Original article :

Association of Mortality with the Serum High Density Lipoprotein Levels in the Patients of Sepsis in ICU: An Prospective Hospital Based Study

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Abstract

Background: Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Mechanisms of low HDL in severe sepsis are multifactorial and limited study was available in India. The aim of this study to association of mortality with the serum HDL levels in patient of sepsis and septic shock.

Materials & Methods: This is a prospective cohort study done on 50 patients with sepsis and septic shock admitted in intensive care unit in Department of General Medicine, Santosh Medical College and Hospital, Ghaziabad, Uttar Pradesh, India. Patient's included in study are based on initial assessment by qSOFA scoring system. Serum HDL was done on the day of admission and repeat on day 4. Detailed clinical examination was done along with relevant blood investigation were done required as per exclusion criteria.

Results: Present study showed that the Maximum no. of cases was seen in 41-60 years of age group. In between age groups was statistical non-significant (P+0.4472) but mean value of SOFA score was higher in advanced age groups. The mean value of SOFA score was 23.47±6.520 in total patients, in survivors was14.00±5.715 & 26.38±3.070 SOFA score in non-survivors, which was statistical significant (P<0.0001) in <10 mg/dl HDL level.

Conclusion: It can be concluded that HDL cholesterol on day of admission can be viewed as a significant predictor of mortality in patients with severe sepsis in medical ICU patients.

Keywords: HDL Cholesterol, Sepsis, ICU, SOFA Score.

INTRODUCTION

Sepsis is a life-threatening condition that arises when the body's response to infection causes injury to its own tissues and organs. Common signs and symptoms include fever, increased heart rate, increased breathing rate, and confusion.[1] There also may be symptoms related to a specific infection, such as a cough with pneumonia, or painful urination with a kidney infection.[1] In the very young, old, and people with a weakened immune system, there may be no symptoms of a specific infection and the body temperature may be low or normal, rather than high.[1] Severe sepsis is sepsis causing poor organ function or insufficient blood flow. Insufficient blood flow may be evident by low blood pressure, high blood lactate, or low urine output. Septic shock is low blood pressure due to sepsis that does not improve after reasonable amounts of intravenous fluids are given. The incidence of sepsis and the number of sepsis-related deaths are increasing, although the overall mortality rate among patients with sepsis is declining. There are also disparities among races and between men and women in the incidence of sepsis. Gram positive bacteria and fungal organisms are increasingly common causes of sepsis.[2]

The incidence of severe sepsis in India was 16.45% of all admissions. Mean age of the population was 58.17 years (SD 18.66), of which 57.71% were male. The median APACHE II score was 13 (IQR 13 to 14) with predominant (90.93%) medical admission. 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. Median duration of stay in the ICU for the severe sepsis cohort who survived was 13 days (IQR 11 to 17). The number of episodes where infection was the primary reason for admission to the ITU (Intensive Therapy Units) was 86.32%. Culture positivity was found in 61.6%. The lung was the predominant source of sepsis (57.45 %).[3]

Lipoproteins are macromolecular complexes used by the body to transport lipid-rich molecules.[4] Lipoproteins are classified into five groups according to their relative density: Chylomicrons Very low density lipoprotein (VLDL) Intermediate density lipoprotein (IDL) Low density lipoprotein (LDL) and High density lipoprotein (HDL).

Lipoproteins have been implicated to play a role in innate immunity.[5] Knowledge of variations in blood lipid levels in patients with sepsis dates to 1980's, when studies showed significantly low HDL-C levels with sepsis, which improved with improvement in sepsis. But studies lacked correlation of with severity of sepsis with decrease in HDL-C levels nor infections agent or underlying illness.[6]

HDL is a heterogeneous group of lipoproteins, varying in both composition and size, falling into a density range between 1.063 and 1.21 g/ml.[7] The major Apo protein present in HDL that provides structural stability to the spherical molecule is Apo lipoprotein A1 (Apo- A1).[8] Primary function of HDL-C is reverse cholesterol transport. Lipid-free or low-lipid Apo proteins (for example, Apo-A1) released from the liver combine with lipids derived from dietary intake (chylomicrons). These accept phospholipids and excess free cholesterol from peripheral tissues in a process promoted by the pore-forming protein ATP-binding cassette A1 transporter, forming disk-shaped pre-β-HDL. Free cholesterol is esterified by lecithin cholesterol acyltransferase (LCAT) and the complex transforms into a spherical structure, HDL3. HDL3 molecules continue to engulf additional lipid molecules and Apo proteins, thereby forming mature HDL 2.[9,10]

Mechanisms of low HDL in severe sepsis are multifactorial and limited study was available in India. So with reference to current situation analysis and limited number of studies related to association of the mortality with the high density lipoprotein level in the patients with sepsis in the ICU, the present study was undertaken on the association of the mortality with the high density lipoprotein level in the patients with sepsis in the ICU.

MATERIALS & METHODS

This is a prospective cohort study done on 50 patients with sepsis and septic shock admitted in intensive care unit in Department of General Medicine, Santosh Medical College and Hospital, Ghaziabad, Uttar Pradesh, India. Patient's included in study are based on initial assessment by qSOFA scoring system. Those patient in which qSOFA score more than 2 are included in the study group and at time of admission patient clinical history noted and detail clinical examination was done. Patient's which fulfill inclusion criteria are further evaluation and investigations was sent on day of admission. All patient's were followed prospectively during their entire course of stay in

hospital. Serum HDL was done on the day of admission and repeat on day 4. Detailed clinical examination was done along with relevant blood investigation were done required as per exclusion criteria:

1) Ultrasonography and Hb, serum calcium, serum phosphorous to rule out chronic kidney disease

2) HIV, ANA, Rheumatoid arthritis factor, Hba1c, TSH, T3, T4 to rule out diabetes mellitus, hypothyroidism, SLE and rheumatoid arthritis

3) Portal vein diameter, liver size and echotexture was studied rule out chronic liver disease

Patient's other investigation were also sent to identify the etiology of disease and for SOFA score calculation to estimate the risk of organ dysfunction and risk of death:

CBC, ESR, dengue serology, scrub typhus, HINI, malaria, blood culture and sensitivity, LFT, ABG, RFT. Mental status examination assesed by glassgow coma scale with systolic and diastolic blood pressure measurement. Respiratory rate and Glassgow coma scale are to be ascertained at the onset. The approval from the Institutional and ethical committee were taken before undertaking the study.

Inclusion Criteria

- Patients with age greater than 18 years and satisfying the criteria for sepsis according to International guidelines for management of sepsis and septic shock: 2016 were included in the study.

Exclusion Criteria

- Patients on treatment or history of treatment with statins.
- Chronic liver disease, chronic kidney disease, thyroid dysfunction, diabetes mellitus.
- Patients with known chronic inflammatory condition like Human immunodeficiency virus disease, SLE (Systemic lupus erythematous) and RA (Rheumatoid arthritis)**.**
- Patients who were discharged against medical advise.

Methodology

1. All patient's admitted with sepsis and septic shock satisfying inclusion criteria were included in our study after obtaining informed consent.

2. All the patients were followed prospectively during their entire course of stay in the hospital. Serum HDL levels were done on the day of admission and repeated on day 4. SOFA score were calculated for all patients on day of admission and sequentially to estimate the risk of death.

3. Early morning serum samples were collected on day 0 of admission and day 4 for HDL cholesterol measurement. Lipid Profile was measured.

Principle of the Method

Serum HDL level are measured by different methods. In our hospital serum HDL level is measured by enymatic method using phosphotungustic acid, directly determination of serum HDLc and (high-density lipoproteins cholesterol) levels without the need for any pre-treatment or centrifugation of the sample.

The method depends on the properties of a detergent which solubizies only the HDL so that the HDL-c is released to react with the cholesterol esterase, cholesterol oxidase and Chromogens to give color .The non HDL lipoproteins LDL, VLDL and chylomicrons are inhibited from reacting with the enzymes due to absorption of the detergents on their surfaces.

The intensity of the color formed is proportional to the HDL-c concentration in the sample.

Preparation

- The reagent is ready to use.
- Dissolve HDL/LDL Calibrator with 1ml of Distilled water.
- Mix thoroughly, avoiding foam forming.
- Bring to room temperature for about 30 min .before use.
- Improper handing and/ or storage can affect results.
- Inaccurate reconstitution and errors in assay technique can cause erroneous results.

Storage and Stability

- All the components of the kit are stable until the expiration date on the label when stored tightly closed at 2-8°C, and contaminations prevented during their use.
- Do not freeze the reagent
- Do not use reagents over the expiration date. After reconstitution, HDL/LDL calibrator is stable for: o R1/R2: Once opened is stable 8weeks at 2-8c

o HDLc/LDLc CAL : Once reconstitute 2weeks at 2-8c or 3 months at -20c

- Signs of reagent deterioration:
- Presence of particles and turbidity

Statistical Analysis

Appropriate statistical tests were used to find significant association. P value < 0.05 was considered.

Table 1: Correlation of age distribution with SOFA Score

Age (yrs)	Total no of patient in age group	SOFA Score (Mean±Sd)	Spearman correlation
18-40 yrs	4	12.25±11.95	P=0.4472 NS
41-60 yrs	29	14.48±10.06	
61-80 yrs	17	16.88±7.449	
Total no of patients	50	15.12+9.312	

Table 2: Comparison of etiological distribution of patients with SOFA and HDL

Etiology	HDL value (Mean+SD)	SOFA score (Mean+SD)	P value
Dengue	26.51±5.759	9.333±5.715	<0.0001***
Scrub typhus	27.00±2.00	8.750±3.50	0.0001**
Swine flue	21.97±8.779	11.20±8.217	0.0110*
Malaria	18.57±7.976	13.00±6.298	0.1726 NS

Table 3: Comparison of mortality between HDL≤10mg/dl and HDL≥11mg/dl

HDL	Survivors	Non-survivors	Total	P value
<10mg/dl	4 (11.42%)	13 (86.66%)	17 (34%)	<0.0001***
≥10 mg/dl	31 (88.57%)	2 (13.33%)	33 (66%)	<0.0001***
Total	35 (70%)	15 (30%)	50 (100%)	

Table 4: Comparison of SOFA score between HDL≤10mg/dl and HDL≥11mg/dl

HDL	SOFA score			
	Total patients (Mean±SD)	Survivors (N=35)	Non-survivors (N=15)	P-value
<10mg/dl	23.47±6.520	14.00±5.715	26.38±3.070	<0.0001***
≥10 mg/dl	10.82±7.443	9.710±6.176	28.00±1.24	<0.0001***

RESULTS

Present study showed that the Maximum no. of cases was seen in 41-60 years of age group. The mean value of SOFA score was 16.88±7.449 in 61-80 years of age group followed by 14.48±10.06 in 41-60 years of age group & 12.25±11.95 in 18-40 years of age group. In between age groups was statistical non-significant (P+0.4472) but mean value of SOFA score was higher in advanced age groups (table 1).

The Comparison of etiological distribution of patients with SOFA and HDL was seen in table 2.

Out of 50 patients, 17 patients had <10mg/dl HDL & 33 patients had ≥10 mg/dl HDL. Out of 17 patients, 13 non-survivors patients had <10mg/dl HDL & 4 survivors. Of 33 patients, only 2 non-survivors patients had ≥10 mg/dl HDL and 31 patients (88.57%) had ≥10 mg/dl HDL (table 3).

The mean value of SOFA score was 23.47±6.520 in total patients, in survivors was14.00±5.715 & 26.38±3.070 SOFA score in non-survivors, which was statistical significant (P<0.0001***) in <10 mg/dl HDL level.

The mean value of SOFA score was 10.82±7.443 in total patients, in survivors was 9.710±6.176 & 28.00±1.24 SOFA score in non-survivors, which was statistical significant (P<0.0001***) in ≥10 mg/dl HDL level (table 4).

DISCUSSION

Present study showed that the maximum no. of cases were seen in 41-60 years of age group. The overall mean age of patients was 54.82 years in our study. In survivors the mean age of patients was 55.23 years and 53.87 years in non-survivors patients, which was statistical significant (P=0.7150). Which was statistical significant with Todi S[11] found that the mean age of the population was 58.17 years (SD 18.66). Another study done by Mitra Barati et al (2011)[12] found that the study population included 28 males and 42 females with mean (± standard deviation) age of years 73.6 ± 15.7 that 29 of them were in sepsis group and 41 of them in non-sepsis group. There wasn't any relationship between sex and mortality (p= 0.34), although by increasing age mortality leveled out (r=-0.58, p= 0.04).

Present study showed that the mean value of SOFA score was 23.47±6.520 in <10mg/dl HDL and 10.82±7.443 in ≥10 mg/dl HDL. But statistical non significant (P=0.5409).

Cintia M et al (2010)[13] concluded that HDL cholesterol may have a protective effect against sepsis. Each 1 mg dL increase in HDL decreased the odds of severe sepsis by 3% during hospitalization. The reduction of plasma CETP was associated with mortality.

Mitra Barati et al (2011)[12] found that the concentrations of total cholesterol (89.3 ± 33.6 vs 100.7 ± 25.3 mg/dl), HDL (20 ± 5.6 vs 30.2 ±8.7

mg/dl), and LDL (61.5 ± 18.7 vs 70.6 ± 14.5 mg/dl) showed significantly lower values in septic group but no difference could be find in triglyceride level (177.7 ± 28.7 vs 182.8± 45.9 mg/dl).

Sabari Das, Seema Bhargava et al (2011)[14] 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). The difference in the triglyceride level was not significant.

Another study done by van Leeuwen HJ et al (2003)[23] to conclude that the patients with severe sepsis, lipoprotein concentrations rapidly change and can be reduced to 50% of recovery concentrations. The pattern of early rapid decline is found primarily in the HDL and a slow recovery in both HDL and LDL fractions.

CONCLUSION

It can be concluded that HDL cholesterol on day of admission can be viewed as a significant predictor of mortality in patients with severe sepsis in medical ICU patients. Trend of HDL correlated with clinical outcome of patients. Raising trend favours improvement in clinical condition and decreasing trend implied worsening of the clinical condition.

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