

# Prognostic Value of Serum Cholesterol and Triglyceride in Septic and Non-septic Patients: Randomized Double-blinded Study

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## Abstract

**Aims:** Is to evaluate the difference between the level of serum cholesterol and triglyceride in septic and non-septic patients and to find a correlation between the level of cholesterol and triglyceride and Acute Physiology and Chronic Health Evaluation Score and quick Sequential Organ Failure Assessment score.

**Materials and Methods:** 95 patients admitted to the SICU, septic patients (group S, n=50) or non-septic patients (NS, n=45). Main outcome measures: length of ICU stay, 28-day mortality, days on mechanical ventilation, (APACHE II) scores, (qSOFA) scores, serum cholesterol, and triglyceride on days 0 and on 1<sup>st</sup>, 3<sup>rd</sup>, 7<sup>th</sup>, 10<sup>th</sup> and 14<sup>th</sup> day.

**Result:**

**Cholesterol level (mg/dL)**

**Day 0:** It was statistically significant lower in septic group (S) compared to the non-septic group (NS); it was  $119.4 \pm 29.33$  versus  $131.2 \pm 35.37$  (p value=0.037).

**Day 1:** It was statistically significantly lower in the septic group (S):  $103.6 \pm 29.19$  than the non-septic group (NS):  $123.56 \pm 36.50$  (p value <0.001).

**Day 3:** It was statistically significantly lower in the septic group (S)  $80.7 \pm 26.87$  than in the non-septic group (NS)  $124.84 \pm 32.4$  (p value <0.001).

**Triglyceride level (mg/dL):**

**Day 1:** Was statistically significantly higher in the septic group (S):  $151.5 \pm 54.79$ , than the non-septic group (NS):  $112.14 \pm 33.02$ , (p value <0.001).

**Day 3:** It was statistically significant higher in the septic group (S):  $185.1 \pm 43.1$  than the non-septic group (NS):  $113.5 \pm 39.56$ , (p value <0.001).

**Conclusion:** Cholesterol levels decreased markedly and triglyceride levels increased in patients with sepsis compared to non-septic patients, in the septic patients there was increasing in length of ICU stay, higher qSOFA, and APACHE II scores.

**Keywords:** Cholesterol; Triglyceride; Sepsis; Non-septic patient

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## Introduction

Sepsis is the most common cause of admission to the Intensive Care Unit (ICU) [1]. The incidence of sepsis is increasing in spite

of the advanced efforts for management of sepsis [2]. Sepsis is associated with severe metabolic alterations, including insulin resistance and increased levels of Triglycerides (TGs) and lower level of both high and Low-density Lipoproteins (LDL) [3].

Several mechanisms could explain hypocholesterolemia in critical illness and sepsis as the disturbance between synthesis and utilization of plasma lipids, usage of lipids to restore damaged cell membranes, and the interaction of bacterial toxins with lipids [1]. The levels of High-density Lipoproteins (HDLs) are reduced in sepsis/septic shock, and the magnitude of this reduction is positively correlated with the severity of the illness [4]. Lipopolysaccharide (LPS) is the major component of the outer membrane of Gram-negative bacteria has a crucial role in the initiation of sepsis [5,6]. It was suggested that serum cholesterol might be a useful prognostic marker of sepsis [7]. The prognostic value of changes in lipoprotein profile is still not confirmed [8]. The inclusion of lipid values in clinical risk assessment scores of critically ill patients has been advocated [9]. There are controversies related to the concentration of lipids because most of these studies were conducted in Western populations [5,10,11].

An early prognostic indicator to identify patients at highest risk for mortality in the ICU was recommended [12] also there are controversies between the results of previous studies in critically ill patients about the value of changes in cholesterol levels, and HDL as predictors of severity of illness by some investigators [10,13,14,] while other studies could not confirm this association [6,15].

### The aim of the study

This observational study was designed to evaluate the difference between the level of serum cholesterol and triglyceride in septic and non-septic patients in the surgical ICU and to find correlation between the level of serum cholesterol and triglyceride and both Acute Physiology And Chronic Health Evaluation Score (APACHE) II and quick Sequential Organ Failure Assessment (qSOFA) score and their relation to mortality in Egyptian population.

## Materials and Methods

### Study design

This study was conducted in the surgical intensive care unit (SICU) of Beni-Suef University hospital between January 2018 and December 2018 after approval of the local ethics and research committee (The FM-BSU REC) and obtaining consents from the patients or their guardians. This study was registered at ClinicalTrials.gov, ClinicalTrials.gov Identifier: NCT03359369.

### Eligibility criteria

The study population included the patients (age range between 20 and 70 years) of both sexes (septic and non-septic patients, e.g., trauma patients, post-surgical patients).

### Exclusion criteria

1. Pregnancy
2. ICU readmission
3. Dyslipidemia
4. Patients with liver disease

5. Concomitant use of immunosuppressive therapy
6. Using statin or steroid ( $\geq 15$  mg/day) within the previous seven days
7. Patients who had been treated with corticosteroid therapy for septic shock before admission to ICU
8. Patients sedated by propofol

### Management of the patients in the SICU, starting from the day of admission

Patients admitted to SICU either postsurgical patients or trauma patient received from the emergency department. Some patients were already intubated and ventilated, and on arrival to SICU, they were connected to the mechanical ventilator. Other patients initially did not need intubation or ventilation, and during the course of the patient stay in the SICU some of these patients deteriorated and needed intubation and mechanical ventilation or administration of vasoactive drugs. For all patients monitors were connected including (Noninvasive Blood Pressure (NIBP), Electrocardiogram (ECG), pulse Oximetry, temperature monitoring) and baseline readings were recorded. Central venous line and arterial line were inserted under complete aseptic technique also urinary catheter was inserted for urine output monitoring.

Inotropes and vasopressors as dopamine, epinephrine and norepinephrine were used if needed and the rate of infusion was adjusted according to the blood pressure. Full investigations were done including (Complete Blood Count (CBC), coagulation profile, serum electrolytes, liver function tests, kidney function tests, Arterial-Blood Gas (ABG), urine analysis). Radiological examination as chest X-ray was done and pelvic-abdominal u/s was done if needed. For the patient with sepsis, cultures were done (urine, sputum, blood culture) and also cultures were done from the suspected source of infection (e.g., from the surgical drain in case of alleged abdominal or pelvic as the source of infection following surgery), and initially empirical antibiotics were started. The patients were randomly assigned into two groups, septic patients (group S, n=50) according to established consensus definitions [16] or non-septic patients (NS, n=45) as post-surgical and trauma patients.

### The following data were recorded by senior SICU resident who was unaware of the study protocol

Age, sex, the cause of SICU admission, administration of vasoactive drugs, length of SICU stay, 28-day mortality, days on mechanical ventilation, Acute Physiology, and Chronic Health Evaluation II (APACHE II) scores [17], Quick Sequential Organ Failure Assessment (qSOFA) scores. The score ranges from 0 to 3 points. The presence of 2 or more qSOFA points near the onset of infection is associated with a higher risk of death or prolonged intensive care unit stay [18]. Serum cholesterol and triglyceride on days 0 (ICU admission), 1<sup>st</sup>, 3<sup>rd</sup>, 7<sup>th</sup>, 10<sup>th</sup> and 14<sup>th</sup> day.

### Statistical methods

**Sample size:** After a pilot study with five patients in each group,

the detectable difference in cholesterol level on the third day between the two groups was 46 mg/dL, and the difference in the standard deviation was 55. Accordingly, the calculated minimum sample size was 39 patients in each group with 95% power and  $\alpha$  level was 0.05 using a t-test, Biostatistics, version 3.01 was used to calculate the sample size. The number was increased to 50 patients in each group in case of the drop in any case.

**Data analysis:** Data were statistically described in terms of mean  $\pm$  standard deviation ( $\pm$  SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student-t-test for independent samples. For comparing categorical data, Chi-square ( $\chi^2$ ) test was performed. The exact test was used instead when the expected frequency is less than 5. Correlation between various variables was done using Pearson moment correlation equation for linear relation of normally distributed variables and Spearman rank correlation equation for non-normal variables/non-linear monotonic relation p values less than 0.05 was considered statistically significant. The correlation was done between APACHE II score and 28 days mortality and cholesterol and triglyceride level in day 0 and also correlation was done between qSOFA score and 28 days mortality and cholesterol and triglyceride level in day 0 for both septic and non-septic group. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

## Results

In this study, 100 patients were assessed for eligibility, allocated into 2 groups, septic group, and non-septic group, 5 patients were excluded from the non-septic group as they died before the third day of the SICU stay.

### Demographic data

There was no statistically significant difference regarding the age and sex of the patients between the septic and non-septic groups (Table 1).

**Table 1** Demographic Data; Data are presented as mean  $\pm$  SD, numbers (%).

Variable	Group S (n=50)	Group NS (n=45)	p value
Sex (M/F)	30/20 (60%/40%)	31/14 (69%/31%)	0.838
Age (Years)	48.96 $\pm$ 5.48	49.6 $\pm$ 7.34	0.728

Group S=Septic Group; Group NS=Non Septic Group  
p values  $\leq$  0.05 are considered statistically significant

**Table 2.** Source of sepsis in the patients of the septic group; Data are presented as number (%).

Source of sepsis	Number of patients
Respiratory tract	20 (40%)
Urinary tract	13 (26%)
Gastroenterological	7 (14%)
Wound infection	5 (10%)
Soft tissue infection	2 (4%)
Unknown	3 (6%)
Total	50

The source of sepsis in the patient of the septic group is presented in Table 2.

The diagnosis of the patients is presented in Table 3.

APACHE II score was statistically significantly higher in the septic group (S): [32(24-48)] than the non-septic group (NS) [8.5(2-35)], (p value <0.001).

qSOFA score was statistically significantly higher in septic group (S) [2(2-3)] than the non-septic group (NS) [1(0-3)], (p value < 0.001) (Table 4).

The number of patients needed vasoactive drugs was statistically significantly higher in the septic group (S) 33 patients (66%) than the non-septic group (NS) 4 patients (8.8%), (p value <0.001) (Table 5).

28 Days mortality was statistically significantly higher in the septic group (S) 88% (44 patients) than the non-septic group (NS) 17.77% (8 patients); (p-value <0.001); (Table 5).

**Table 3** The diagnosis of the patients; Data are presented as number (%).

Diagnosis of patient	Number of patients in the Septic group (S)	Number of the patient in the Non-septic group (NS)
Postoperative	38 (76%)	37 (82.2%)
CNS surgery	11 (22%)	4 (9%)
Abdominal surgery	7 (14%)	3 (6.7%)
Uro-surgery	4 (8%)	6 (13.3%)
Vascular surgery	4 (8%)	3 (6.7%)
Malignancy surgery	7 (14%)	5 (11%)
Orthopedic surgery	1 (2%)	8 (17.8%)
Gynecological surgery	1 (2%)	3 (6.7%)
ENT surgery	2 (4%)	1 (2%)
Plastic surgery	1 (2%)	4 (9%)
Trauma	12 (24%)	8 (17.8%)
<b>Total</b>	<b>50</b>	<b>45</b>

**Table 4** Acute physiology and chronic health evaluation II (APACHE II) score and quick sequential organ failure assessment (qSOFA) score: Data are presented as median (range).

Variable	Group S (n=50)	Group NS (n=45)	p value
APACHE II	32 (24-48)*	8.5 (2-35)	<0.001
qSOFA	2 (2-3)*	1 (0-3)	<0.001

Group S=Septic Group; Group NS=Non Septic Group  
\*p values <0.05 are considered statistically significant

**Table 5** Administration of vasoactive drugs, 28-days Mortality, length of Surgical Intensive Care Unit (SICU) stay, and days on Mechanical Ventilation, Data are presented as mean  $\pm$  SD, numbers (%).

Variable	Group S (n=50)	Group NS (n=45)	p value
Administration of vasoactive drugs	33 (66%)*	4 (8.8%)	<0.001
28 day Mortality	44 (88%)*	8 (17.7%)	<0.001
Length of Surgical Intensive Care Unit (SICU) stay	13.9 $\pm$ 9.3*	4.4 $\pm$ 1.9	<0.001
Days on Mechanical ventilation (MV)	13.9 $\pm$ 9.3*	0.76 $\pm$ 1.8	<0.001

Group S=Septic Group  
Group NS=Non-Septic Group \*p values  $\leq$  0.05 are considered statistically significant

The length of SICU stay was statistically significantly longer in the septic group (S)  $13.9 \pm 9.3$  than the non-septic group (NS)  $4.4 \pm 1.9$ , (p value <0.001); (Table 5).

Days on mechanical ventilation were statistically significantly longer in the septic group (S)  $13.9 \pm 9.3$  than the non-septic group (NS);  $0.76 \pm 1.8$ , (p value <0.001); (Table 5).

**Cholesterol level (mg/dL): Day 0:** It was  $119.4 \pm 29.33$  in the septic group (S) versus  $131.2 \pm 35.37$  in the non-septic group (NS) and it was statistically significantly lowering the septic group versus the non-septic group (p-value=0.037).

**Day 1:** Cholesterol level in day 1 was statistically significantly lower in the septic group (S)  $103.6 \pm 29.19$  versus the non-septic group (NS)  $123.56 \pm 36.5$  (p-value <0.001).

**Day 3:** Cholesterol level in day 3 was statistically significantly lower in the septic group(S)  $80.7 \pm 26.87$  than in the non-septic group (NS)  $124.84 \pm 32.4$  (p-value <0.001) (Table 6).

**Triglyceride level (mg/dL): Day 0:** Triglyceride level in day 0 showed no statistically significant difference between the two groups (p value=0.08) it was  $134.94 \pm 73.06$  in the septic group (S) and it was  $116.8 \pm 52.05$  in the non-septic group (NS).

**Day 1:** Triglyceride level in day 1 was statistically significantly higher in the septic group (S)  $151.5 \pm 54.8$  than the non-septic group (NS)  $112.14 \pm 33.02$  (p value <0.001).

**Day 3:** Triglyceride level in day 3 was statistically significant higher in the septic group (S)  $185.1 \pm 43.2$  than the non-septic group (NS)  $113.5 \pm 39.56$  (p value <0.001) (Table 7).

For the non-septic group the length of Surgical Intensive Care Unit (SICU) stay was  $4.4 \pm 1.9$  days and the patients were discharged to the ward, so we continue following up the cholesterol and triglyceride levels; cholesterol level (mg/dL) was increasing it was  $125.28 \pm 34.05$ ,  $127.71 \pm 26.65$  and  $129.77 \pm 24.45$  on day 7, 10 and 14 respectively.

Triglyceride level (mg/dL) was  $115.04 \pm 42.35$ ,  $114.47 \pm 43.00$  and  $114.27 \pm 43.4$  on days 7, 10 and 14 respectively, (Figure 2).

For the septic group 11 patients died before the tenth day, so cholesterol and triglyceride levels were measured for the

remaining 39 patients; cholesterol level (mg/dL) was markedly reduced it was  $62.07 \pm 16.10$ ,  $59.97 \pm 16.24$  and  $56.33 \pm 14.4$  on day 7, 10 and 14 respectively, The triglyceride level was increasing it was  $205.97 \pm 30.25$ ,  $236.52 \pm 32.48$  and  $286.64 \pm 30.46$  on days 7, 10 and 14 respectively (Figure 1).

**Regarding the correlation in the septic (S) and non-septic group (NS)**

**For the septic group (S):** There was no significant correlation between APACHE II score and 28 days mortality (p-value=0.933, correlation coefficient=-0.012).

There was a weak negative correlation between APACHE II score and cholesterol level on the day 0 of admission (p-value=0.030, correlation coefficient=-0.308) (Figure 3).

There was no significant correlation between APACHE II score and triglyceride level on the day 0 of admission (p-value=0.0541, correlation coefficient=-0.089), (Table 8).

There was no significant correlation between qSOFA score and 28 days mortality (p-value=0.517, correlation coefficient=-0.094), (Table 8).

There was no significant correlation between qSOFA score and

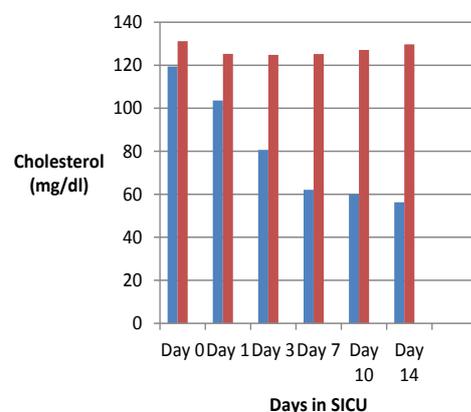


Figure 1 Cholesterol level (mg/dL) of the study groups.

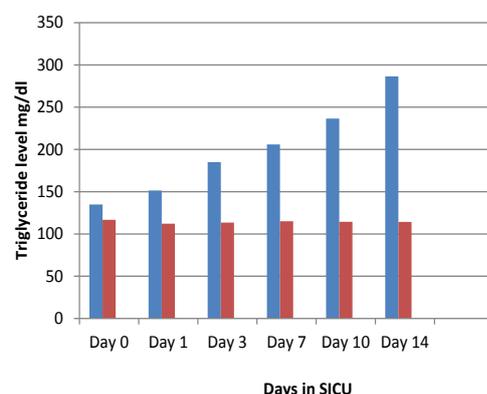


Figure 2 Triglyceride level (mg/dL) of the study groups.

Table 6 Cholesterol level (mg/dL): Data are presented as mean ± SD

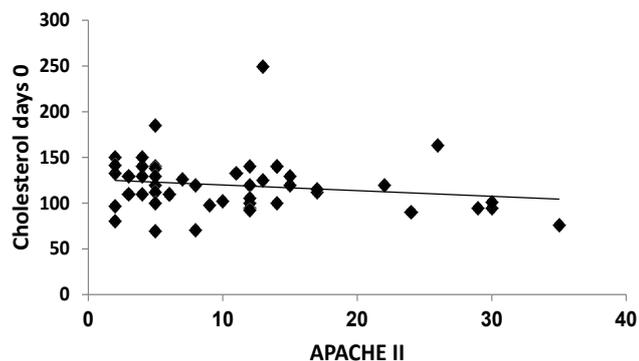
Cholesterol level (mg/dL)	Group S (n=50)	Group NS (n=45)	p value
Day 0	119.4 ± 29.33*	131.2 ± 35.37	0.037
Day 1	103.6 ± 29.19*	123.56 ± 36.5	<0.001
Day 3	80.7 ± 26.87*	124.84 ± 32.4	<0.001

Group S= Septic Group; Group NS=Non Septic Group  
\*p values <0.05 are considered statistically significant

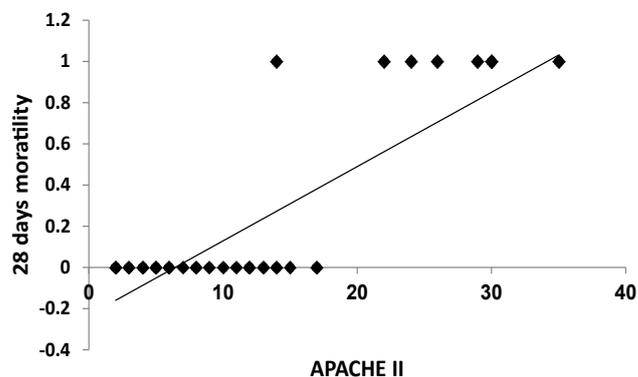
Table 7 Triglyceride level (mg/dL): Data are presented as mean ± SD.

Triglyceride level (mg/dL)	Group S (n=50)	Group NS (n=45)	p value
Day 0	134.94 ± 73.06	116.8 ± 52.05	0.163
Day 1	151.5 ± 54.79*	112.14 ± 33.02	<0.001
Day 3	185.1 ± 43.2*	113.5 ± 39.56	<0.001

Group S= Septic Group; Group NS=Non Septic Group  
\*p values < 0.05 are considered statistically significant



**Figure 3** Correlation between APACHE II score and cholesterol day 0 in the septic group (S).



**Figure 4** Correlation between APACHE II score and the 28 days mortality in the non-septic group (NS).

**Table 8** Correlations in the septic (S) and non-septic groups (NS); Values represent the correlation coefficient (p value).

	Group S (n=50)		Group NS (n=45)	
	APACHE II	qSOFA	APACHE II	qSOFA
28 days Mortality	-0.012	0.094	0.813	0.804
Cholesterol 0	0.933	0.517	(< 0.001)	(< 0.001)
TGs 0	-0.308	-0.107	0.085	0.034
	0.03	0.458	0.558	0.815
	-0.089	0.096	-0.039	-0.056
	0.541	0.508	0.786	0.699

cholesterol level on the day 0 of admission (p-value=0.458, correlation coefficient=-0.107), (**Table 8**).

There was no significant correlation between qSOFA score and triglyceride level on the day 0 of admission (p-value=0.508, correlation coefficient=-0.096), (**Table 8**).

**For the non-septic group (NS):** There was a strong positive correlation between APACHE II score and 28 days mortality (p value <0.001, correlation coefficient=0.813) (**Figure 4**).

There was no significant correlation between APACHE II score and cholesterol level on the day 0 of admission (p-value=0.558, correlation coefficient=0.085), (**Table 8**).

There was no significant correlation between APACHE II score and triglyceride level on the day 0 of admission (p-value=0.786, correlation coefficient=-0.039), (**Table 8**).

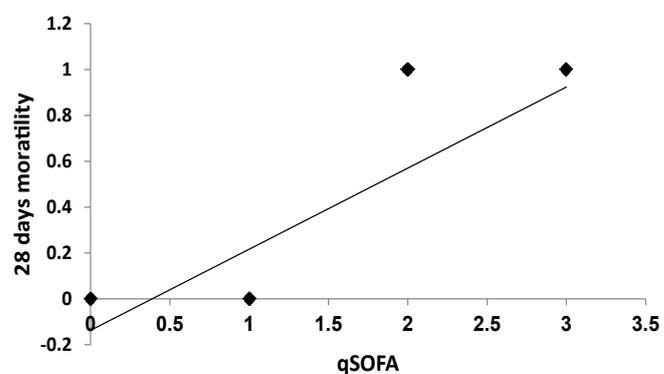
There was a strong positive correlation between qSOFA score and 28 days mortality (p value <0.001, correlation coefficient=0.804) (**Figure 5**).

There was no significant correlation between qSOFA score and cholesterol level on the day 0 of admission (p-value=0.815, correlation coefficient=0.034).

There was no significant correlation between qSOFA score and triglyceride level on the day 0 of admission (p-value=0.699, correlation coefficient=-0.056); (**Table 8**).

## Discussion

The results of the present study showed that serum cholesterol



**Figure 5** Correlation between qSOFA score and the 28 days mortality in the non-septic group (NS).

levels decreased markedly, and triglyceride levels increased in patients with sepsis compared to non-septic patients, and there was a significant difference between septic and non-septic patients. The septic patients had a higher rate of mortality than the non-septic patients, in septic patients there was increasing in length of SICU stay, administration of vasoactive drugs, days on mechanical ventilation, higher qSOFA, and APACHE II scores compared to non-septic patients. Patients with severe sepsis have low levels of cholesterol and high levels of triglycerides [3]. Hypertriglyceridemia is due to reduced plasma Triglyceride (TG) clearance rate [16]. An increase in triglyceride levels during sepsis might have beneficial effects on the host because triglyceride-rich lipoproteins bind and neutralize the effects of endotoxin [19]. The hypocholesterolemia of acute illness is associated with a moderate increase in triacylglyceride levels [20]. Mechanisms are an imbalance between synthesis and utilization of plasma lipids, usage of lipids to restore damaged cell membranes [21].

Cetinkaya et al. [5], observed that patients with sepsis had high TG levels and that the TG level 150 mg/dL at 0 hours (onset of sepsis) were a significant predictive marker of sepsis mortality rate. Barati et al. [9] investigated changes in plasma lipid levels in patients with sepsis found markedly lower levels of cholesterol, LDL, and HDL on admission and ten days later, which was online with the presented study but no difference could be found

in triglyceride level which also went in line with the results of the given research, in their study on non-septic patients, total cholesterol level increased on 10 days than the day of admission, triglyceride level showed no significant change it was  $182.8 \pm 45.9$  mg/dL and after 10 days it was  $181.4 \pm 40$  mg/dL, in the presented study triglyceride level was  $116.8 \pm 52.6$  mg/dL on day 0,  $115.04 \pm 42.35$ ,  $114.47 \pm 43.00$  and  $114.27 \pm 43.40$  on day 7, 10 and 14 respectively. A study by Lekkou et al. [22] included 50 patients with severe sepsis. Sepsis survivors had significantly higher HDL-C concentrations than non survivors. They concluded that low cholesterol and lipoprotein concentrations are detected in septic patients especially in individuals with poor prognosis, which went in line with the results of the presented study. Jeyasuriya et al. [23] concluded that ICU patients showed an increasing trend of total cholesterol levels had a higher rate of survival. Lee et al. [24] concluded that persistent hypocholesterolemia ( $<61$  mg/dL) independently predicted in-hospital mortality, after emergency GI surgery in patients with diffuse peritonitis. Abdollahi et al. [25] showed that patients with severe sepsis and septic shock had lower levels of serum lipid compared with patients without sepsis. Tanaka et al. [26] concluded that HDL levels were low in septic patients, whereas their concentration was not changed in trauma patients. The mortality was not associated with lipid levels in the sepsis group, and a significant negative correlation was found between HDL concentration and the length of ICU stay in the group of survivor septic patients at ICU discharge. Whitney [27] reported that total cholesterol might be a superior prognostic marker of mortality in patients with sepsis compared to Procalcitonin (PCT) and C-reactive Protein (CRP). Das, et al [28] ., also observed that the cholesterol level at the onset of sepsis (0 hour) could be an indicator of survival. The cholesterol level was changed and there was a positive association between low serum cholesterol levels, and increased mortality which agreed with the results of the presented study. Chiarla et al. [29] reported that hypocholesterolemia is often paralleled by low TG levels in surgical, sepsis, and critical illness patients. Fahila et al. [30] showed that the triglyceride value in the sepsis group was  $120 \pm 5.1$  mg/dL on day 1, non-sepsis  $117.53 \pm 36.37$  mg/dL. On the fifth day, in the sepsis group triglyceride values were  $124.2 \pm$

$50.29$  mg/dL and the non-sepsis group triglyceride values  $134.03 \pm 68.12$  mg/dL. They found no significant correlation between the severity of sepsis and triglyceride value in the patient with sepsis. Vyroubala et al. [31] reported very low levels of total cholesterol in polytrauma, after extensive surgery, in severe infections, in severe hypovolemic shock. Dunham et al. [32] concluded that hypocholesterolemia was observed after severe injury. Discharged patients had improved cholesterol levels, whereas dying patients had progressive hypocholesterolemia which went online with the results of the presented study. Wilson [33] reported that hypocholesterolemia observed following trauma. Lüthold et al. [34] showed that HDL-C and total cholesterol levels were lower in critically ill infected patients than they were in non-infected patients and this agrees with the results of the presented study and that no significant difference was seen in the serum TG level in critically ill infected patients when compared with non-infected critically ill patients which disagreed with the results of the presented study.

## Conclusion

Cholesterol levels decreased markedly and triglyceride levels increased in patients with sepsis compared to non-septic patients and there was a significant difference between septic and non-septic patients for cholesterol and triglyceride levels. The septic patients had a higher rate of mortality than the non-septic patients, in septic patients there was increasing in length of ICU stay, administration of vasoactive drugs, days on mechanical ventilation, higher qSOFA, and APACHE II scores compared to non-septic patients.

## Recommendation

Since the mechanism which alters cholesterol and triglyceride level in the critically ill patients is not clearly identified so further studies in larger populations with lipid monitoring for longer duration are recommended.

## Competing Interests

None declared.

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