

## The role of serum HDL, LDL, and uric acid levels in predicting the prognosis of community-acquired pneumonia

### Serum HDL, LDL ve ürik asit düzeyinin toplum kökenli pnömönide prognoz tahminindeki rolü

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#### Abstract

**Purpose:** Community-acquired pneumonia (CAP) leads to inflammation and oxidative stress as a result in infection. In the present study, we aimed to investigate the relationship between initial serum high-density lipoprotein (HDL), low-density lipoprotein (LDL), and uric acid levels on short-term (30-day) changes in the course of CAP.

**Materials and methods:** The retrospective study included 113 patients with CAP that received inpatient care between 2012 and 2018. The HDL, LDL and uric acid values in the blood received in hospital admission were examined for their relationship with short-term mortality and correlation with hospitalization.

**Results:** The 113 patients comprised 71 (62.8%) men and 42 (37.2%) women with a mean age of 74±11 years. Of the 113 patients, 30-day mortality occurred in 12 (10.6%) patients. Of the 113 patients, 17 (16.5%) patients were hospitalized in ICU. All cases detected as mortality were followed in ICU. Normal ranges of HDL, LDL, and uric acid concentrations were accepted as 40-70 mg/dL, 60-130 mg/dL, and 1.8-8 mg/dL, respectively. The mean serum LDL, HDL, and uric acid levels were 97.95±42.11 (range, 26-271) mg/dL, 40.94±13.70 (range, 5.10-83.20) mg/dL, and 5.99±2.18 (range, 1.40-13.20) mg/dL, respectively. HDL and LDL levels were found to be insignificant predictors of 30-day mortality ( $p=0.482$  and  $p=0.725$ , respectively). Similarly, serum HDL, LDL, and uric acid levels were found to be insignificant predictors of the duration of hospitalization and ICU requirement. On the other hand, multivariate logistic regression analysis indicated that uric acid concentration was a protective factor for 30-day mortality (OR, 0.694; 95% CI, 0.478-0.989,  $p=0.048$ ), whereby increased uric acid concentration was found to decrease the risk of mortality and reduced uric acid concentration was found to increase the risk of mortality by 1.44 times (1/0.694).

**Conclusion:** We suggest that monitoring uric acid levels with serial measurements in patients with CAP may be useful for predicting the short term prognosis. Further prospective multicentric studies with larger patient series are needed to investigate the correlation between serum uric acid levels and clinical risk scores.

**Key words:** CAP, HDL, LDL, uric acid.

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#### Öz

**Amaç:** Toplum kökenli pnömönide (TKP) enfeksiyona bağlı inflamasyon ve oksidatif stres oluşmaktadır. Bu çalışmamızda amacımız; başlangıç yüksek dansiteli lipoprotein (HDL), düşük dansiteli lipoprotein (LDL) ve ürik asit serum düzeylerinin TKP'de kısa dönem (30 gün) hastalık sürecindeki değişikliklerle ilişkisini değerlendirmektir.

**Gereç ve yöntem:** 2012-2018 tarihleri arasında hastaneye yatırılarak tedavi edilen 113 TKP olgusu retrospektif olarak değerlendirildi. Hastaneye başvuru esnasındaki ilk 24 saatte ölçülen HDL, LDL ve ürik asit düzeyleri incelendi. Hastane kabulünde alınan kandaki HDL, LDL ve ürik asit değerlerinin kısa dönem mortaliteyle ilişkisi ve hospitalizasyonla korelasyonunu araştırıldı.

**Bulgular:** 71'i (%62,8) erkek, 42'si (%37,2) kadın olan 113 hasta dahil edildi. Ortalama yaş 74±11 yıl olarak bulundu. Otuz günlük mortalite oranı %10,6 (113 hastanın 12'sinde) olarak saptandı. Yoğun bakım yatış oranı %15 olarak (113 hastanın 17'sinde) tespit edildi. Mortalite saptanan tüm vakaların yoğun bakımda takip edildiği

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tespit edildi. HDL, LDL ve ürik asit konsantrasyon normal aralığı sırasıyla 40-70 mg/dL, 60-130 mg/dL ve 1,8-8 mg/dL olarak kabul edilirken; kan serum LDL, HDL ve ürik asit serum düzeylerimiz sırasıyla 97,95±42,11 mg/dL (min:26, maks:271), 40,94±13,70 mg/dL (min:5,10, maks:83,20), 5,99±2,18 mg/dL (min:1,40, maks:13,20) bulundu. HDL ve LDL düzeyleri istatistiksel olarak anlamlı saptanmadı ( $p=0,482$ ,  $p=0,725$ ). HDL, LDL ve ürik asit düzeylerinin klinik yatış süresi ve yoğun bakım ihtiyacını öngörmeye ilişkisi istatistiksel olarak anlamlı değildi. Çoklu değişkenli logistik regresyon analizinde ürik asit düzeyi koruyucu faktör olarak tespit edildi (OR, 0,694; %95 CI, 0,478-0,989,  $p=0,048$ ). Sonuçta ürik asitin artması mortalite riski azaltırken; düşük ürik asit düzeyleri (1/0,694) 1,44 kat mortalite olasılığını artırmaktadır.

**Sonuç:** TKP'de kısa dönem prognoz takibinde serum ürik asit düzeylerinin seri ölçümlerle takip edilmesinin faydalı olabileceği düşünülmüştür. Serum ürik asit düzeyinin TKP'de klinik risk skorlamalarında yer alması için çok merkezli, gözlemsel çalışmalar yapılmalıdır.

**Anahtar kelimeler:** TKP, HDL, LDL, ürik asit.

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## Introduction

High-density lipoprotein (HDL), low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL) are the most significant lipoproteins in plasma. Elevated triglyceride concentrations, reduced HDL-cholesterol (HDL-C) concentration rates, in particular, are known as significant risk factors for atherosclerosis. Previous studies suggested that clinical conditions such as acute infection are effective on lipid metabolism [1, 2]. Moreover, it has also been suggested that gram-negative infections (Chlamydia pneumonia) predominantly affect triglyceride and HDL levels [1]. On the other hand, reduced lipid concentration is known to be a prognostic factor in critical diseases such as sepsis [2].

Uric acid is produced by endogenous sources including vascular endothelium, liver and kidneys. It has been found that the level of uric acid increases in the case of oxidative stress, thereby indicating its antioxidant and proinflammatory effects. The most important antioxidant effect occurs by neutralizing free radicals in serum [3, 4].

Community-acquired pneumonia (CAP) is a clinical condition caused by infectious diseases and also a leading cause of mortality and morbidity. CAP is often accompanied by infection-associated inflammation and oxidative stress [5]. To date, a variety of scoring systems [(Confusion Urea Respiratory Rate Blood Pressure-65 (CURB-65) and pneumonia severity index (PSI)] and biochemical markers (c-reactive protein, procalcitonin) have been used in the assessment of hospitalization, mortality and prognosis in CAP patients. However, although uric acid concentration

has been shown to be correlated with the severity, prognosis, and incidence of respiratory diseases, there is no clear evidence regarding the effect of lipid concentration on the prognosis of these diseases [2, 6]. Moreover, some previous studies found reduced HDL levels in CAP patients [7, 8]. The aim of this study was to investigate the relationship between initial serum HDL, LDL, and uric acid levels on short-term (30-day) changes in the course of CAP.

## Materials and methods

The retrospective study included 113 patients with CAP that received inpatient care between 2012 and 2018. After obtaining an approval from the local ethics committee (Ufuk University Non-Interventional Clinical Research approved by the Ethics Committee), clinical records including laboratory findings, hospital discharge reports, and 30-day mortality records were retrieved from hospital databases. The HDL, LDL and uric acid levels of the patients were measured within the first 24 hours after hospital admission. Inclusion criteria were as follows: a diagnosis of CAP based on the British Thoracic Society (BTS) and American Thoracic Society (ATS) guidelines, a history of treatment at the inpatient service or intensive care unit (ICU), and a CURB-65 and PSI score [9-11]. Exclusion criteria were as follows: pregnancy, active systemic diseases, infections other than CAP, acute or chronic kidney disease, chronic lung disease, chronic obstructive pulmonary disease (COPD), active malignancy, use of drugs that could affect HDL, LDL, and uric acid concentrations and a diagnosis of connective tissue disease or vasculitis. HDL, LDL, and uric acid concentrations were assessed spectrophotometrically using an Abbot C8000

device. Normal ranges of HDL, LDL, and uric acid concentrations were accepted as 40-70 mg/dL, 60-130 mg/dL, and 1.8-8 mg/dL, respectively.

### Statistical analysis

Statistical analyses were performed using SPSS for Windows version 23.0 (IBM SPSS Inc., Armonk, NY, USA). Descriptives were expressed as frequencies (n), percentages (%), mean  $\pm$  standard deviation (SD), and median (minimum-maximum). Normal distribution of data was assessed using Kolmogorov-Smirnov and Shapiro Wilk tests. Homogeneity of variances was tested by Levene's test. Continuous variables were compared using Student's *t*-test or Mann-Whitney U test and categorical variables were compared using Chi-square test. Correlations between variables were determined using Spearman's Correlation Coefficient. Factors affecting the 30-day mortality were determined using univariate and multiple analyses of logistic regression. ROC curves were constructed to illustrate the sensitivity and specificity performance of HDL, LDL, and uric acid levels on ICU requirement. A *p* value of  $<0.05$  was considered significant.

### Results

The 113 patients comprised 71 (62.8%) men and 42 (37.2%) women with a mean age of  $74\pm 11$  years. Of the 113 patients, 30-day mortality occurred in 12 (10.6%) patients. All mortality developing patients were observed in ICU. In the 17 patients that were hospitalized in ICU, mean APACHE II score was  $26.36\pm 5.03$  and the expected mortality rate was  $52.86\pm 21.65$ . In all patients, mean hospital stay was  $6.92\pm 3.08$  days. Table 1 presents the demographic characteristics, 30-day mortality, duration of ICU and hospital stay, and CURB-65 and PSI scores for all patients. Mean serum LDL, HDL, and uric acid levels were  $97.95\pm 42.11$  (range, 26-271) mg/dL,  $40.94\pm 13.70$  (range, 5.10-83.20) mg/dL, and  $5.99\pm 2.18$  (range, 1.40-13.20) mg/dL, respectively (Table 2).

In univariate logistic regression analysis CURB-65 scores was found to be significant factors affecting 30-day mortality ( $p<0.001$ ) while HDL, LDL and uric acid levels were found to be insignificant factors ( $p=0.482$ ,  $p=0.117$  and  $p=0.725$ , respectively). In multivariate logistic regression analysis, uric acid concentration was found to be a protective factor (OR, 0.694; 95%

**Table 1.** Demographic and clinical characteristics

Variables	n (%)		
<b>Gender</b>	Male	71 (62.8)	
	Female	42 (37.2)	
<b>Mortality</b>	Yes	12 (10.6)	
	No	101 (89.4)	
<b>ICU requirement</b>	Yes	17 (15)	
	No	96 (85)	
<b>CURB-65</b>	2	49 (43.4)	
	3	55 (48.7)	
	4	8 (7.1)	
	5	1 (0.9)	
<b>PSI score</b>	2	20 (17.7)	
	3	55 (48.7)	
	4	37 (32.7)	
	5	3 (2.7)	
<b>Variables</b>	<b>Mean<math>\pm</math>SD</b>	<b>Median</b>	<b>Min-Max</b>
<b>Age (years)</b>	$74\pm 11$	75	39.00-94.00
<b>Duration of hospitalization</b>	$6.92\pm 3.08$	7.00	1.00-16.00
<b>APACHE II</b>	$26.36\pm 5.03$	26.50	19.00-35.00
<b>Expected mortality rate</b>	$52.86\pm 21.65$	51.35	3.80-83.10
<b>CURB-65</b>	$2.65\pm 0.65$	3.00	2.00-5.00
<b>PSI</b>	$3.20\pm 0.76$	3.00	2.00-5.00

ICU: Intensive care unit, CURB-65: Confusion Urea Respiratory Rate Blood Pressure-65, PSI: Pneumonia severity index, SD: Standard deviation

**Table 2.** LDL, HDL and uric acid levels

Variables	Mean±SD	Median	Min-Max
<b>LDL</b>	97.95±42.11	93.00	26.00-271.00
<b>HDL</b>	40.94±13.70	40.00	5.10-83.00
<b>Uric acid</b>	5.99±2.18	6.00	1.40-13.20

LDL: Low-density lipoprotein  
HDL: High-density lipoprotein

CI, 0.478-0.989,  $p=0.048$ ), whereby increased uric acid concentration was found to decrease the risk of mortality and reduced uric acid concentration was found to increase the risk of mortality by 1.44 times (1/0.694) (Table 3).

On the other hand, PSI and CURB-65 scores and HDL, LDL, and uric acid concentrations were found to have no insignificant effect on the duration of hospitalization ( $p=0.195$ ,  $p=0.662$ ,  $p=0.917$ ,  $p=0.080$  and  $p=0.996$ ) (Table 4). Similarly, no significant difference was found between mortality and non-mortality groups with regard to LDL, HDL, and uric acid concentrations ( $p=0.592$ ,  $p=0.479$  and  $p=0.132$ ) (Table 5) (Figure 1).

Uric acid, LDL, and HDL concentrations were found to be insignificant predictors of ICU requirement due to the small number of patients hospitalized in ICU ( $p=0.109$ ,  $p=0.472$ , and  $p=0.472$ , respectively) (Figure 2). Similarly, CURB-65 and PSI scores were found to be significant predictors of ICU requirement in CAP ( $p=0.005$  and  $p=0.007$ , respectively).

### Discussion

The current retrospective, single-centered study evaluated the correlation between HDL, LDL, and uric acid concentrations and 30-day mortality, duration of hospitalization, and ICU requirement in 113 patients with CAP so that

**Table 3.** Effect of CURB-65 scores, HDL, LDL, and uric acid levels in predicting 30-day mortality

Univariate Logistic Regression analysis					
Variables	B	Standard Error	Odds ratio	95% Confidence Interval (CI) Lower limit – Upper limit	<i>p</i>
<b>CURB-65</b>	2.057	0.582	7.820	2.496-24.502	<0.001
<b>HDL</b>	-0.017	0.024	0.983	0.939-1.030	0.482
<b>LDL</b>	-0.003	0.008	0.997	0.983-1.020	0.725
<b>Uric acid</b>	-0.257	0.164	0.773	0.561-1.067	0.117
Multiple Logistic Regression Analysis					
Variables	B	Standard Error	Odds ratio	95% Confidence Interval (CI) Lower limit – Upper limit	<i>p</i>
<b>CURB-65</b>	2.249	0.633	9.447	2.742-32.756	<0.001
<b>Uric acid</b>	-0.365	0.185	0.694	0.478-0.989	0.048

LDL: Low-density lipoprotein, HDL: High-density lipoprotein,  
CURB-65: Confusion Urea Respiratory Rate Blood Pressure-65

**Table 4.** Effect of PSI, CURB-65 scores and HDL, LDL, and uric acid levels on the duration of hospitalization

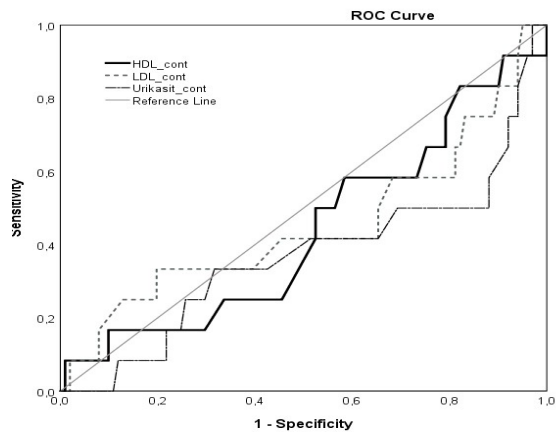
Spearman's Rho (r;p)	LDL	HDL	Uric acid	PSI	CURB-65
<b>Duration of hospitalization (n=103)</b>	-0.172 0.080	0.010 0.917	0.001 0.996	0.128 0.195	-0.043 0.662

LDL: Low-density lipoprotein, HDL: High-density lipoprotein, CURB-65: Confusion Urea Respiratory Rate Blood Pressure-65,  
PSI: Pneumonia severity index

**Table 5.** HDL, LDL, and uric acid levels mortality and non-mortality groups

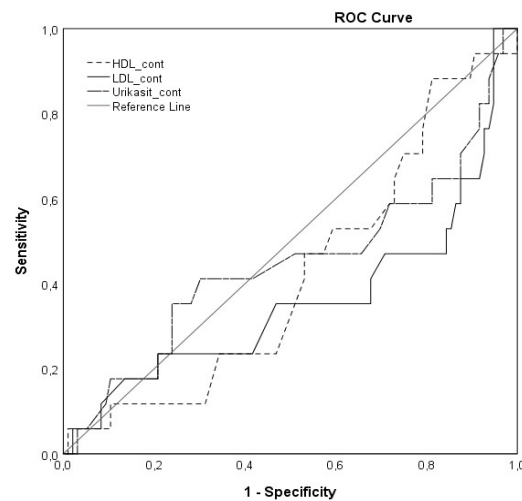
Variables	non-mortality	mortality	p
	Mean±SD-[Median-(Min-Max)]	Mean±SD-[Median-(Min-Max)]	
LDL	98.43±41.43-[93.00 (26.00–271.00)]	93.93 ±49.23-80.96[(35.00–181.00)]	0.592
HDL	41.25±13.25-[40.00(16.90–83.20)]	38.31±17.47-[38.25 (5.10–76.98)]	0.479
Uric acid	6.10±2.15-[6.00 (1.40–13.30)]	5.05±2.22-[4.18 (2.80–8.90)]	0.132

LDL: Low-density lipoprotein, HDL: High-density lipoprotein

**Figure 1.** Correlation between LDL, HDL, and uric acid levels and 30-day mortality

HDL and LDL levels are insignificant factors. Additionally, multivariate analysis indicated that uric acid concentration was a protective factor for 30-day mortality, whereby increased uric acid concentration was found to decrease the risk of mortality and reduced uric acid concentration was found to increase the risk of mortality, which was consistent with the findings of numerous studies in the literature (2,6).

Previous studies indicated that plasma lipoproteins neutralize lipopolysaccharides and lipoteichoic acid in gram-negative and positive bacteria. Therefore, it has been determined to play a role in body defense [12, 13]. Additionally, HDL has been reported to have anti-inflammatory, antioxidant, and immunomodulatory effects [14]. LDL, on the other hand, has been shown to facilitate the clearance of bacterial toxins in sepsis [15]. LDL and HDL levels are known to decrease in response to oxidation, infection, and inflammation [16]. Some previous studies evaluated patients hospitalized for CAP and indicated a strong correlation between reduced HDL concentration and causes of clinical

**Figure 2.** Correlation between LDL, HDL, and uric acid levels and ICU requirement

worsening such as hemodynamic instability and pleural effusion [14, 17].

In our study, initial serum HDL and LDL levels were found to be insignificant predictors of 30-day prognosis and mortality. In the 17 patients with sepsis, serum lipid levels (cholesterol, HDL, LDL) were assessed on admission and on days 3 and 28 after admission. The assessments indicated that lipoprotein concentrations decreased by 50%, this reduction initially occurred in HDL concentration, and LDL concentration decreased more slowly compared to HDL concentration [18]. In our study, however, no reduction could be detected in LDL and particularly in HDL levels since no serial measurement was performed for any of these two parameters. Moreover, since no data was available regarding initial serum HDL and LDL levels in our patients, no comparison was achieved. Therefore our results were thought to be incompatible with the literature.

Uric acid, which is a product of purine metabolism, is excreted from the urine and



gastrointestinal systems [19-21]. Therefore, kidney-function tests [glomerular filtration rate (GFR)] are one of the important factors affecting the uric acid level. Oxidative stress may alter serum uric acid concentration as a result of infection [22]. Additionally, reduced uric acid levels have been shown to be associated with the underlying malnutrition in patients [23]. A previous prospective study evaluated the effect of serum uric acid concentration on mortality in hospitalized in several ICUs and reported that elevated serum uric acid levels increased the mortality rate by 2.638 times. The authors suggested that serum uric acid level could be integrated into risk scoring systems through advanced studies [24, 25]. In our study, multivariate analysis indicated that serum uric acid concentration is a significant predictor of 30-day mortality ( $p=0.048$ ). Additionally, serum uric acid concentration was also found to be a protective factor in CAP, whereby increased uric acid concentration was found to decrease the risk of mortality and reduced uric acid concentration was found to increase the risk of mortality by 1.44 times (1/0.694). These findings of our study were consistent with those reported in the literature.

In the present study, initial serum uric acid levels were found to be an insignificant predictor of ICU requirement. Akbar et al. [21] evaluated hyperuricemia as an early marker of sepsis and they showed the APACHE II score correlates with increase uric acid level. Zhu and Cao [19] retrospectively found no correlation between initial uric acid levels and prognosis of infection in hospitalized ICU patients due to infection. It has been determined that serum uric acid levels vary due to changes in renal functions due to lactic acid deposition in severe infections [19, 26, 27]. In sepsis patients, in particular, lactic acid monitoring is of paramount importance. In the present study, however, no information could be obtained regarding the lactic acid levels of the patients due to the retrospective nature of the study. Moreover, the correlation between serum uric acid concentration and the severity assessment systems used in ICU could not be analyzed. Literature indicates that there is no consensus regarding the effect of serum uric acid concentration in predicting ICU requirement in hospitalized CAP patients. Our results were evaluated based on a small number of literature results.

Our study was limited in several ways. First, the study had a retrospective design and thus serum HDL, LDL, and uric acid levels of the patients were measured within the first 24 h after hospital admission. Accordingly, the serial measurements proposed in recent reports could not be performed and the relationship between serum uric acid concentration and the factors affecting this concentration such as body mass index (BMI), GFR, and serum glucose levels could not be analyzed due to the retrospective nature of the study. Second, the study was conducted in a single center, had a small patient population, and included no information regarding specific microbiological culture results and radiological outcomes of the patients. Based on we suggest that monitoring uric acid levels with serial measurements in patients with CAP may be useful for predicting the short term prognosis. Further prospective multicentric studies with larger patient series are needed to evaluate short-term mortality, microbiological and radiographic results, hemodynamic changes, and serial HDL and LDL measurements in CAP patients and also to investigate the correlation between these parameters and other acute-phase reactants.

**Conflict of interest:** No conflict of interest was declared by the authors.

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**Contributions of the authors to the article**

D.H., E.E.A. set up the main idea and hypothesis of the study. E.E.A., E.S.G. and N.O. developed the theory and edited the material method section. C.A. made the evaluation of data in results section. The discussion part of the article was written by D.H., B.A.K. and E.E.A. reviewed, made necessary corrections and approved. In addition, all authors discussed the entire study and approved its final version.