International Journal of Advances in Medicine
Gaddam BK et al. Int J Adv Med. 2019 Apr;6(2):312-317
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20191084

Original Research Article

Study of serum HDL-cholesterol levels in sepsis patients and its prognostic significance

Bhargav Kiran Gaddam, M. Narayanan*

Department of General Medicine, Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth, Pillaiyarkuppam, Pondicherry, India

Received: 28 February 2019
Accepted: 19 March 2019

***Correspondence:**
Dr. M. Narayanan,
E-mail: kahanam@gmail.com

ABSTRACT

Background: Sepsis is the second leading cause of mortality in the ICU. Despite advances in aggressive management, sepsis continues to have a high mortality rate, hence a prognostic marker is essential. Recently HDL-cholesterol was found to be have significant association between mortality and its levels. Hence, this study is being conducted to assess the association between sepsis and HDL-C levels.
Methods: It is a prospective study conducted in MGMCRI involving 100 sepsis patients. Among them 66 people survived, and 34 people expired. Serum HDL-cholesterol levels and variables required for SOFA score are measured at two intervals, one during admission and on day 5 of admission. The correlation between SOFA scores and HDL-C levels were assessed.
Results: Among non-survivors SOFA score was found to be high and low in the survived patients. Similarly, HDL-C values, were high in survived patients and low in dead patients. The correlation between SOFA scores and HDL in both survivors and non survivors, both at the time of admission and at day 5 were found to be statistically significantly correlated.
Conclusions: This study proves the significant relationship between the HDL values and the SOFA scores. Hence, HDL-cholesterol levels can be used to measure the prognosis and therapeutic efficacy in cases of sepsis. Rising values of HDL cholesterol favour improvement in clinical condition and falling values imply worsening and there by providing a prognostic indicator.

Keywords: Correlation, HDL-cholesterol, Sepsis, SOFA score, Survival

INTRODUCTION

Sepsis is a significant public health concern.[1] Sepsis affects persons of all ages is the leading cause of morbidity and mortality for patients admitted to an intensive care unit (ICU) and may be considered the tenth leading cause of death overall in the United States. The incidence of sepsis is projected to increase by 1.5% per year, rising to more than 1,110,000 cases or more annually by 2020.[2] The incidence of severe sepsis in India was 16.45% of all 5478 total admissions. Mean age of the population was 58.17 years of which 57.71% were male.[3]

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[4] The clinical criteria for sepsis include suspected or documented infection and an acute increase of two or

more Sequential Organ Failure Assessment (SOFA) points as a proxy for organ dysfunction.

Despite advances in aggressive management, a diagnosis of sepsis continues to have a high mortality rate, which increases with sepsis severity from 20.8% in patients with sepsis and as high as 48.8% in patients with septic shock.

Currently a few reliable therapeutic strategies for the management of sepsis including empiric antibiotic therapy, aggressive volume repletion and tight insulin control are employed. Given that the reversibility of severe sepsis is poor, the need for an "early prognostic marker" to identify those at highest risk for mortality in order to optimize therapeutic options is critical in order to reduce the ICU mortality secondary to sepsis.

Recent evidence suggests that serum High density lipoprotein cholesterol (HDL-C) 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.[5] Additional studies have demonstrated that patients diagnosed with severe sepsis in the ICU have a measured decrease in circulating level of lipoproteins and an increase in triglycerides independent of comorbidities.[6] These changes have been noted to occur early (within hours) in the inflammatory cascade associated with sepsis. A reduction in serum cholesterol was also negatively correlated to clinical outcome.[7]

A low HDL-C cholesterol level on day 1 of severe sepsis is significantly associated with an increase in mortality and adverse clinical outcomes. The aim of this study was to investigate the association between HDL-C and clinical outcome in patients with sepsis.

HDL-C value can be used as a biomarker of septicaemia because it is easily available, cheap and as septicaemia biomarker due to the wide range of HDL-C normal value (40-60 mg/dl) compared with other biomarkers. In sepsis HDL-C value can drop from 40 mg/dl to as low as 15 mg/dl).

METHODS

This was a prospective observational study, which was conducted at the Mahatma Gandhi Medical College and Research Institute Hospital, Pondicherry, India, a rural tertiary care hospital. Those patients diagnosed to be in sepsis will be the study participants. Whenever patient is diagnosed to be in sepsis, those patients will be contacted immediately. Details of the study will be explained in detail. Permission is sought in the form of informed written consent and the study was conducted. After Institutional Ethical Committee approval all the patients diagnosed to have sepsis in High dependency units/wards of MGMCRI Hospital were recruited for the study. Blood samples from each patient were taken for HDL-C-cholesterol levels, creatinine, bilirubin levels, and platelet levels at the time of admission and on the day 5 after admission. Respiratory status by Pao2 and Fi02 and Central nervous system assessed by Glasgow Coma Scale and SOFA scores were calculated accordingly on day of admission and day 5. The HDL-cholesterol measurement was done by ROCHE COBAS C systems clinical chemistry automated analyzer.

Inclusion criteria

Patients with age greater than 18 years and satisfying the criteria for sepsis according to International guidelines for management of severe sepsis and septic shock 2016.[4]

Exclusion criteria

- Patients on treatment with statins,
- Patients with chronic kidney disease, chronic liver disease, thyroid dysfunction, diabetes mellitus and mal-absorbption disorders,
- Patients with known chronic infective and inflammatory conditions like Human immunodeficiency virus disease, SLE (Systemic lupus erythematous) and RA (Rheumatoid arthritis).

Statistical method

Statistical analysis was carried out using SPSS version 19.0 (IBM SPSS, US) software with regression modules installed and Microsoft Word and Excel have been used to generate graphs, tables etc.

Results on continuous measurements are presented on Mean±SD (Min-Max) and results on categorical measurements are presented in number (%). Significance is assessed at 5% level of significance. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Significant figures

- + Suggestive significance (P value: $0.05<P<0.10$)
- Moderately significant (P value: $0.01<P\leq0.05$)
- ** Strongly significant (P value: $P\leq0.01$).

RESULTS

Among the 100 study patients, mean age of patients is 59.72±11.07 years and age distribution wise most of the patients belonged to the elderly age group of more than 60 years. There were 56 male patients and 44 female patients. Among the 100 participants 66 people survived and 34 people expired. Among non survivors, most of the age group belonged to elderly of age >60 years (67.6%). Among the Survivors age group 18-29 years amounted to 43.9%. Among the gender distribution male population (64.7%) has higher mortality compared to female population (35.3%). Most of the non survivors were found to be hypertensive (70.6%) and duration of ICU

stay (10.4 days mean) was higher when compared to survivor group (6.5 days) which were statistically significant (0.001*).

The variables required to calculate the SOFA score were compared and found to be statistically significant. The median platelet counts in case of non survivors was found to be 2.45 lakhs on admission and dropped to 86,000 on the day 5 in case of non survivors and improved in case of survivors from 1.69 lakhs to 2.5 lakhs. Mean GCS levels where lower in the non-survivor group when compared to survivor group on both the days, median creatinine levels in non survivors were 2.3 mg% and 3.0 mg% respectively and median bilirubin levels were found to 1.8 mg% on day of admission in non survivors and 5.9 mg% on day 5 and were found to be statistically significant which depicts the progressing multi organ dysfunction in non-survivor groups. Similarly, in respiratory analysis the Pa02 and Fi02 values when compared to survivors and non survivors it was significantly lower in non survivors and it was found to be statistically significant (Table 1).

Table 1: Variables for SOFA SCORE when compared in non survivors and survivors.

Variable	Non survivors (N=34)		Survivors (N=66)		p value
	Median	IQR /SD	Median	IQR /SD	
Platelet D0 (in lakhs)	2.45	1.06-2.84	1.69	0.87-3.25	0.57
Platelet D5	0.86	0.37-3.1	2.5	1.5-3.5	0.002*
GCS D0	12.2	2.5	14.6	0.7	<0.001*
GCS D 5	9.0	4.9	13.9	3.3	<0.001*
Creatinine D0	2.3	1.17-4.12	1.1	0.97-2.02	0.001*
Creatinine D5	3.0	1.62-8.1	1.1	0.9-1.8	0.001*
Bilirubin D0	1.8	1.07-2.7	1.1	0.8-1.82	0.008*
Bilirubin D5	5.9	2.0-8.1	1.0	0.8-1.32	0.001*
SBP D0	107.7	36.4	125.0	31.7	0.02*
SBP D 5	90.3	33.9	128.9	27.5	<0.001*
DBP D0	67.6	20.6	77.6	17.5	0.02*
DBP D 5	53.2	20.8	81.9	14.6	<0.001*

The mean systolic blood pressure and diastolic blood pressures of the non-survivor group both at the day of admission (107.7, 67.6 mmHg) and on the day 5 (90.3, 53.2 mmHg) were found to be on the lower side when compared to the survivor group (125, 77.6 mmHg) and (128.9, 81.9 mmHg).

It showed a significant relation with mortality and there by having important role of cardiovascular system in sepsis and there by requiring Inotropic support. The use of inotropic support was increased from 38.2% in non survivors on day of admission to 76.5% on day 5 and it implies worsening hemodynamic status and it was statistically significant (Table 1).

The median SOFA value in survivors ranged only between 2 and 1 where as it was increased from a value of 8.5 to 15 from day of admission to day 5 and both the values were found to be statistically significant. It proves worsening of the clinical scenario and probable involvement of multi organ dysfunction (MODS) and thereby increasing the mortality (Figure 1).

The HDL value of the survivors remained higher and near normal on both the day of admission and day 5, where as in the non survivors it dropped from mean of 34.3 to 26.4 mg% from day of admission to day 5 and it was statistically significant.

This shows that HDL value drops when sepsis is increasing and is lower in non survivors in relation with survivors (Figure 2).

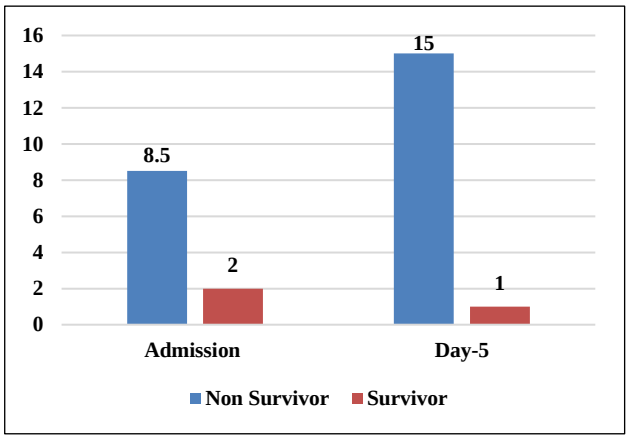

Figure 1: SOFA value of study participants at various time points.

SOFA score was correlated along with HDL levels and there was a statistically significant relationship among the survivors (with correlation of coefficient of -0.63 and p value of <0.001* on admission and -0.50 and <0.001* on day 5) and non survivors at (with correlation coefficient -0.42 and p value <0.001* on admission and -0.50 and <0.001* at day 5) (Table 2).

ROC analysis was carried out to find out the cut off value of HDL that indicates the survival of patients admitted. The area under the curve was 60% and it was significant statistically. For the cut off at 33 mg/dl the sensitivity and specificity of HDL to diagnose survival was 65% and 50% respectively. For the cut off at 35 mg/dl the sensitivity and specificity of HDL to diagnose survival was 64% and 50% respectively (Figure 3).

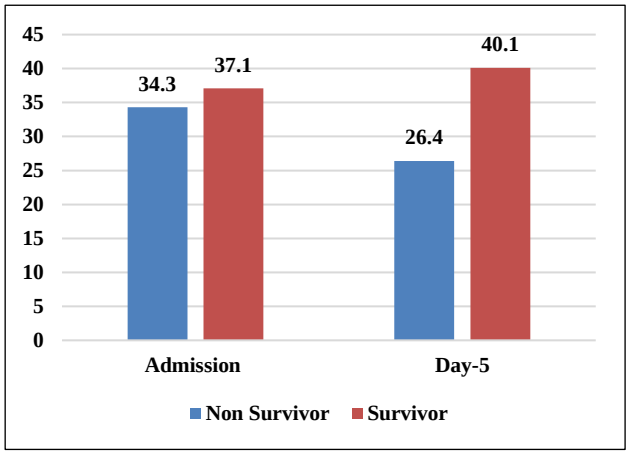

Figure 2: HDL value of study participants at various time points.

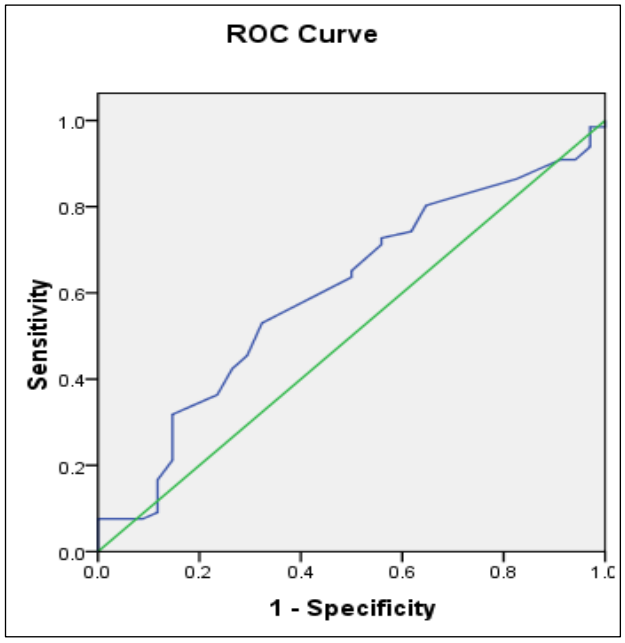

Figure 3: Area under the curve based on ROC analysis for diagnosing survival.

Table 2: Correlation between SOFA scores and HDL-cholesterol levels in survivors and non survivors.

Time point	HDL and SOFA score	
	Correlational coefficient	p value#
On admission	-0.54	<0.001*
On day 5	-0.62	<0.001*
Survivors D0	-0.63	<0.001*
Survivors D5	-0.50	<0.001*
Non survivors D0	-0.42	<0.001*
Non survivors D5	-0.50	<0.001*

DISCUSSION

Sepsis is one of the leading causes of mortality worldwide. There is need for development of more sensitive biomarkers for early detection of sepsis.

Among the 100 patients in this study, male patients were 56 and female 44 and the survival rate is 66%. In a similar study done by Sunayana P et al, among 70 patients, 42 were male and 28 were female and survival rate was 72.8%.[8] In a study conducted by Naresh et al, had total of 111 patients, of which 67 (60.4%) were males and 44 (39.6%) were female with survival rate of 54%.[9]

Age distribution

In this study, 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%. This can be attributed to the additional risk factors for sepsis in the elderly when compared to the young age group with good immunity and health. In an observational study using hospital discharge data, Martin GS et al, determined that incident rates of sepsis in older adults aged 65 years above increased 20.4% faster than in those aged less than 65 years (mean increase 11.5% vs 9.5% per year, P <0.001).[10] In a similar study done by Naresh et al, most of the non survivors aged between 41-60 years and survivors of age 18-40 yrs.[9]

Sex distribution

In this study, sex distribution shows most of the males (22:64.7%) have higher mortality rate compared to that of females (12:35%) owing to the additional risk factors linked to that of hormonal factors, increased exposure to the infections, stress etc. A retrospective analysis of 261,255 consecutive patients, reviewing the data available in the APACHE database, revealed an increased mortality in males younger than 50 years compared with women of the same age group.[11] According to Martin GS et al, female gender has been demonstrated to be protective, whereas male gender may be deleterious due to a diminished cell-mediated immune response and cardiovascular functions. Male sex hormones, i.e.,

androgens, have been shown to be suppressive on cell-mediated immune responses. In contrast, female sex hormones exhibit protective effects which may contribute to the natural advantages of females under septic conditions. Thus, the hormonal status has to be considered when treating septic patient12. In a similar study conducted by Naresh et al, also showed higher mortality rate in male population (70.9%).[9]

Hypertension status

In this study, among the non survivors 70.6% are hypertensive patients when compared to survivors of 29.4% which implies that chronic medical conditions like that of hypertension play a significant role in survival and sepsis. In longitudinal cohort study using the 30,239 community-dwelling participants of the REGARDS cohort (Reasons for Geographic and Racial Differences in Stroke (REGARDS) by Henry et al, there were 975 incident cases of sepsis, they showed that incident sepsis episodes were associated significantly with chronic medical conditions like that of hypertension.[13]

SOFA variables:

As a variable for assessing SOFA score serum bilirubin was measured at different intervals and was found to be 1.8 mg% and 5.9 mg% (median) among non survivors and 1.1 mg% and 1.0 mg% among survivors which were statistically significant. In a similar study done by Naresh et al, median bilirubin levels were 3.7 and 2.85 among non survivors and survivors and it was not statistically significant. Similarly mean GCS levels were found to be statistically significant in this study in both survivors and non-survivor groups with values of 14.6, 13.9 and 12.2 and 9.0 on day of admission and day 5, which conveys that acute liver injury and neurological derangement play pivotal roles in mortality and morbidity of the patient with sepsis.

To assess the renal involvement serum creatinine values were measured and found to be have a median of 2.3 and 3.0 mg% in non-survivor group when compared to survivor group of having 1.1 and 1 mg% on both the day of admission and on day 5, and it was found to be statistically significant. The lung involvement was assessed by using Pa02 and Fi02 values. They were significantly lower in non survivors and it was found to be statistically significant.

Similarly, hematological involvement was assessed by the platelet counts, the median platelet counts dropped from the day of admission to day 5 in non-survivor group. The median platelet count was ranging around 2.45 lakhs/cmm during admission and dropped to 86,000/cmm on day 5 in expired patients implying significant mortality as in cases of dengue and scrub typhus. The platelet count in survivors were 1.69 lakhs/cmm and 2.5 lakhs/cmm on day of admission and day 5 respectively and were found to be statistically significant. The duration for ICU stay was assessed to measure the morbidity was found to be prolonged in cases of expired patients with a mean duration of stay of 10.4 days when compared to survived patients of 6.5 days, and it was statistically significant. Similarly, the use of the inotropic support was found to have a median of 13 on day of admission and 26 on day 5 when compared to 7 and 5 in survivor's group. The use of inotropic support was increased from 38.2% in non survivors on day of admission to 76.5% on day 5 and it implies worsening hemodynamic status and it was statistically significant.

SOFA score

In this study, SOFA score was used to assess the sepsis score and is compared at the time of admission and day 5 and it was correlated with survival rate. Among non survivors SOFA score was found to be high both at date 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. In a similar study conducted by Naresh et al, APACHE 2 score was used and was found to be 22 (median) among non survivors and 14 among survivors.[9]

Serum HDL-cholesterol values

Serum HDL-C values were measured during the admission day and day 5 and were compared with non-survival group and survivor group. The mean value during the day of admission was found to be 34.3 and 37.1 mg% in non-survivor and survivor group respectively. The mean value of HDL-C in non-survivor group on day 5 was 26.4 mg% and 40.1 mg % in survivor group and it was statistically significant with a p value of <0.001. Among the non-survivors most of the HDL values were found to be less than 20 which implies that HDL levels less than 20 mg/dl are at higher risk for mortality and may require urgent lifesaving interventions. In a similar study conducted by Jeyasuriya et al, mean HDL level in non-survival group (at day 0, 3) were found to be 33 and 31 mg% with a non-significant p value of 0.137 and survival group of 31 and 36 mg% and was statistically significant with a p value of 0.033.[14] In a similar study conducted by Naresh et al, mean HDL value among non survivors was 5.8 and survivors 11.8 mg%.[9] In a study conducted in Kerala by Sunayana P et al, the HDL values were compared between sepsis and severe sepsis patients and found to have mean HDL was 52. 17 mg/dl, 41.81 mg/dl and 40.08 mg/dl respectively. In patients with HDL more than 50 mg/dl, 11.8% mortality was observed and in patients with HDL less than 50 mg/dl, 32.1% mortality was observed but this was not statistically significant (p value 0.1).[8]

Correlation between SOFA and HDL-C levels

In this study, SOFA score was used as an sepsis score and is correlated along with HDL-C levels at various times of hospital stay and it showed a statistically significant

relationship even among the survivors (with correlation of coefficient of -0.63 and p value of <0.001* on admission and -0.50 and <0.001* on day 5) and non survivors at (with correlation coefficient -0.42 and p value <0.001* on admission and -0.50 and<0.001* at day 5. In a similar study conducted by Naresh et al, has used APACHE 2 score and had a correlation of -450 among survivors and -163 among non survivors with p value of <0.003 and was statistically significant.[9]

Thus, HDL-C can be identified as a prognostic marker in comparison to the levels with either SOFA Score or APACHE 2 score.

This was a non-randomized trial, single centre study with a relatively small number of patients. A larger study may give one better results.

In this study, author did not compare the prognostic value HDL-C with other biomarkers like that of lactate, CRP.

CONCLUSION

Based on the results and the methodology employed, author have concluded that trend of HDL-C correlated with clinical outcome of patients. Rising trend favored 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 ICU Patients. Most of the patients whose HDL-C score was found to be less than 20 mg/dl are at high risk for mortality. Hence, HDL can be used as a prognostic marker in sepsis thereby monitoring the patients to give adequate lifesaving treatments in terms of antibiotics or prevent multi organ dysfunction syndrome (MODS).

Recommendations

In sepsis, the measurement of HDL-cholesterol has important prognostic implications. A high initial value or rising value of HDL-C is possibly associated with better prognosis and survival. A very low HDL-C or falling values imply poorer outcomes and Survival.

ACKNOWLEDGEMENTS

Authors would like to acknowledge Vice chancellor, Sri Balaji Vidyapeeth, India, The Dean, MGMCRI, Pondicherry, India and Professor Dr. S. Lokesh, Head of Department of Medicine, MGMCRI, Pondicherry, India for their invaluable contribution.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional human ethics committee (IHEC) on 25/02/2017

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Cite this article as: Gaddam BK, Narayanan M. Study of serum HDL-cholesterol levels in sepsis patients and its prognostic significance. Int J Adv Med 2019;6:312-7.