Analysis of Prognostic Significance of Serum HDL Level in Patients of Sepsis Admitted to a Tertiary Care Hospital of Southern Odisha

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ABSTRACT

BACKGROUND

Sepsis is the body's overwhelming and life-threatening response to infection that may cause tissue damage, organ failure and death. High density lipoproteins (HDL) are relevant players in both innate and adaptive immunity involved in response to infection. So, with this reference and limited number of studies showing association of prognosis with high-density lipoprotein level in sepsis patients, this study was done to find out the changes in HDL level of sepsis patients and its association with prognosis.

METHODS

This is a prospective hospital-based study done on 210 patients with sepsis admitted in medicine ward and intensive care unit (ICU) of M.K.C.G Medical College, Odisha from November 2017 to November 2019. Patient's included in study are based on initial assessment by quick SOFA (Qsofa) scoring system. At the time of admission, patient's clinical history, relevant biochemical parameters were noted and detail clinical examination was done. All the patients were followed prospectively during their entire course of stay. Serum HDL was done on the day of admission and was repeated on day 4 and on day of discharge. Outcome was measured in terms of survival and duration of hospital stay.

RESULTS

Out of 210 patients, 168 (80 %) survived and 42 (20 %) cases died. Survival rate was significantly higher in patients admitted to ward than those in ICU. HDL level on day 1 showed significant inverse correlation with SOFA score. Inverse correlation was also observed between the duration of stay in hospital and HDL on day 1. Significantly higher level of HDL was observed in patients who survived than non-survivors. In cases which survived, a statistically significant increase was observed in HDL level from day 1 to day of discharge.

CONCLUSIONS

HDL cholesterol on day of admission can be viewed as a significant predictor of mortality in patients of sepsis.

KEYWORDS

HDL, sepsis, prognosis, qSOFA, SOFA

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BACKGROUND

Sepsis is the body's overwhelming and life-threatening response to infection that can lead to tissue damage, organ failure, and death. In other words, it is body's overactive and toxic response to an infection.[1] It is a dysregulated inflammatory response to microbial agent with infections being the most common. Although there has been progress in understanding the problem pathogenesis and management of sepsis, it is associated with very high morbidity and mortality and places a huge economic burden on societies.[2]

31.5 million cases of sepsis and 19.4 million cases of severe sepsis occur globally each year, with potentially 5.3 million deaths annually occurring in high income country.[3] However, data on incidence and mortality of sepsis in low-income and middle-income countries is scarce due to the difficulty of generating population-level estimates in these regions.[4]

Pathogenesis of sepsis is related to deregulation of inflammatory response to microbial infection and involves interplay between host immune defense and the infecting agents. The dysregulation involves an imbalance between pro- inflammatory and anti-inflammatory response, the former being the result of infecting agents and the later being the host response to contain the infection and the imbalance can lead to excessive host tissue damage. Despite advances in understanding of the pathogenesis of sepsis, the exact cause of organ damage in sepsis is not known, however impairment in oxygenation of the affected tissue is believed to play an important role. The most commonly affected system in sepsis are cardiovascular and respiratory systems causing acute respiratory distress syndrome (ARDS) and hypotension respectively. Brain and kidney involvement is not uncommon and the common symptoms associated with their involvement being obtundation or delirium and acute kidney injury reflected by a decrease in urinary output and elevated creatinine level.[5]

High density lipoproteins are heterogeneous group of lipoproteins, varying in both composition and size, falling into a density range between 1.063 and 1.21 gm/ml. The major apo protein present in HDL that provides structural stability to the spherical molecule is apo lipoprotein A1 (Apo-A1). High-density lipoproteins are a family of particles characterized by their ability to transport cholesterol from peripheral tissues back to the liver that confers to them a cardiovascular protective effect.[6,7] HDLs also appear to emerge as relevant players in both innate and adaptive immunity.[8] Because of their pleiotropic properties, including anti-inflammatory, anti-apoptotic or antioxidant functions, experimental studies have tested the efficacy of both reconstituted HDL and ApoA1 mimetic peptide perfusion in animal models of septic shock.[8-10] Some of these have demonstrated a protective effect of these HDL mimetic on mortality and have shown a decrease in the inflammatory state.[9,11,12] Several clinical studies have been conducted to assess HDL concentration in septic conditions. Van Leeuwen et al. underlined that in septic patients, HDL concentrations rapidly fall and can be reduced to 50 % of recovery conditions.[13] Chien et al. had shown that low HDL levels on day 1 of severe sepsis were significantly associated with an increase in mortality and adverse clinical outcomes.[14] In an observational study involving 151 consecutive septic patients, a low HDL concentration was independently related to 30-day mortality.[15]

In this perspective, the present study was conducted with the following objectives.

1. To determine the change in HDL level in sepsis patients.
2. To assess the prognostic significance of serum HDL level in sepsis patients.

METHODS

After obtaining IEC clearance from Institutional Ethics Committee M.K.C.G Medical College, Brahmapur, Odisha vide IEC no 624 and permission from HOD, Department of General Medicine, this prospective hospital based longitudinal study was conducted in inpatient department and ICU of Department of General Medicine, M.K.C.G Medical College Odisha. Informed written consent was taken and participants were assured that complete confidentiality would be maintained.

The study was conducted for a duration of 24 months from November 2017 to November 2019.

Study population included all cases of sepsis admitted to medicine ward and medicine ICU of M.K.C.G Medical College, Odisha. Universal sampling was done and total 210 cases were included fulfilling the following inclusion and exclusion criteria.

Prognosis in sepsis patients was assessed in terms of survival i.e., as survivors and non-survivors. Also, duration of hospital stay in survivors was included as a parameter for knowing the prognostic impact of serum HDL levels.

Inclusion Criteria

1. Patients giving informed consent
2. Patients aged 18 years and above admitted to medicine ward and ICU of M.K.C.G Medical College and diagnosed as sepsis on the basis of SOFA and qSOFA score.

Exclusion Criteria

1. Patients who were on statins.
2. Patients suffering from chronic liver disease (CLD), chronic kidney disease (CKD), thyroid dysfunction, diabetes and malignancy.
3. Patients with chronic inflammatory conditions like human immunodeficiency virus (HIV), systemic lupus erythematosus (SLE) and rheumatoid arthritis.
4. Patients diagnosed with malabsorption syndrome
5. Patients who died before the second HDL reading.
6. Patients who were referred to higher centers and those who left the hospital against medical advice.

Data collection was done using a predesigned format. Data was collected from the bed head records of the patients and by interview method using a predesigned pre tested semi structure questionnaire. There were total 7 units in

medicine department and each unit was visited on its 2nd post OPD day. Patients admitted with diagnosis of sepsis and full filling the inclusion and exclusion criteria were included in the study. The medicine ICU was also visited daily and the study participants were selected from here too. Also, any new patients diagnosed with sepsis during the follow up visit to the wards were also included. Data from the initial baseline investigation was collected, repeated investigations were done on day 4 following admission and on the day of discharge. In cases of discharge on 5th day, the HDL recording of day 4 was considered as HDL on day of discharge. Patients were followed till death or discharge from the hospital. For patients who died before day 4, the day 1 value was used for analysis.

Statistical Analysis

Data entry and analysis was done using Microsoft Excel. Data was coded, entered and analysed using IBM Statistical Package for Social Sciences (SPSS ver.21.0).

Proportions were calculated for categorical variables and compared using chi square test. Mean and standard deviations were estimated for continuous variables as measures of central tendency and dispersion respectively. Means were compared using unpaired and paired t-test. Proportions were analysed using chi square test. Appropriate charts and diagrams were obtained wherever necessary. All analysis was done at a pre-set alpha error of 5 % and result was expressed at confidence level of 95 %.

RESULTS

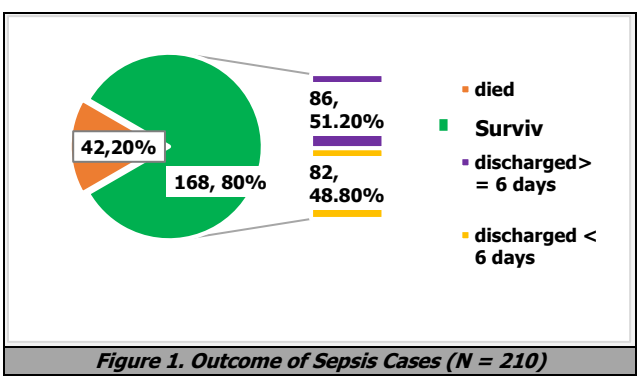

Figure 1. Outcome of Sepsis Cases (N = 210)

Coming to the outcome of the study subjects (figure I), out of 210 cases, 42 (20 %) cases died and 168 (80 %) cases survived. Out of which, 86 (51.2 %) were discharged in ≥ 6 days and 82 (48.8 %) were discharged in < 6 days.

Total 210 study participants were included in the study. The mean age was 37.4 ± 16.23 years ranging from 18 to 79 years. Majority (51.4 %) were males and were staying in rural areas (67.6 %).

Amidst the 210 cases of sepsis, 52 (24.8 %) were direct cases, 114 (54.2 %) were referred from government hospitals and 44 (21 %) from private hospitals. Coming to the presenting symptoms, the most common symptom was fever (92.4 %) followed by vomiting, diarrhoea, shortness of breath, joint pains etc. Many of the study participants presented with multiple overlapping symptoms.

Out of the 210 cases, most common cause of sepsis was found to be pneumonia (50, 30 %), followed by malaria (42, 25 %), empyema (16, 9.5 %) other less common causes included dengue, scrub typhus, urinary tract infection (UTI), lymphangitis, sickle cell, acute gastroenteritis (AGE), snake bite, lung and liver abscess.

In 35.7 % of cases, no organism was found in C/S. Out of the cases in which organisms were found, the most common organism identified was *Plasmodium falciparum*, followed by *Staphylococcus aureus* and *Streptococcus pneumoniae.*

Variable		Survivors (n = 168)	Non-Survivors (n = 42)	P Value
ICU admission	Yes (N =44)	24 (54.6%)	20 (45.4%)	X2= 22.5
	No (N =166)	144 (86.7%)	22 (13.3%)	P < 0.001*
Mean duration of presenting symptoms		6.96 ± 4.049 days	6.71 ± 3.379	P = 0.795

Table I. Clinical Characteristics of Study Participants (n = 210)

*indicates statistical significance at P<0.05

Table I shows clinical characteristics of the study participants, comparing them between survivors and non survivors. Out of the 44 sepsis cases admitted in ICU, 20 i.e., 45.4 % passed away, while only 10 % of cases admitted to general ward died. The prevalence of death was statistically significantly higher in sepsis cases admitted to ICU.

Mean duration of presenting symptoms was longer in patients who survived, than those who died, however, this finding was not statistically significant.

Variable (Mean ± S. D)	Survivors (n = 168)	Non-Survivors (n = 42)	P Value
GCS score	14.55 ± 0.718	14.05 ± 0.740	0.001*
Respiratory rate/min	25.60 ± 5.137/min	29.62 ± 4.544/min	0.001*
SBP mmHg	87.92 ± 7.76 mmHg	87.90 ± 10.88 mmHg	0.856
DBP mmHg	56.88 ± 7.86 mmHg	57.61 ± 10.74 mmHg	0.062
Platelet count ($\times 10^3$ μl^{-1})	82.51 ± 37.814	93.86 ± 49.663	0.078
S. Bilirubin (mg/dl)	2.008 ± 1.439 mg/dl	3.738 ± 2.756 mg/dl	0.004*
S. creatinine (mg/dl)	2.155 ± 1.16 mg/dl	4.167 ± 2.10 mg/dl	0.002*
MAP (mmHg)	67.25 ± 7.315	67.81 ± 10.657	0.593
TLC /cumm	11228.21 ± 7500.55	21372.38 ± 6485.72	0.003*
Total cholesterol (mg/dl)	125.77 ± 25.984	147.19 ± 55.143	0.005*
HDL day 1 (mg/dl)	20.63 ± 8.484	12.0 ± 1.549	0.007*
SOFA score Mean± SD range	6.01 ± 1.859 3 - 12	8.76 ± 1.972 6 - 12	0.000*
qSOFA score Mean± SD range	1.93 ± 0.861 0 - 3	2.62 ± 0.498 2 - 3	0.000*
VP used Yes No	84 (50 %) 84 (50 %)	20 (47.61 %) 22 (52.39 %)	X^2 = 0.076 P = 0.782

Table 2. Distribution of Baseline Characteristics among Survivors and Non-Survivors (n = 210)

*indicates statistical significance at P<0.05

Table II compares the baseline characteristics of those cases of sepsis who died and those who were discharged. It was observed that in survivors GCS score, S. HDL on day 1 was significantly higher. On the other hand, respiratory rate, serum bilirubin, serum creatinine, total leukocyte count (TLC), serum total cholesterol was found to be significantly higher in cases who died than those who were discharged.

No association was seen between systolic blood p[pressure (SBP), diastolic blood pressure (DBP), platelet count, mean arterial pressure (MAP) and the use of VP with prognosis.

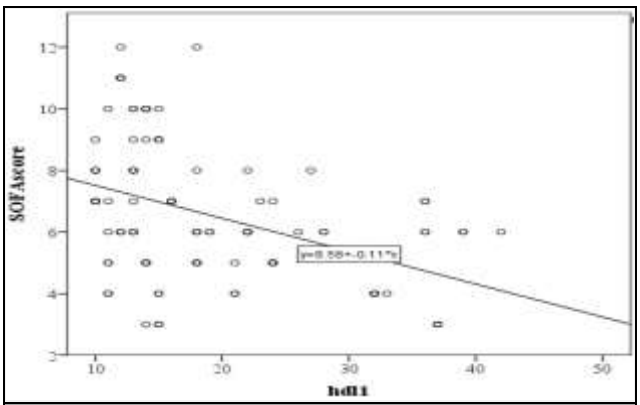

Figure 2. Correlation between SOFA Score and HDL Level on Day 1

Correlation coefficient (R) = - 0.410, P value = 0.000*
*indicates statistical significance at P < 0.05

Figure II: Correlation between HDL D1 and SOFA score

Figure II illustrate the correlation between the HDL level on Day 1 and the SOFA score of study subjects. A statistically significant inverse correlation was observed, with a correlation coefficient of -0.410. Indicating that higher HDL level on day of admission were associated with lower SOFA scores.

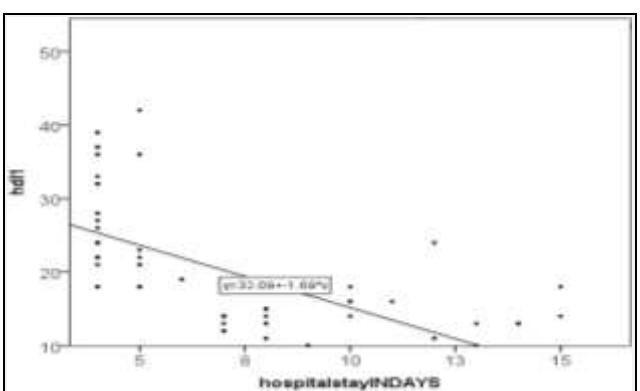

Figure 3. Correlation between HDL on Day 1 and no. of days of hospital stay among survivors

Correlation coefficient (R) = - 0.633, p value = 0.000*
*indicates statistical significance at P<0.05

Figure III: Correlation between HDL day 1 and duration of hospital stay in survivors. Figure IV demonstrates correlation between HDL level on day 1 and duration of hospital stay in sepsis patients who were discharged. A negative correlation was observed with a correlation coefficient of -0.633, which was again found to be statistically significant. Implying that higher HDL levels are associated with lesser duration of hospital stays.

Variable	Survivors (N = 168)	Non-Survivors (N = 42)	P Value
HDL D1 (mg/dl)	20.63 ± 8.48	12 ± 1.54	0.001*
HDL D4 (mg/dl)	24.32 ± 8.35	11.33 ± 2.59	0.007*

Table 3. Comparison between HDL Levels and Outcome of Study Participants (N = 210)

*indicates statistical significance at P<0.05

Table III depicts the association between HDL level and outcome of the sepsis cases. On comparing the mean HDL levels, we found that for both day 1 and day 4, the serum HDL levels were significantly higher among survivors than non survivors.

Variable	HDL-D1 (mg/dl)	HDL-D4 (mg/dl)	P Value
Non survivors	12.01 ± 1.54	11.33 ±2.59	0.235
Survived discharged < 6 days	26.91 ± 7.2	30.72 ± 6.08	0.000*
Survived discharged ≥ 6 days	14.05 ± 2.84	17.61 ± 3.94	0.000*

Table 4. Comparing the Changes in HDL Levels among the Study Participants from Day 1 and Day 4 (N = 210)

*indicates statistical significance at P<0.05

Changes in serum HDL level observed on day 1 and day 4 estimation is compared in Table 4. This table shows that there is significant increase in the mean HDL level from day 1 and day 4 in patients who survived, this trend was observed in both cases who were discharged early and those who had a longer stay in the hospital. However, it was seen that there had been a decline in the mean HDL level from day 1 to day 4 in case of non survivors, although this was not found to be statistically significant.

Variable	Discharged < 6 Days (N = 82)	Discharged ≥ 6 Days (N = 86)	P Value
HDL D1 (mg/dl)	26.91 ± 7.2	14.05 ± 2.84	0.000*
HDL D4 (mg/dl)	30.72 ± 6.08	17.61 ± 3.9	0.000*

Table 5. Comparison between HDL Levels and Duration of Stay in Survivors (N = 168)

*indicates statistical significance at P<0.05

Table V portrays the association between HDL level on day 1 and day 4 and duration of hospital stay in those who were discharged. Here also, higher HDL level on day 1 and day 4 are associated with lesser duration of hospital stay.

DISCUSSION

The mean age of study participants in our study was 37.4 years with S.D of 16.23 years. In another study conducted by Dhamija et al. the mean age was 54.28, older than our study. In another study by Mitra Barati et al. the mean age was 73.6 ± 15.7 years.[16] The lower mean age in our study was because of sepsis cases in younger age group, the youngest being 19 years. Similar to our study, in another study conducted in Jaipur, India also majority were males and from rural area.

In our study common causes of sepsis were pneumonia followed by malaria and empyema. However, in a study conducted in Jaipur, the commonest cause of sepsis was dengue, followed by scrub typhus, swine flu and malaria. Odisha being a malaria endemic zone, malaria was the 2nd highest underlying cause which was found in our study.

On culture sensitivity of sepsis cases, 35.7 % cases had no organism, out of those positive for organisms, most common organism was *Plasmodium falciparum*, followed by *Staphylococcus aureus* and *Streptococcus pneumoniae*. Seyed Ali Javad Mousav et al. found out that only 38.4 % of sepsis patients had positive blood culture. The most

common organism was gram negative enteric pathogen (Klebsiella and *E. coli*).[17]

In this study, 168 cases (80 %) survived, out which 82 (48.8 %) were discharged in < 6 days while remaining 86 (51.2 %) cases stayed longer than 6 days. 20 % of the cases i.e. 42 cases passed away. In another study conducted by Tanaka et al. mortality was found to be 15 % in sepsis cases.[18] Another study by Dhamija et al. showed relatively high mortality rate in sepsis i.e. around 42.8 %. Similar study conducted by Gaddam et al. in Pondicherry, India showed a mortality rate of 33 % where 34 of the 100 cases of sepsis taken died.[19]

On comparing the baseline characteristics of survivors and non survivors in our study, we found that in survivors GCS score and serum HDL on day 1 was significantly higher than those who died. Gaddam et al. in their study also found the same, significantly lower GCS score in those who died (20). On the other hand, respiration rate, serum bilirubin, serum creatinine, TLC, serum total cholesterol was found to be significantly higher in cases of sepsis who died than those who were discharged. Likewise, in another study conducted, the researchers found significantly higher serum bilirubin, serum creatinine, TLC, SBP, DBP levels in non survivors (20). The qSOFA score and SOFA scores of patients who died was significantly higher than those who survived. Similar results were also seen by study by Gaddan et al.[19] and Dhamija et al. We found an inverse correlation between HDL on day 1 and SOFA score of the participants, also similar correlation was seen between the days of hospital stay and HDL D1. Gaddam et al. in their study found a correlation coefficient of -0.631, indicating a significant negative correlation between HDL and SOFA score, similar to our study (20). Similar correlation was also observed by Dhamija et al. and Tanaka et al.[18]

In the present study, the mean HDL level on both day 1 and day 4 was significantly higher in cases who survived than those who died indicating that higher HDL levels are associated with better prognosis. Gaddan et al. in their study also found higher levels of serum HDL in patients surviving, both for day 1 and day 5 estimation,[19] similar results were seen in studies by Jeysurya et al.[20] Naresh et al.[21] and Sunanyna et al.[22]

Further, we also observed that those cases which survived had significant improvement in their HDL levels as measured on day 1 and day 4. Additionally, on comparing the HDL level on day 1 and on day of discharge among survivors, we found that those who had higher HDL levels were discharged earlier. In another study conducted by Chien et al. they also found that lower HDL level on day 1 is not only associated with increased mortality but also with longer hospital stay.

CONCLUSIONS

Based on the results and the methodology employed, we concluded that trend of HDL-C correlated with clinical outcome of patients.

Rising trend favoured improvement in clinical condition and decreasing trend implied worsening of the clinical condition. Baseline HDL-C value correlated with SOFA score in predicting mortality in sepsis patients.

Hence, HDL can be used as a prognostic marker in sepsis thereby monitoring the patients to give adequate life-saving treatments in terms of antibiotics or prevent multi-organ dysfunction syndrome (MODS).

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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