., most non-survivors aged between 41-60 years and survivors aged 18-40 yrs.<sup>[11]</sup>

The platelet count assessed haematological involvement. The platelet counts in different patients were between 50-99 in 32% of patients. Followed by between 20-49 in 24%, less than 20 in 23%, between 100-149 in 16% and more than 150 in 5% of patients. A similar study was carried out by Gaddam et al., where the median platelet counts dropped from the day of admission to day 5 in the non-survivor group. The platelet count in survivors was 1.69 lakhs/cm and 2.5 lakhs/cm on the day of admission and day 5, respectively and was found to be statistically significant ( $p < 0.05$ ).<sup>[13]</sup>

The SOFA score was used to assess the sepsis score in this study. SOFA score was correlated with HDL levels, and there was a statistically significant relationship among the patients on day one and day 5. The mean value of HDL during admission was 40.5 on day 1 and 26.5 on day 5. These findings were statistically significant, with a p-value of  $< 0.001$ . A study of serum HDL levels in severe sepsis patients by Naresh et al. showed a significant association of low HDL value on day 1 with mortality.<sup>11</sup> A study by Kumarasamy et al. showed plasma concentrations of HDL was low in severe sepsis patients and reflected the severity of the disease.<sup>[14]</sup>

Similarly, the qSOFA score was also correlated with HDL levels. At the time of admission and on day five, a p-value of  $< 0.0001$  was recorded, which is statistically significant. Lo RSL et al. conducted a literature review and retrospective data analysis of 380,920 patients, finding that the qSOFA score had a ROC of 0.68 for predicting in-hospital mortality, consistent with our surgical ICU findings IMCU patients.<sup>15</sup> Furthermore, a meta-analysis of 229,480 patients evaluated the qSOFA score and SIRS criteria for their capacity to predict patient death and found that the qSOFA score performed only marginally better, confirming our findings.<sup>[16]</sup> Ventilation requirements were correlated with HDL levels. ROC analysis was carried out on day one and day 5 to find the cut-off value of HDL that indicates the ventilation requirement. On day one, the area under the curve was 0.779, which was statistically significant. On day five, the area under the curve was 0.76, also found to be statistically significant.

The mean value on the day of admission was 32, and on day five was 31, with an accuracy of 97.00% and

95.00%. These findings were found to be statistically significant. In a similar study by Jeyasuriya et al., the mean HDL levels in the non-survival group at days 0 and 3 were 33 and 31 mg/dL with a non-significant p-value of 0.137. In the survival group, the mean values of HDL at days 0 and 3 were reported as 31 and 36 mg/dL, and the effect was statistically significant with a p-value of 0.033.<sup>[17]</sup>

The significance of the association between HDL levels and SOFA scores is demonstrated in this study. There was a strong link between sepsis and serum HDL levels in the patients. Patients with severe sepsis and significant organ failure had low HDL levels. Low HDL levels were related to higher SOFA scores. The levels of HDL and SOFA have a strong relationship. As a result, HDL cholesterol levels can be utilized to assess prognosis and therapy success in situations of sepsis. Raising HDL cholesterol levels indicates improvement in the clinical state, whereas dropping levels indicate deterioration and serve as a prognostic indicator

## CONCLUSION

There was a strong link between sepsis and serum HDL levels in the patients. Patients with severe sepsis and significant organ failure had low HDL levels. Therefore, serial monitoring of patients with SOFA, qSOFA, and HDL levels is necessary for better prognostication and clinical outcomes in patients with sepsis than a single measurement. In sepsis, HDL may be utilized as a prognostic marker, allowing doctors to keep track of patients and provide appropriate life-saving antibiotics or avoid multi-organ failure syndrome.

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