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Changes in plasma lipid and in-hospital deaths in patients with sepsis

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Abstract

Background: Lipid profiles are infrequently measured in clinical management of sepsis patients. Sepsis leads to significant alterations in the metabolism of lipids. The aim of the present study was to determine whether changes in plasma lipid concentrations during sepsis treatment were associated with clinical outcome.

Methods: In this study, 74 adult septic patients were included in this prospective observational study from January to December 2017. Patients taking lipid lowering agents were excluded. A detailed medical history was obtained and clinical examination was performed. Serum total cholesterol (STC) and its fractions [low-and high-density lipoprotein] and triglyceride levels were measured in the morning of the first day after admission and then once weekly. The primary outcomes of the study were in-hospital mortality, and hospital stay and hypocholesterolemia were defined as STC levels < 50 mg/dL. Manne-Whitney U and chi-squared tests were used for data analysis, and significance level was set at $p<0.05$.

Results: In this study, 78.4% (CI 95%: 67.3-87.1) of patients had hypocholesterolemia. During the study period, 21.6% (CI 95%: 12.9- 32.7) of patients died. All lipid (except TG) concentrations continuously decreased in deceased sepsis patients but increased in recovering patient (p value for STC (p=0.004), LDL (p=0.006), HDL (p=0.010), and TG (p=0.052)). The serum lipids concentration was not associated with length of hospital stay (p value for STC (p=0.524), LDL (p=0.813), HDL (p=0.799) and TG (p=0.581)).

Conclusion: In this study it was found that the additional decline of lipid profile was significantly associated with increased mortality rate of sepsis patients. Thus, the clinically termed 'the lipaemia of sepsis' is not true in all situations.

Keywords: Cholesterol, Lipoprotein, LDL, HDL, Triglyceride, Sepsis, Emergency service, Hospital

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Introduction

Sepsis is a frequent cause of admission and a frequent fatal condition characterized by a dysregulated inflammatory response to microbial infection and altered metabolic state, leading to tissue injury and organ failure (1). Several

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↑What is "already known" in this topic:
Lipid profiles are infrequently measured in clinical management of sepsis patients. The majority of previous studies focused on the comparative analysis of mean values of serum lipids between survivor and nonsurvivor groups or between sepsis and severe sepsis groups.

→What this article adds:
In this study, serum lipid levels were analysed over time and the association between lipid levels and survival in patients with sepsis was examined. The prevalence of hypocholesterolemia in sepsis patients was significantly higher than in the general population. However, absolute STC, LDL, HDL, and TG levels at the time of admission was not suitable to predict mortality in sepsis patients. The data of this study support the hypothesis that higher decline of serum total cholesterol and other lipid profile during hospital stay are associated with a higher mortality in sepsis patients. Thus, the clinically termed 'the lipaemia of sepsis' is not true in all situations.

reports have revealed the incidence of sepsis and severe sepsis increasing in excess of the growth of the population (2). Many studies showed dramatic lipid profile changes when individuals became ill (3, 4). These alterations have been described in patients with a wide range of disorders, including infection (4). During the course of infection, significant changes are observed in patients' serum profile of lipids (5). Early reports have described a cytokine-induced hyperlipoproteinaemia, the so called "lipaemia of sepsis", which was originally thought to represent the mobilization of lipid stores, especially serum total cholesterol and triglyceride (6, 7). However, some studies have challenged this concept in the presence of severe infection and indicated that total and high-density lipoprotein cholesterol (HDL-C) levels are commonly decreased, with varying changes in triglyceride (TG) levels in sepsis; they also noted that the magnitude of the changes seems to reflect the severity of inflammation (6, 8, 9). Lipid profiles are rarely measured or interpreted in clinical management of sepsis and are not mentioned in the Surviving Sepsis Campaign guidelines (3, 10). Thus, this longitudinal study aimed to determine whether change in plasma lipid concentrations during sepsis treatment were associated with clinical outcome (death and duration of admission).

Methods

Setting

This prospective observational study was performed at Bou-Ali University Hospital, a 250-bed tertiary center with a referral population of 1 270 000 in Qazvin province, northern Iran. The study participants were recruited from the sepsis patients who referred to the Emergency Department (ED) from January to December 2017.

Patients

Informed consent was obtained from all participants and their caregivers. A total of 74 adult sepsis patients (aged 18 years or older) who referred to the ED were enrolled. Patients were interviewed at the ED or within the first 24 hours after hospital admission. The following data were gathered: smoking status; sex; age comorbidities abstracted from the patient history including hypertension, diabetes mellitus (DM), ischemic heart disease, neurologic disease (cerebrovascular accident (CVA) and dementia, renal failure, and chronic obstructive pulmonary disease. Detailed medical history was obtained and clinical examination performed. Patients taking lipid lowering agents were excluded. During the hospital stay, information on the final diagnosis and therapeutic procedures was recorded, including starting and ending dates. The criteria for including the patients into the case group were having 2 to 4 of the following signs, which are considered as septic: hypo or hyperthermia (temperature <36 or >38 ℃), tachycardia (pulse rate of 90 or more per minute), tachypnea (respiratory rate (RR) above 20 per minute), increased or decreased total white blood cells (WBC) counts (WBC >12000 or <4000), and identification of an infection site. The term sepsis applies to patients who meet Systemic Inflammatory Response Syndrome (SIRS) criteria in response to a known source of infection (11). Information on variables associated with sepsis (eg, microorganism in blood culture) was also gathered. The severity of sepsis was classified according to the criteria proposed by the Third International Consensus Definitions for Sepsis and Septic Shock as death anticipated during hospitalization (12).

Blood sampling and laboratory methods

Serum samples were obtained from whole blood samples collected in tubes without anticoagulant and analyzed for C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), WBC (and poly morphonuclears [PMN]%), blood sugar (BS), and creatinine (Cr) by conventional methods. Serum total cholesterol (STC) level and its fractions [levels of low-density lipoprotein cholesterol (LDL-C) and HDL-C] and TG levels were measured in the first morning after admission and then once weekly. Serum samples were analyzed immediately or stored at 4°C and analyzed within 12 hours of collection at the Bou-Ali hospital laboratory using standardized enzymatic methods. All samples were analyzed in the same laboratory. To ensure the reliability and validity of all biochemical measures, 32.4% of samples were rechecked. Also, arterial blood samples were obtained to measure arterial blood gas (ABG) values (bicarbonate (HCO3-) and Pao2/Fio2) in the initial emergency department (ED) evaluation of patients. Blood cultures were obtained before initiating antimicrobial therapy. Hypocholesterolemia and hypotriglyceridemia were defined as TC < 150 mg/dL and TG < 50 mg/dL, respectively (13, 14). For analytic purposes, 3 categories of STC levels were defined: < 150 mg/dL (hypocholesterolemia), 150 to 199 mg/dL (normal cholesterol levels), and > 200 mg/dL (hypercholesterolemia). Erythrocyte sedimentation rate was measured by the Westergren method. The secondary endpoint was to assess differences in hospital length of stay. The study was approved by the ethics committee of Qazvin University of Medical Sciences (ethical approval number: IR.QUMS.REC.1395.265).

Statistical analysis

A sample size was calculated based on published data of an earlier study, in which plasma lipid levels with the exception of TG were significantly lower in patients who developed multiorgan dysfunction syndrome (MODS) compared to those who did not (total cholesterol: 91.4±45.0 vs. 129.9±43.7) (9). Also, it was estimated that 74 patients were needed to detect a mean difference 38 mg mg/dL between primary STC, with a power of 80% and an alpha level of 0.05. Data were analyzed using SPSS 22.0 (IBM Inc., USA). The primary independent variable was TC and its fractions and TG; the secondary independent variables were age, sex, comorbidities, prescribed medications, and biochemical variables, and the primary outcome variable was survival. Distributions of continuous data were assessed for normality using the Kolmogorove Smirnov test. Continuous variables were described as mean ± SD or median (interquartile range) and were compared using t test for independent samples or Manne-Whitney U as appropriate. Categorical variables were de-

scribed as percent of indicator value and compared by vital status using chi-squared test or the Fisher's exact test as appropriate. All tests were 2-sided and considered significant at p<0.05. Prevalence of hypocholesterolemia in sepsis patients was compared with Iranian general population. In this study, serum lipid profile levels (mg/dL) were divided into 5 groups by age, 2 groups by sex (male, female and total), and 7 groups by percentiles of lipid level (5th, 10th, 25th, 50th, 75th, 90th, 95th). Overall, 8% of the population had STC levels below 150 mg/dL (15).

Results

Population

The mean±SD of patients' age was 65.1±18.6 years, which varied from 21 to 92 years (median 68 year). The female to male ratio was 0.85; 54.1% of the participants (n=40) were male. During the study period, 21.6% (CI 95%: 12.9- 32.7) of patients (n=16) died and 78.4% were discharged from the hospital. Only 7 patients were hospitalized for longer than 3 weeks. Characteristics of the study population are presented in Table 1.

Participants who survived to the end of follow-up were significantly younger (p=0.025). Also, qSOFA score was elevated in the nonsurvivor group and odds ratio for qSOFA (low risk / high risk) was 22.83 (CI 95%: 2.82-184.82).

A positive blood culture result was obtained in 21.6% of the patients. The percentage of patients that survived was not different for those with a positive blood culture result (17.2%) than for those that had a negative culture (37.5%). In this study, 17.6% positive cultures were Gram-negative infections (the most common: pseudomonas and E. coli) and 5.4% of cultures yielded Gram-positive organisms. In addition, bicarbonate levels were significantly lower in survivors, but no significant differences were observed for other clinical parameters (eg, CRP, ESR, and Cr).

On admission lipid profile and in-hospital mortality

Table 2 shows the results of the lipid profile of both groups. In this study, overall, 78.4% (CI 95%: 67.3-87.1) of the patients had hypocholesterolemia (77.6% and 81.3% of the survivor and nonsurvivor patients).

The prevalence of hypocholesterolemia in sepsis patients was significantly higher than the Iranian general population (78.4% vs 8%) [95% confidence interval (CI) of the difference was 59.7 - 78.3, (p<0.001)]. Only 2 patients (2.3%)

Table 1. Baseline clinical features and laboratory investigations of patients (n = 74, day 0).

Characteristics	All participants (74)	Survived (58)	Dead (16)	p
Age (year)	68.0 [54.0, 81.0]	65.0 [53.0, 76.0]	80.5 [64.5, 83.0]	0.025*
Male (%)	40 (54.1)	32 (55.2)	8 (50.0)	0.713
Current smokers (%)	11 (14.9)	9 (15.5)	2 (12.5)	0.764
Length of Hospital stay (days)	9.5 [6.0, 15.0]	9.5 [7.0, 14.0]	8.0 [2.0, 18.5]	0.418
q_SOFA	36 (48.6)	35 (60.3)	1 (6.3)	<0.001*
Low risk				
High risk	38 (51.4)	23 (39.7)	15 (93.8)	
Underlying disease				
Diabetes mellitus (%)	19 (25.7)	18 (31.0)	1 (6.3)	0.042*
Hypertension (%)	21 (28.4)	17 (29.3)	4 (25.0)	0.764
Coronary artery disease (%)	12 (16.2)	11 (19.0)	1 (6.3)	0.247
Neurologic (%)	20 (27.0)	16 (27.6)	4 (25.0)	0.863
Other (%)	15 (20.3)	8 (13.8)	7 (43.7)	0.017*
Number of underlying diseases	1.0 [0.0, 2.0]	1.0 [0.0, 2.0]	1.0 [0.5, 1.0]	0.615
Infection site (%)				0.117
Respiratory tract	30 (40.5)	22 (37.9)	8 (50.0)	
Abdomen	10 (13.5)	9 (15.5)	1 (6.3)	
Urogenital tract	16 (21.6)	15 (25.9)	1 (6.3)	
Skin/soft tissue	7 (9.5)	6 (10.3)	1 (6.3)	
Other infections	11 (14.9)	6 (10.3)	5 (31.2)	
Glasgow Coma Scale (GCS)	14.00 (11.00, 15.00)	15.00 (13.00, 15.00)	8.00 (6.00, 10.50)	<0.001*
Systolic blood pressure (mmHg)	120.0 [100.0, 130.0]	120.0 [100.0, 130.0]	102.5 [100.0, 120.0]	0.083
Diastolic blood pressure (mmHg)	70.0 [60.0, 80.0]	80.0 [65.0, 80.0]	70.0 [60.0, 80.0]	0.092
Pulse Rate (beats/min)	109.5 [100.0, 120.0]	109.5 [100.0, 120.0]	105.0 [96.5, 120.0]	0.428
Respiratory rate (breath/min)	22.0 [20.0, 26.0]	22.0 [20.0, 26.0]	27.0 [23.0, 32.5]	0.001*
Temperature (℃)	38.8 [38.0, 39.1]	39.0 [38.0, 39.2]	38.5 [37.8, 39.0]	0.252
Laboratory Investigations				
Creatinine (mg/dL)	1.2 [1.0, 1.4]	1.1 [1.0, 1.4]	1.4 [1.1, 2.2]	0.102
Blood sugar (mg/dL)	129.0 [100.0, 167.0]	130.5 [99.0, 174.0]	122.5 [105.0, 162.0]	0.622
Bicarbonate (mg/dL)	22.0 [18.9, 25.0]	23.2 [19.4, 25.4]	19.3 [15.9, 22.3]	0.005*
Pao_2/Fio_2 ratio	274.5 [196.0, 333.0]	291.0 [199.0, 341.0]	210.0 [190.5, 294.5]	0.062
White blood cells (/mL)	12.4 [8.3, 15.7]	12.5 [8.1, 16.8]	12.1 [9.2, 14.4]	0.641
Poly morphonuclears (%)	83.5 [78.0, 88.0]	83.0 [80.0, 88.0]	85.0 [76.0, 88.5]	0.963
Blood Culture (%)				
Negative	16 (21.6)	10 (17.2)	6 (37.5)	0.051
Gram-negative bacilli (%)	13 (17.6)	10 (17.2)	3 (18.7)	
Gram-positive cocci (%)	4 (5.4)	1 (1.7)	3 (18.7)	
ESR (mm/h)	36.5 [22.0, 61.0]	34.0 [20.0, 61.0]	47.0 [28.0, 64.5]	0.183
CRP (mg/dL)	77.0 [63.0, 89.0]	78.5 [63.0, 89.0]	70.0 [63.5, 87.0]	0.660

Data are presented as numbers (percentages) or the median [interquartile range]. q SOFA, quick Sequential Organ Failure Assessment. *: Significant

Table 2. Baseline serum lipids profile

Characteristics	All participants (74)	Survived (58)	Dead (16)	p
Total cholesterol (mg/dL)	124.9±37.9	125.6±34.8	122.4±48.8	0.524
Hypocholesterolemia (<150) (%)	58 (78.4)	45 (77.6)	13 (81.3)	0.755
Normal (150-199) (%)	13 (17.6)	11 (19.0)	2 (12.5)	
Hypercholesterolemia (>200) (%)	3 (4.1)	2 (3.4)	1 (6.3)	
Triglycerides (mg/dL)	114.5 [85.0, 159.0]	112.5 [88.0, 151.0]	121.5 [80.0, 227.5]	0.581
LDL-C (mg/dL)	67.5 [53.0, 94.0]	66.5 [52.0, 95.0]	72.5 [61.0, 81.0]	0.813
HDL-C (mg/dL)	22.0 [20.0, 27.0]	22.0 [20.0, 27.0]	23.5 [20.0, 27.5]	0.799

HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol
Data are presented as numbers (percentages) or the median [interquartile range].

had TG <50 mg/dL (hypotriglyceridemia). The prevalence of hypotriglyceridemia in sepsis patients was not different from the Iranian general population (2.3% vs 4%) (15).

There were no significant differences between groups in serum levels of STC, LDL-C, HDL-C, and TG. For example, means of the primary STC were 125.6±34.8 and 122.4±48.8 in survived and deceased levels, respectively (p=0.524). There were no significant differences between the STC, HDL-C, LDL-C, and TG levels and sex in this study (all p>0.05). None of the serum lipids concentrations were associated with length of hospital stay (data not shown).

Lipid profile change and in-hospital mortality

The mean difference in the absolute change (from baseline to final measurement in mg/dl) of STC, LDL-C, HDL-C, and TG were compared between the 2 groups (the survived against the deceased). The mean difference in reduction of STC, LDL-C, HDL-C, and TG between 2 groups was 25.60 mg/dL (p=0.004), 28.10 mg/dL (p=0.006), 6.90 mg/dL (p=0.010), and 37.25 mg/dL (p=0.052). The changes in serum lipid levels over time are summarized in Table 3 and Figure 1.

There were positive correlations between clinical outcome of sepsis patients and STC and other lipid profile level changes during hospital stay (not on admission).

Discussion

Most studies performed to date focused primarily on the comparative analysis of serum lipids between sepsis and severe sepsis groups or between survivor and nonsurvivor groups (7, 16, 17). In this study, serum lipid levels were analyzed over time, and the association of lipid levels with survival in sepsis patients was also determined.

In this study, the prevalence of hypocholesterolemia in sepsis patients was significantly higher than in the general population. However, absolute STC, LDL, HDL, and TG levels in admission time was not suitable for the prediction of mortality in sepsis patients (based on comparison of survive with nonsurvive groups). The data of this study support the hypothesis that higher decline of STC and other lipid profile during hospital admission are associated with a higher mortality in sepsis patients. Recently, in a study in South Korea, the changes in serum lipid levels over time were examined from the day of admission to ICU (day 0 to day 7). There was a significant gap in the mean value for each lipid and lipoprotein between survivor and non-survivor groups at different time points (18).

Some studies on healthy volunteers injected with a low dose of endotoxin or on septic patients have shown that the systemic inflammatory response is associated with disruption of lipid metabolism (19, 20). These changes include reductions in HDL levels and increases in STC and TG (clinically termed the lipaemia of sepsis). On the other hand, some studies revealed that high levels of serum cytokines decrease STC levels during the course of infection, and in critically ill patients, hypocholesterolemia is associated with poor outcomes (21). In this study, comparing the recovered and nonrecovered patient groups, it was found that lipid metabolism was different in the 2 subgroups. Serum lipid concentration in deceased sepsis patients decreased continuously but increased in recovered patients. Changes in lipid profile during sepsis seem to be related to increased cytokines, and excessive cytokine increase may reduce (but not increase) the level of serum lipids. In other words, clinically termed 'the lipaemia of sepsis' is not true in all situations (8). Changes in lipid profile in sepsis may be associated with cytokines level, and their excessive increase may reduce (rather increase) serum lipids level.

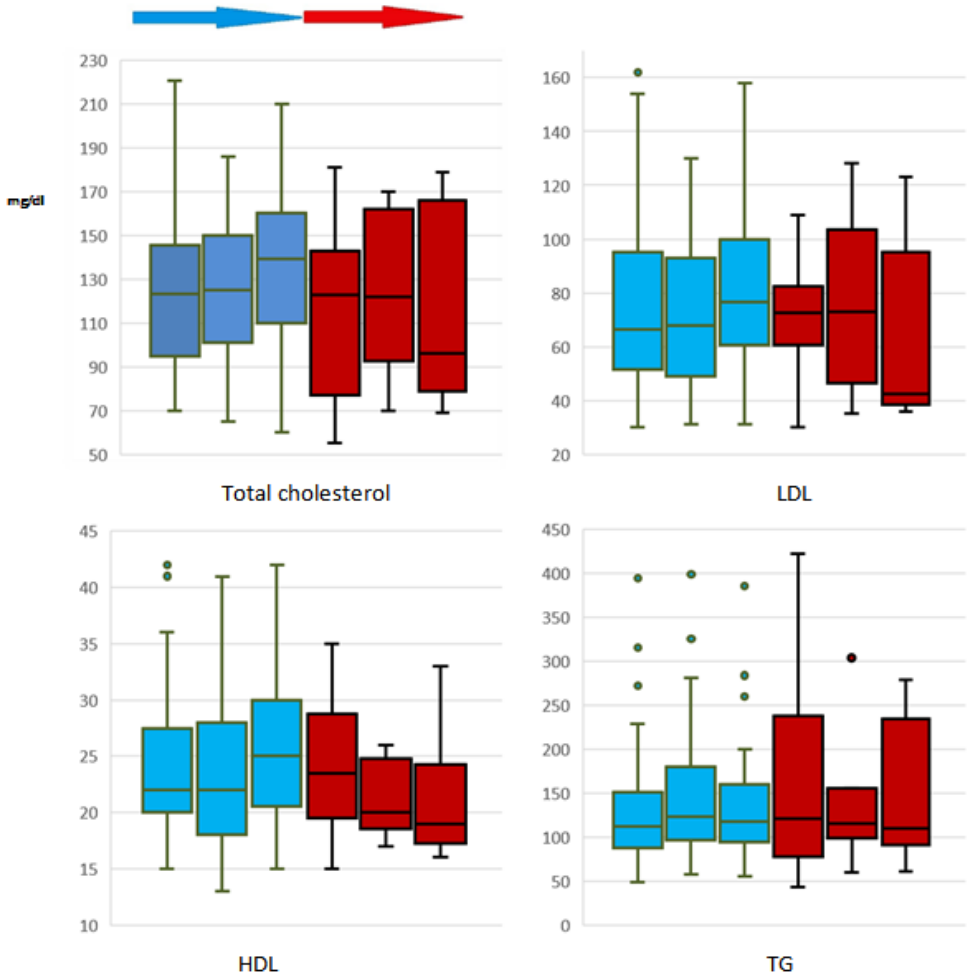
Results of this study and similar studies showed that hypocholesterolemia s is more prevalent in sepsis patients than in the general population; however, the mechanisms are not well delineated (22).

Similar to this study, some studies have shown that in emergency departments, adult patients with sepsis can be rapidly identified as being more likely to have poor outcomes if they have positive quick SOFA (qSOFA) scores (23, 24). The qSOFA score was introduced as a rapid bedside clinical score to identify patients with a suspected

Table 3. Results of the lipid profile changes during the hospital stay

	ΔCh1	ΔCh2	ΔChT	ΔHDL1	ΔHDL2	ΔHDLT	ΔLDL1	ΔLDL2	ΔLDLT	ΔTG1	ΔTG2	ΔTGT
Mean difference (mg/dL)	15.62	12.43	25.60	4.02	3.26	6.90	13.92	13.49	28.10	42.35	-7.21	37.25
P value	0.072	0.116	0.004*	0.077	0.191	0.010*	0.088	0.206	0.006*	0.207	0.642	0.052

ΔCh1: cholesterol1- cholestero0 1, ΔCh2: cholesterol2- cholesterol1, ΔChT: cholesterol2 – cholesterol0
ΔHDL1: HDL1- HDL0, ΔHDL2: HDL2- HDL1, ΔHDLT: HDL2- HDL0
ΔLDL1: LDL1- LDL0, ΔHDL2: LDL2- LDL1, ΔLDLT: LDL2- LDL0
ΔTG1: triglyceride1- triglyceride0, ΔTG2: triglyceride2- triglyceride1, ΔTGT: triglyceride2- triglyceride0
0: on admission, 1: middle of hospitalization, 2: before discharge or death



0: On admission, 1: Middle of hospitalization, 2: Before discharge or death, Blue plot: Discharged, Red plot: Deceased.

Fig. 1. Box plot of the serum lipids trends during hospital admission for 2 study groups (discharged and deceased patients)

infection that are at greater risk for a poor outcome (eg, in-hospital mortality predictor) (12). The qSOFA score includes "RR≥22 breath/min", "systolic blood pressure≤100 mmHg", and "altered mental status (Glasgow Coma Scale <15)]". A "positive" qSOFA Score (≥2) suggests high risk of poor outcome in patients with suspected infection (3- to 14-fold increase risk for in-hospital mortality) (23). These patients should be carefully assessed for evidence of organ dysfunction.

There are several pre-existing illnesses that increase susceptibility to development of sepsis and severe sepsis. In this study, history of DM was present in 25.7% of patients with sepsis. DM alters immunity through several different mechanisms. DM is a common disorder with well-established deleterious effects on immunity and confirmed consequences on the incidence of sepsis or severe sepsis (11).

In this study, Gram-negative isolated bacteria were 3-fold higher than Gram-positive organisms. According to the most recent estimates in sepsis, the most common cause of sepsis in developed countries are Gram-positive microorganism. Conversely, the responsible organisms of sepsis in the developing world are more likely to be Gram-negative enteric pathogens (2).

This study had 2 limitations. First, cytokines was not measured, which may help explain the findings. Second, data on the patients' nutrition status before and during hospital admission were not collected. Another limitation of the study was its observational design, although data were collected prospectively.

Conclusion

This study showed that the variations in lipid profiles differed significantly between the survivor and nonsurvivor groups. Also, more decline of lipid profile was significantly associated with increase of mortality in sepsis patients. However, further studies are required to approve the role of lipid profile in the outcomes of sepsis patients.

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Conflict of Interests

The authors declare that they have no competing interests.

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