

## “Association of the Mortality with the High Density Lipoprotein Level in the Patients with Sepsis in the ICU”

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### Abstract:

**Background:** The incidence of sepsis and the number of sepsis-related deaths are increasing, although the overall mortality rate among patients with sepsis is declining. Sowith 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 will be undertaken on the association of the mortality with the high density lipoprotein level in the patients with sepsis in the ICU.

**Material & Methods:** This is a prospective cohort study done on 50 patients with sepsis and septic shock admitted in intensive care unit in Mahatma Gandhi Medical College & hospitals, Jaipur, Rajasthan from January 2017-june 2018. 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. 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.

**Results:** Our study showed that the overall mean age of patients was 54.82 years. Gender wise distribution in survivors and non-survivors was statistical non significant. In non-survivors, the serum Bilirubin level was >1.2mg/dl. Which was statistical non –significant (P=0.0870 NS). The difference of mean value of serum Bilirubin was also non statistical significant (P=0.26). The serum Creatinine level was statistical non-significant in different stages of AKI. The mean value of serum Creatinine level was higher in non-survivors as compared to survivors and the mean value of HDL level at 1 day & day 5 was statistical significant in comparison between survivors and non-survivors (P<0.0001\*\*\* respectively).

**Conclusion:** We 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.

**Key Words:** HDL, Survivors, non-survivors, AKI, Sepsis, SOFA score

Date of Submission: 15-04-2019

Date of acceptance: 30-04-2019

### I. Introduction

Sepsis is a life-threatening condition that arises when the body's response to infection causes injury to its own tissues and organs.<sup>1</sup> Common signs and symptoms include fever, increased heart rate, increased breathing rate, and confusion.<sup>2</sup> There also may be symptoms related to a specific infection, such as a cough with pneumonia, or painful urination with a kidney infection.<sup>2</sup> 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.<sup>2</sup> 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.<sup>1</sup> Septic shock is low blood pressure due to sepsis that does not improve after reasonable amounts of intravenous fluids are given.

Previously, SIRS criteria had been used to define sepsis. If the SIRS criteria is negative, it is very unlikely the person has sepsis; if it is positive, there is just a moderate probability that the person has sepsis. According to SIRS, there were different levels of sepsis: sepsis, severe sepsis, and septic shock.<sup>3</sup>

In 2016 a new consensus was reached to replace screening by systemic inflammatory response syndrome (SIRS) with qSOFA.<sup>4,5</sup> However, the American College of Chest Physicians (CHEST) raised concerns that qSOFA and SOFA criteria may lead to delayed diagnosis of serious infection, leading to delayed treatment.<sup>5</sup> Although SIRS criteria can be too sensitive and not specific enough in identifying sepsis, SOFA also has its own limitation and is not intended to replace the SIRS definition. qSOFA has also been found to be poorly sensitive though decently specific for the risk of death with SIRS possibly better for screening.

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.<sup>6</sup>

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 %)<sup>7</sup>.

Lipoproteins have been implicated to play a role in innate immunity.<sup>8</sup> 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.<sup>9</sup> Mechanisms of low HDL in severe sepsis are multifactorial:

- 1) Neutralizing of toxic bacterial substances
  - 2) Suppression of lipoprotein synthesis and LCAT activity
  - 3) Rapid clearance of LPS bound HDL-C
  - 4) Decreased activity of ABC 1 activity
  - 5) Increased Human secretory phospholipase A2 (sPLA2) activity
  - 6) Dilutional effect due to resuscitation fluids.
- Sowith 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 will be undertaken on the association of the mortality with the high density lipoprotein level in the patients with sepsis in the ICU.

## **II. Material & Methods**

This is a prospective cohort study done on 50 patients with sepsis and septic shock admitted in intensive care unit in Mahatma Gandhi Medical College & hospitals, jaipur, rajasthan from January 2017-june 2018.

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:

### **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 erythematosus) and RA (Rheumatoid arthritis).
- Patients who were discharged against medical advise.

### **PRINCIPLE OF THE METHOD:**

Serum HDL level are measured by different methods. In our hospital serum HDL level is measured by enzymatic method using phosphotungstic acid MGC/12 reagent, 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 solubizes 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.

### III. Results

Our study showed that the overall mean age of patients was 54.82 years. In survivors the mean age of patients was 55.23 years and 53.87 years in non-survivors patients, which was statistical non significant (P=0.7150). Gender wise distribution in survivors and non-survivors was statistical non significant (table 1).

In correlation of HDL level with SOFA score was statistical significant in different etiological profile of patients (table 2).

The present study showed that the out of 50 patients, 43 patients had serum Bilirubin level was >1.2mg/dl and only 7 patients had 1.2mg/dl. In non-survivors, the serum Bilirubin level was >1.2mg/dl. Which was statistical non –significant (P=0.0870 NS). The difference of mean value of serum Bilirubin was also non statistical significant (P=0.26) (table 3). The serum Creatinine level was statistical non-significant in different stages of AKI. The mean value of serum Creatinine level was higher in non-survivors as compared to survivors (table 4).

Our study showed that the hospital mortality rate was nearly 75% in patients with a SOFA score of more than 21 (graph 1). The mean value of SOFA score was  $23.47 \pm 6.520$  in total patients, in survivors was  $14.00 \pm 5.715$  &  $26.38 \pm 3.070$  SOFA score in non-survivors, which was statistical significant (P<0.0001\*\*\*) in <10 mg/dl HDL level (table 5).

Our study showed that the mean value of HDL level at 1 day & day 5 was statistical significant in comparison between survivors and non-survivors (P<0.0001\*\*\* respectively).

### IV. Discussion

Our 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). Gender wise distribution in survivors and non-survivors was statistical non significant. Which was statistical significant with Todi S<sup>7</sup> found that the mean age of the population was 58.17 years (SD 18.66). Another study done by Mitra Barati et al (2011)<sup>10</sup> found that the study population included 28 males and 42 females with mean ( $\pm$  standard deviation) age of years  $73.6 \pm 15.7$  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).

Out of 36, 15 patients had dengue followed by 10 cases had scrub typhus, 7 cases had swine flue and only 4 patients had malaria. Out of 14 patients had growth in culture, pseudomonas, E.coli & Staphylococcus aureus (4 cases each respectively) and only 2 cases had actinobacter growth.

Seyed Ali JavadMousav et al (2003)<sup>11</sup> found only 38.4% of them had positive blood culture in septic patients. The most common organism was gram negative enteric pathogen (Klebsiella and E. coli ).

Our study showed that the difference of mean value of serum Bilirubin, serum Creatinine, platelets, SOFA score was statistical significant (P<0.0001\*\*\* each respectively) in between survivors & non-survivors. The WBC count was higher in non-survivors group, which was statistical significant (P<0.05\*) and the mean value of SOFA score was  $23.47 \pm 6.520$  in <10mg/dl HDL and  $10.82 \pm 7.443$  in  $\geq 10$  mg/dl HDL. But statistical non significant (P=0.5409).

Cintia M et al (2010)<sup>12</sup> 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)<sup>10</sup> found that the concentrations of total cholesterol ( $89.3 \pm 33.6$  vs  $100.7 \pm 25.3$  mg/dl), HDL ( $20 \pm 5.6$  vs  $30.2 \pm 8.7$  mg/dl), and LDL ( $61.5 \pm 18.7$  vs  $70.6 \pm 14.5$  mg/dl) showed significantly lower values in septic group but no difference could be find in triglyceride level ( $177.7 \pm 28.7$  vs  $182.8 \pm 45.9$  mg/dl).

Sabari Das, Seema Bhargava et al (2011)<sup>13</sup> 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.

Sébastien Tanaka et al (2017)<sup>14</sup> concluded that lipid profile was totally different between sepsis and trauma in ICU patients: HDL levels were low in septic patients, whereas their concentration was not altered in trauma patients. This major difference reinforces the necessity to explore the therapeutic potential of HDL in sepsis.

Our study showed that the mean value of HDL level at 1 day was  $19.41 \pm 9.543$  mg/dl, in survivors  $24.21 \pm 7.013$ mg/dl & in non-survivors was  $8.207 \pm 2.676$  mg/dl. The difference of mean was statistical significant (P<0.0001\*\*\*). The mean value of HDL level at 5 day was  $23.90 \pm 11.24$ mg/dl, in survivors  $29.97 \pm 7.334$  mg/dl & in non-survivors was  $9.733 \pm 2.068$  mg/dl. The difference of mean was statistical significant (P<0.0001\*\*\*).Naresh Monigari et al (2015)<sup>15</sup> observed that significant association was seen between mortality and <10 mg/dl. HDL level on day 1. Relative risk of death in patients with day 1 HDL value<10mg/dl was 7.01

times higher than patients with day 1 HDL value >10mg/dl. Another study done by Sébastien Tanaka et al (2017)<sup>14</sup> found poor outcome defined as death or a SOFA score >6 at day 3 was associated with lower HDL levels (median [IQR] = 0.20 mmol/l [0.11–0.41] vs. 0.35 mmol/l [0.19–0.86] in patients with poor outcome versus others; *P* = 0.03).

### V. Conclusion

We 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. Rising trend favours improvement in clinical condition and decreasing trend implied worsening of the clinical condition.

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**Table 1:** Shows baseline characteristics of survivors and non survivors.

		Total patients (Mean±SD)	Survivors (N=35)	Non-survivors (N=15)	P-value
Age (yrs)		54.82±11.91	55.23±12.32	53.87±11.22	0.7150 NS
Gender	Male	41	29	12	1.000 NS
	Female	9	6	3	

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

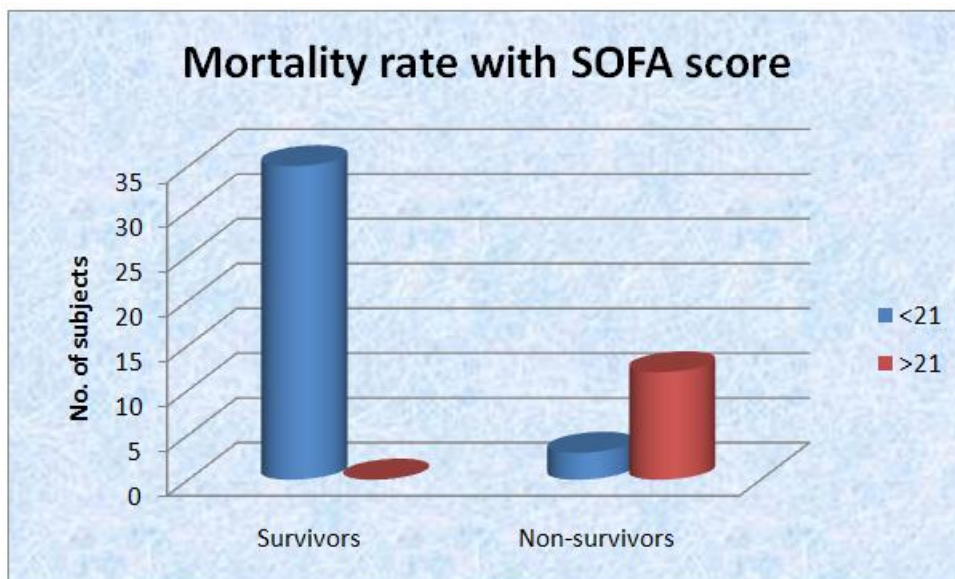
Etiology	HDL value (Mean+SD)	SOFA score (Mean+SD)	P value
Dengue	26.51±5.759	9.333±5.715	<0.0001***
Scrub typhus	27.00±2.00	8.750±3.50	0.0001**
Swine flue	21.97±8.779	11.20±8.217	0.0110*
Malaria	18.57±7.976	13.00±6.298	0.1726 NS

**Table 3:** Shows biochemical analysis of survivors and non survivors.

Serum Bilirubin	Total no of patients (n=50)	Survivors (n=35)	Non-survivors (n=15)	P-value
Serum bilirubin normal or <1.2mg/dl	7	7	0	0.0870
Serum bilirubin>1.2mg/dl	43	28	15	
Total patients (Mean±SD)	6.004±4.726	3.229±2.262	9.36±1.287	0.26

**Table 4:** Shows serum Creatinine level of survivors and non survivors patients.

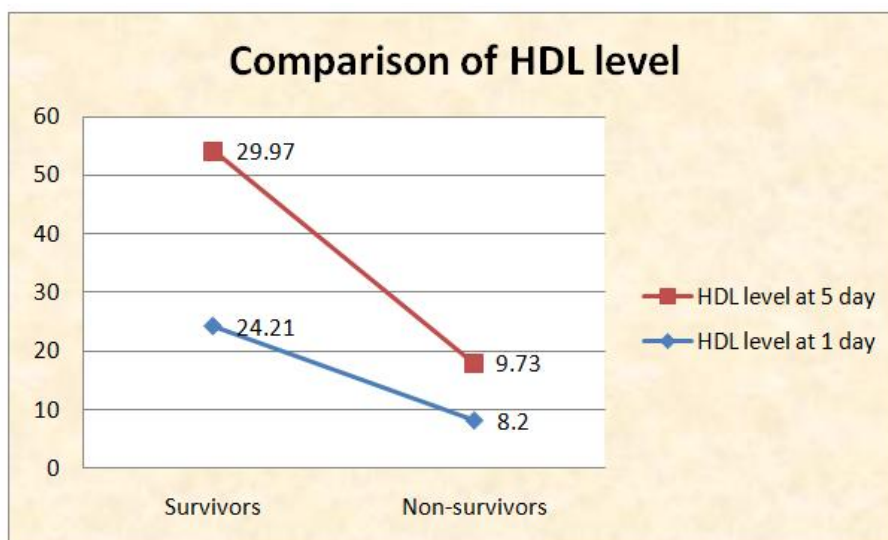
Serum Creatinine level in stages of AKI	No of patient	Survivors (N=35)	Non-survivors (N=15)	P-value
Stage 1	10	1.256±0.4335	1.605±0.1636	0.1375
Stage 2	03	2.869±0.3219	2.905±0.2163	0.8350
Stage 3	30	4.000±0.3606	5.171±1.072	0.1104



**Graph 1:** Mortality rate with SOFA score

**Table 5:** 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***



**Graph 2:** Comparison of day of admission HDL and day 5 HDL cholesterol with outcome

Dr. Sumit Patter. “Association of The Mortality with The High Density Lipoprotein Level in The Patients with Sepsis in The ICU.” IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 18, no. 04, 2019, pp 01-05.