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Predictive Implications of Serum Lipid Metabolism over Time in Intensive Care Unit Admitted Patients

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Abstract

Introduction: Serum lipoprotein levels change during hospitalization and effect patient's outcome in case of sepsis. The aim of this study was to investigate the prognostic values of the serum levels of lipids in Intensive Care Unit (ICU) admitted patients.
Methods: Intensive Care Unit admitted patients with various etiologies were enrolled in this study. Serum lipid level was collected on the first and seventh day of admission. Clinical outcome and baseline characteristics, including age, gender, cause of admission, length of ICU stay, and discharge or death were monitored prospectively in a short cohort.
Results: A total of 108 patients were enrolled in this study. The overall mortality rate was 45%. The average duration of hospitalization at the ICU was significantly lengthier in the un-survived group. Lipid profile had a similar pattern in both genders. Triglyceride level seemed to increase from Day one to Day seven. These changes were observed in both unsurvived and survived group and were not significantly different. A considerable decline of 24% in High Density Lipoprotein (HDL) was detected among unsurvived patients. The mean value of TG on day seven among unsurvived patients was significantly higher than that of the survived group. Receiver Operating Characteristic (ROC) curve illustrated the higher diagnostic ability of HDL level in comparison with other parameters. On day seven, serum HDL cutoff value of 32 (sensitivity 75%; specificity 60%) was observed for predicting the mortality.
Conclusions: Cholesterol is essential for integrity as well as the function of the cell membrane, therefore, dyslipidemia occurring during hospitalization may negatively influence the outcome. Consequently, changes in lipid profile could be a prognostic biomarker for predicting mortality in ICU-admitted patients.

INTRODUCTION

Patients admitted to the intensive care unit experience multiple underlying disorders that can increase the duration of hospitalization and the risk of mortality in case of insufficient medical care. The severity of the patient and prognosis could be assessed using newly designed technologies for healthcare. The necessity of choosing a highly efficient approach to predict the patients' clinical prognosis and outcome in a short time at the ICU is still a challenge. One of these methods, which is already commonly used, is Acute Physiological and Chronic Health Evaluation (APACHE) at the Intensive Care Units (ICU) [1]. This method can calculate the mortality risk and the duration of hospitalization at the ICU through providing information, such as previous experience of illness, vital signs and blood indices, including electrolytes, arterial blood gas, and etc. This criterion is very time consuming with the calculation of more than 17 parameters, and its software is not widely available [2]. Therefore, efforts are being made to use methods that, at the same time, provide the necessary efficiency, reliability, and ease of use.

Lipoproteins, especially High-Density Lipoprotein (HDL), can be considered as an anti-inflammatory agent, which modulates immune responses due to inhibiting immune system activity [3]. Also, it has been reported that infection and inflammation affect lipid profile [4], which is in the form of a decrease in lipoproteins or triglycerides. It has also been indicated that insulin resistance is created in the field of inflammation and infection, which in addition to increasing blood glucose, increases Triglyceride (TG) and decreases HDL and

Low-Density Lipoprotein (LDL) [5, 6]. Changes in the metabolism of lipoproteins during inflammation and infection can increase TG levels due to increased Very Low-Density Lipoproteins (VLDL) production or reduced clearance in the liver [7]. Indeed, HDL induces production of antioxidant proteins, such as Platelet Activating Factor-Acetyl Hydrolase (PAF-AH), transferrin, and serovoluclamine Paraoxonase (PON) [8]. Hence, lipid profile fluctuation could be employed as a biomarker for evaluating other situations, such as blood glucose control [9]. Since, in the diabetic patients, there was a linear relationship between TG serum level and mortality. Moreover, LDL and HDL of less than 20 mg/dl and15 mg/dl respectively, increased mortality [10].

Furthermore, the protective effect of lipoproteins and apoproteins has been confirmed by neutralization of antigenicity of Lipopolysaccharides (LPS), as well as reduction of adhesion molecules; thus, belonging to the diagnostic value of lipid profile, they are considered as therapeutic agents as well [10, 11]. In this situation, HDL detaches LPS-binding to the monocyte membrane, while LDL, apoB, and VLDL neutralize free LPS in the serum by attachment [12]Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand. Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host.

Accordingly, serum lipoprotein levels and its alterations are appropriate factors for patient prognosis evaluation, especially since serum cholesterol, TG, HDL, and LDL levels against APACHE score are dependent on the quality of care provided at the ICU.

In 2008, Carlo Chiario reported considerable changes in lipid profiles in SEPSIS [13]. However, Yassin Arabi et al. conducted a study in 2013, in which they did not report a relationship between changes in TG and patients mortality [14]. The purpose of this study was to introduce a method to predict clinical prognosis in ICU patients with regards to both simplicity and availability [11].

METHODS

This study was a prospective analysis of a cohort research at the ICU; admitted patients at a tertiary university medical center (Labbafinejad hospital) in Tehran, Iran. The study protocol was reviewed and approved by the ethical committee of Shahid Beheshti University of Medical Sciences (1394/11/13-425). Informed consent was obtained from patients or their next of kin. Among patients admitted to the ICU with various etiologies, patients were excluded if they met specific criteria, including age of less than 18 years, pregnancy, patients with respiratory failure and transplantation, history of dyslipidemia, or a history of steroid within the previous seven days and received serum containing intera-lipid or Total Parenteral Nutrition (TPN). Finally, a total of 108 ICU patients were enrolled in the study between March 2017 and August 2017.

All eligible patients in this study were managed, according to their chief complaint and specific disorders. For each patient, demographic data, including age and gender, were collected and also, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Glasgow Coma Scale (GCS) and laboratory data, including cholesterol, TG, HDL, LDL, and serum levels, were gathered on the first and seventh day of admission.

The levels of total cholesterol (normal range: 100 to 220 mg/dL), HDL (normal range: 40 to 86 mg/dL), TG (normal range: 44 to 240 mg/dL), LDL (normal range: 70 to 169 mg/dL), were measured using commercial kits with an automated analyzer (Hitachi 7600 to 200-DDP, Hitachi Ltd., Tokyo, Japan).

Statistical Analysis

To analyze the gathered data, continuous variables were assessed by Kolmogorov Spinoff test for normal distribution. Considering $P > 0.5$, variables were compared using student's t-test and were presented as the mean ± standard deviation. For categorical variables, Pearson's chi-squared test or Fisher's exact test were chosen, and the frequencies were reported. The impact of serum lipid levels in two categories, including normal versus low level on survival, was evaluated using Cox proportional hazard models. Receiver Operating Characteristic (ROC) curve was used to examine the capacity of serum HDL and LDL cholesterol level in differentiating the status of survival. The Area under the Curve (AUC) and 95% Confidence Interval (CI) were reported. All statistical analyses were performed using the SPSS version 20 software (SPSS, Chicago, IL, USA).

RESULTS

The total number of patients was 108, of which 47 (43.5%) were females and 61 (56.5%) were males. The baseline characteristics of the patients are presented in Table 1. The mean age of the patients was 71 ± 12.1 years, and the average duration of hospitalization at the ICU was 12.15 ± 4.7 and 7.4 ± 2.4 days in survived and un–survived cases, respectively. The overall mortality rate was 45%.

Lipid profile had a similar pattern in both genders. There was a significant difference in both duration of admission and GCS between survived and un-survived patients. The most prevalent underlying diseases were Chronic Obstructive Pulmonary Disease (COPD), End Stage Renal Disease (ESRD), and cancer with a rate of 24.1%, 22.2%, and 11.1% respectively. Moreover, 21.3% of all patients experienced sepsis.

In total, the highest death rates belonged to cancer and ESRD with a prevalence of 66% and 58%, respectively. However, COPD patients achieved a great level of improvement (73%). The baseline characteristics of the patients are presented in Table 1, and in Table 2, the mean level of serum lipid profile is compared. According to the analysis of the data, there was a reverse correlation between the ages of patients with blood TG level (correlation coefficient of -0.37 with $P < 0.001$). This correlation was not approved in the serum cholesterol level.

Table 1. General Characteristics of the Patients in both Groups

	Total, N = 108	Survivors, N = 60	UN-Survivors, N = 48	P Value
Male Gender	56.5	61.7%	50%	N/S
Age	12.1 ± 71	18.02 ± 69.75	14.69 ± 72.48	N/S
Duration of Admit	4.4 ± 9.5	2.4 ± 7.4	4.7 ± 12.15	0.01
GCS	2 ± 10	1 ± 12	2 ± 7	0.01
COPD	(24.1) 26	(73.1)	(26.9)	0.01
Cancer	(11,1) 12	(33.3)	(66.7)	N/S
Sepsis	(21.3) 23	(39.1)	(60.9)	N/S
DHF	(6.5) 7	(71.4)	(28.6)	0.01
CKD/ESRD	(22.2) 24	(41.7)	(58.3)	N/S
PTE	(8.3) 9	(55.6)	(44.4)	N/S
Others	(6.5) 7	(42)	(58)	N/S

Data in table are presented as Mean ± SD or Number (%) or (%)

Abbreviations: GCS: Glasgow Coma Scale; COPD: Chronic Obstructive Pulmonary Disease; DHF: Decompensated Heart Failure; CKD: Chronic Kidney Disease; ESRD: End Stage Renal Disease; PTE: Pulmonary Thromboemboli

Table 2. Lipid Profile of Serum on Day One and Seven

	Survivors, N= 60	Un-survivors, N= 48	P Value
TG1	34.64 ± 107.78	76.7 ± 128.60	0.86
TG7	34.43 ± 111.55	68.20 ± 138.38	0.01
Pared t-test	N/S	N/S	
Cholestrol-1	41.91 ± 128.83	38.34 ± 125	0.62
Cholestrol-7	32.99 ± 127.17	40.34 ± 119.81	0.23
Pared t-test	N/S	N/S	
LDL1	22.33 ± 69.21	22.32 ± 68.35	0.84
LDL7	21.23 ± 68.78	24.16 ± 63.89	0.26
Pared t-test	N/S	N/S	
HDL1	15.86 ± 37.16	13.4 ± 32.18	0.08
HDL7	13.57 ± 37.28	10.3 ± 24.45	0.01
Pared t-test	N/S	P-value: 0.04	

Abbreviations: N/S: Not significant; TG: triglyceride(s); HDL: high-density lipoprotein; LDL: low-density lipoprotein

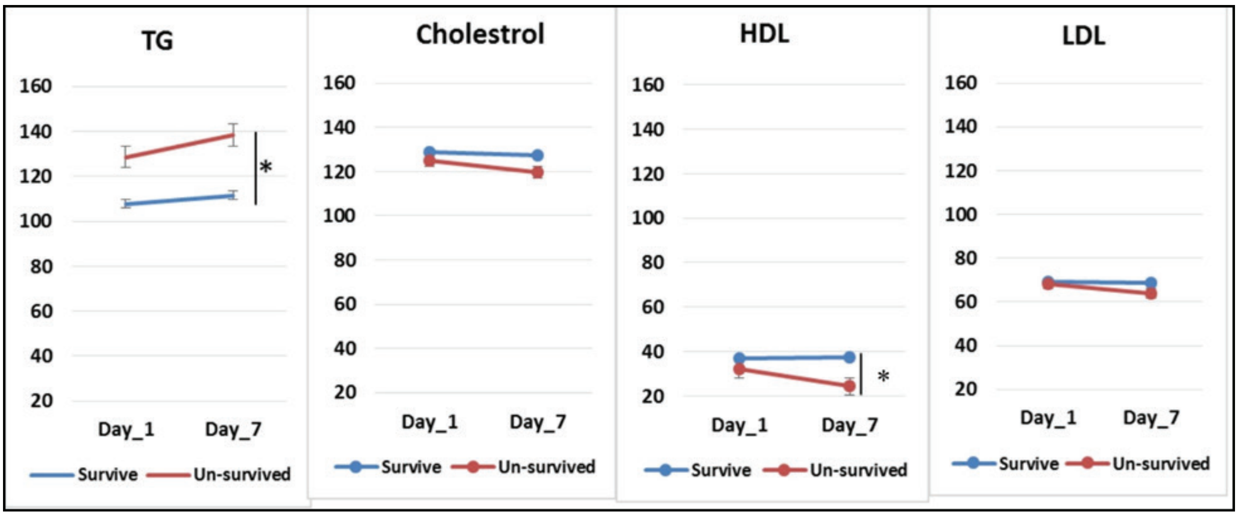

Figure 1. Changes in Lipid Profile over Time after ICU Admission
Abbreviations: TG: *Triglyceride*(s); HDL: High-density lipoprotein; LDL: Low-density lipoprotein
*Significance difference (P < 0.05)

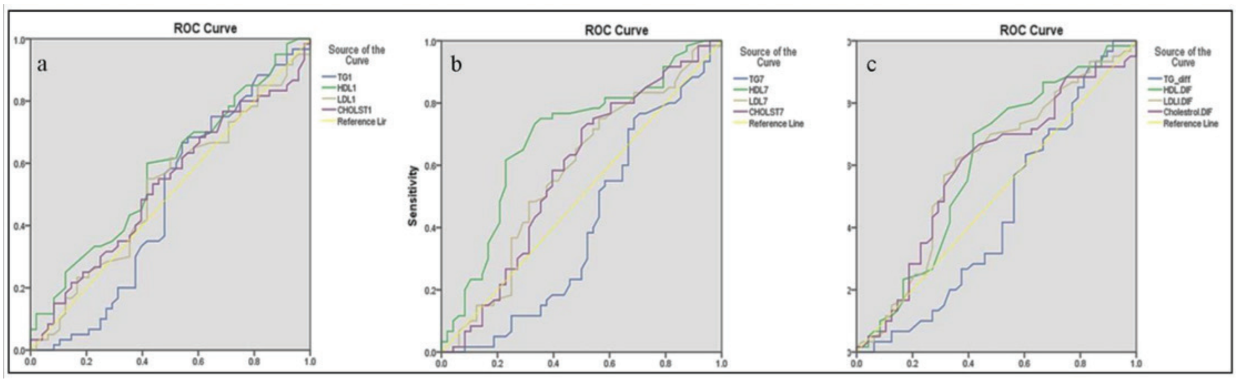

Figure 2. Receiver Operating Characteristic Curve of Serum HDL Cholesterol, LDL Cholesterol, and HDL Cholesterol on Day One and Seven for Prediction of Survival of ICU Admitted Patients
a: Serum Lipid Profile on day one; b: Serum Lipid Profile on day seven; c: The difference obtained during the seven-day follow up. As the figure shows, the most area under the curve belongs to HDL 7.

Triglyceride level seemed to increase from Day one to Day seven. These changes were observed in both populations and were not significantly different. However, the mean value of TG on day seven among unsurvived patients was significantly higher than that of the survived group (Table 2).
The changes in the mean level of LDL, as well as cholesterol over seven days of follow up, were fairly stable (Table 2). The HDL decreased 25% on day seven of admission in unsurvived patients whereas it was steady among survived ones. Moreover, it was found that there was a significant correlation between the duration of hospitalization at the ICU with HDL on day seven and the correlation coefficient ($P < 0.001$, -0.24) (Figure 1).
The ROC curve illustrated the higher diagnostic ability of HDL level on the seventh day in comparison with other parameters as a survival marker. On day seven, a serum HDL best cutoff value of 32 (sensitivity 75%; specificity 60%; AUC 70, 95% CI) and a serum LDL cholesterol best cutoff value of 60 (sensitivity, 70%; specificity, 60%; AUC 68, 95% CI) were selected by ROC curve for efficacy analysis (Figure 2). Using the new parameter obtained from age multiplication by the deduction of HDL level during seven days, improved both sensitivity and specificity. In the range of -100 to -200, sensitivity and specificity were 80 and 65, respectively. The area under the curve and diagnostic ability of the levels of TG, cholesterol, HDL, and LDL, as well as changes, occurred in the lipid profile was not considerable at all.

DISCUSSION

The current study indicated a correlation between serum lipoprotein levels and the short-term clinical outcome of the patients. Some of these findings have been mentioned in previous studies, and the current study confirmed this relationship as well. Based on this study, in patients with the acute phase of the disease, lower serum HDL level was associated with poor prognoses condition, and it was found that patients, who died during hospitalization, had higher levels of triglycerides on the first day of hospitalization, yet lower HDL than those with longer survival. The alteration in the amount of lipid profile would also increase in the course of hospitalization. In this regard, Ben Weil et al. reported a relationship between the reductions of serum lipoproteins and death in patients with Systemic Inflammatory Response Syndrome (SIRS) at the ICU [15]. The patients enrolled in the current study had various complaints, and in all study groups, the same pattern of lipid profile changes was observed.
In a study conducted by Al-Dawoodet al. in 2013, the decrease in blood lipoprotein levels in poor prognostic patients was common and total cholesterol level, as well as HDL, was reversely correlated with mortality rate [14]. However, there was no significant relationship between total cholesterol and mortality in the current study. The findings of the current study also confirmed the results of the study conducted by Chien et al. in 2015, which indicated a relationship between decrease in HDL-lipoprotein level and mortality, and the total decline from the first day to the seventh day has prognostic value [16]. In their study, a cutoff point of 17 mg/dL HDL had a diagnostic value of 83.3% sensitivity and 94.7% specificity while the current study indicated the best sensitivity (75%) and specificity (60%) at the level of 32 mg/dL of HDL. The population size in the current study was 108 patients with heterogeneous diagnoses, and the decline that occurred in the HDL cholesterol level was 24% in unsurvived patients. On the contrary, in the study implemented by Chien et al., there was a total of 40 patients with various etiologies and the decline was more than 50%. This considerable decline in lipid profile at the ICU was multifactorial and should be taken into account.
The anti-inflammation role of lipoproteins has led researchers to administer them as a therapeutic option in poor prognoses patients. High Density Lipoprotein injections in animal models reduce mortality and, in humans, they also inhibit the activity of pro-coagulant and endotoxins, yet increase the risk of fungal infections at higher doses [17]. Other clinical trials, including prescribing (soybean oil) and (fish oil) and olive oil, have revealed that enriched oils containing high and low would reduce inflammation and improve the ARDS condition [18, 19].
It has also been recently shown that there is a significant inverse correlation between lipid profile changes and APACHE score among ICU admitted patients [20, 21]. In another point of view, all ICU admitted patients inevitably need respiratory care. Both LDL and HDL effect local pulmonary cholesterol biosynthesis by supplying cholesterol to lung-resident cells [22].

Besides, HDL acts as the antioxidant for alveolar type II pneumocytes and stimulus production of surfactant as well as lung fibroblasts proliferation, which are affected by high serum cholesterol level due to altering compositions [23]. In this regard, several studies have indicated the impact of cholesterol targeted medications on respiratory disorders such as asthma, COPD, and fibrosis. Among modified items induced by these agents, reduction in BAL eosinophils, reduction of lung injury, and collagen deposition, reduction of cytokines and inflammation and so on are considerable [21, 22, 24].

CONCLUSION

Cholesterol is essential for integrity as well as the function of the cell membrane thus; dyslipidemia occurring during hospitalization may negatively influence the outcome. Consequently, changes in lipid profile could be a prognostic biomarker, an alternative or an additive parameter to the improve APACHE II score.

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CONFLICTS OF INTEREST

There is no conflict of interest for this study.

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AUTHOR'S CONTRIBUTIONS

Mehdi Motafaker Azad: data collection; Mohammad Amin Abbasi: data analysis and writing; Niloofar Basharzad: data collection and writing; Abbas Fadaei: data collection and supervision.

REFERENCES

1. Parajuli BD, Shrestha GS, Pradhan B, Amatya R. Comparison of acute physiology and chronic health evaluation II and acute physiology and chronic health evaluation IV to predict intensive care unit mortality. Indian J Crit Care Med. 2015;19(2):87-91.DOI: 10.4103/0972-5229.151016 PMID: 25722550
2. Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. Crit Care Med. 2006;34(5):1297-310.DOI: 10.1097/01.CCM.0000215112.84523.F0 PMID: 16540951
3. Samson S, Mundkur L, Kakkar VV. Immune response to lipoproteins in atherosclerosis. Cholesterol. 2012;2012:571846.DOI: 10.1155/2012/571846 PMID: 22957222
4. van Diepen JA, Berbee JF, Havekes LM, Rensen PC. Interactions between inflammation and lipid metabolism: relevance for efficacy of anti-inflammatory drugs in the treatment of atherosclerosis. Atherosclerosis. 2013;228(2):306-15.DOI: 10.1016/j.atherosclerosis.2013.02.028 PMID: 23518178
5. Beigneux AP, Moser AH, Shigenaga JK, Grunfeld C, Feingold KR. The acute phase response is associated with retinoid X receptor repression in rodent liver. J Biol Chem. 2000;275(21):16390-9.DOI: 10.1074/jbc.M000953200 PMID: 10747970
6. Vanttinen M, Nuutila P, Kuulasmaa T, Pihlajamaki J, Hallsten K, Virtanen KA, et al. Single nucleotide polymorphisms in the peroxisome proliferator-activated receptor delta gene are associated with skeletal muscle glucose uptake. Diabetes. 2005;54(12):3587-91. PMID: 16306381
7. Akgun S, Ertel NH, Mosenthal A, Oser W. Postsurgical reduction of serum lipoproteins: interleukin-6 and the acute-phase response. J Lab Clin Med. 1998;131(1):103-8. PMID: 9452133
8. Rodrigo L, Mackness B, Durrington PN, Hernandez A, Mackness MI. Hydrolysis of platelet-activating factor by human serum paraoxonase. Biochem J. 2001;354(Pt 1):1-7. PMID: 11171072
9. Lee JS. Effects of soy protein and genistein on blood glucose, antioxidant enzyme activities, and lipid profile in streptozotocin-induced diabetic rats. Life Sci. 2006;79(16):1578-84.DOI: 10.1016/j.lfs.2006.06.030 PMID: 16831449
10. Marik PE. Adrenal-exhaustion syndrome in patients with liver disease. Intensive Care Med. 2006;32(2):275-80.DOI: 10.1007/s00134-005-0005-5 PMID: 16432671
11. Sprong T, Netea MG, van der Ley P, Verver-Jansen TJ, Jacobs LE, Stalenhoef A, et al. Human lipoproteins have divergent neutralizing effects on E. coli LPS, N. meningitidis LPS, and complete Gram-negative bacteria. J Lipid Res. 2004;45(4):742-9.DOI: 10.1194/jlr.M300453-JLR200 PMID: 14754910
12. Khovidhunkit W, Kim MS, Memon RA, Shigenaga JK, Moser AH, Feingold KR, et al. Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. J Lipid Res. 2004;45(7):1169-96.DOI: 10.1194/jlr.R300019-JLR200 PMID: 15102878
13. Chiarla C, Giovannini I, Siegel JH. Hypotransferrinemia and changes in plasma lipid and metabolic patterns in sepsis. Amino Acids. 2009;36(2):327-31.DOI: 10.1007/s00726-008-0072-3 PMID: 18392771
14. Chiang CK, Ho TI, Hsu SP, Peng YS, Pai MF, Yang SY, et al. Low-density lipoprotein cholesterol: association with mortality and hospitalization in hemodialysis patients. Blood Purif. 2005;23(2):134-40. DOI: 10.1159/000083529 PMID: 15665509
15. Bonville DA, Parker TS, Levine DM, Gordon BR, Hydo LJ, Eachempati SR, et al. The relationships of hypocholesterolemia to cytokine concentrations and mortality in critically ill patients with systemic inflammatory response syndrome. Surg Infect (Larchmt). 2004;5(1):39-49.DOI: 10.1089/109629604773860291 PMID: 15142422
16. Chien YF, Chen CY, Hsu CL, Chen KY, Yu CJ. Decreased serum level of lipoprotein cholesterol is a poor prognostic factor for patients with severe community-acquired pneumonia that required intensive care unit admission. J Crit Care. 2015;30(3):506-10.DOI: 10.1016/j.jcrc.2015.01.001 PMID: 25702844
17. Netea MG, Curfs JH, Demacker PN, Meis JF, Van der Meer JW, Kullberg BJ. Infusion of lipoproteins into volunteers enhances the growth of Candida albicans. Clin Infect Dis. 1999;28(5):1148-51. DOI: 10.1086/514757 PMID: 10452650
18. Koch T, Heller A. Effects of intravenous fish oil on pulmonary integrity and function. Clin Nutrition. 2002;21(3):41-5.
19. Lekka ME, Liokatis S, Nathanail C, Galani V, Nakos G. The impact of intravenous fat emulsion administration in acute lung injury. Am J Respir Crit Care Med. 2004;169(5):638-44.DOI: 10.1164/rccm.200305-620OC PMID: 14656749
20. Moini L, Mozafari A, Peyroshabani B. [Evaluation of the relationship between serum lipid level (total cholesterol, LDL, HDL) and APACHE IV score in ICU patients]. Arak Med Uni J. 2014;17(83):64-72.
21. Kim TH, Lee YH, Kim KH, Lee SH, Cha JY, Shin EK, et al. Role of lung apolipoprotein A-I in idiopathic pulmonary fibrosis: antiinflammatory and antifibrotic effect on experimental lung injury and fibrosis. Am J Respir Crit Care Med. 2010;182(5):633-42.DOI: 10.1164/rccm.200905-0659OC PMID: 20463180
22. Gowdy KM, Fessler MB. Emerging roles for cholesterol and lipoproteins in lung disease. Pulm Pharmacol Ther. 2013;26(4):430-7.DOI: 10.1016/j.pupt.2012.06.002 PMID: 22706330
23. Vockeroth D, Gunasekara L, Amrein M, Possmayer F, Lewis JF, Veldhuizen RA. Role of cholesterol in the biophysical dysfunction of surfactant in ventilator-induced lung injury. Am J Physiol Lung Cell Mol Physiol. 2010;298(1):L117-25.DOI: 10.1152/ajplung.00218.2009 PMID: 19897745
24. Lind L, Lithell H. Impaired glucose and lipid metabolism seen in intensive care patients is related to severity of illness and survival. Clin Intensive Care. 1994;5(3):100-5. PMID: 10150538