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Research Article

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EVALUATION OF THE RELATIONSHIP BETWEEN HIGH-DENSITY LIPOPROTEIN CHOLESTEROL LEVELS AND COMMUNITY-ACQUIRED PNEUMONIA SEVERITY IN ADULT PATIENTS

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Abstract

Objectives: Inflammation and acute phase reactions lead to altered high-density lipoprotein cholesterol (HDL-C) concentrations. This study aimed to evaluate HDL-C levels in community-acquired pneumonia (CAP) and to determine the predictive value of disease severity in CAP.

Materials and Methods: This prospective study was conducted in the Department of Pulmonary Diseases. One hundred twenty-five adult patients with CAP were included in the study. Patients were classified into three groups as follows: Group 1; outpatients, Group 2; hospitalized patients and Group 3; patients admitted to the intensive care unit. C-reactive protein (CRP), procalcitonin (PCT) and HDL-C levels were evaluated at baseline, 7th and 30th days in all CAP patients. The relationship between CRP, PCT and HDL-C levels was investigated. Diagnostic performance of baseline HDL-C levels was assessed using receiver-operating characteristic (ROC) curve analyses.

Results: HDL-C levels were found to be decreased in all groups compared to their normal ranges. There was a significantly negative correlation between HDL-C and CRP and PCT (Spearman's r=-0.557, r=-0.841, respectively; p< 0.001). The sensitivity and specificity of HDL-C cut-off value were 0.738 (95% CI=0.580-0.861) and 0.875 (95% CI=0.732-0.958), with an overall accuracy of 0.861 (95% CI=0.728-0.935).

Conclusion: HDL-C levels can be used as an acute phase reactant in patients with CAP.

Keywords: Community-acquired pneumonia, high-density lipoprotein cholesterol, biomarker.

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Introduction

Community-acquired pneumonia (CAP) represents a major infectious cause of mortality that is associated with significant utilization of healthcare resources all over the world. Almost 40% of the patients with CAP require hospitalization, with a further 10% requiring admission to intensive care unit (ICU).[1] Determinant of mortality in CAP patients includes the severity of the disease, treatment regimens and admission status (i.e., admission to hospital and/or ICU). Therefore, scoring systems have been developed to assist physicians in defining the disease severity and predicting possible clinical outcomes. As, CURB-65 (confusion, blood urea nitrogen >20 mg/dL (>7 mmol/L), respiratory rate ≥30 breaths per minute, systolic blood pressure <90 mmHg or diastolic blood pressure ≤60 mmHg, and age ≥65 years), and Pneumonia Severity Index (PSI) represent two scoring systems to predict the clinical response and long-term outcomes in CAP patients.[2] In recent years, various biomarkers have been extensively studied in CAP for diagnosis, disease severity, and treatment monitoring. C-reactive protein (CRP) and procalcitonin (PCT) are the most commonly used biomarkers in CAP.[3] In recent years, several studies have been published investigating the relationship between CAP and serum lipoproteins.[4,5]

High-density lipoprotein cholesterol (HDL-C) and other plasma lipoproteins act as neutralizing agents against endotoxins, inactivating the bacterial endotoxins and leading to anti-inflammatory effects.[6,7] Patients with sepsis and multi-organ dysfunction have significant reductions in total cholesterol and HDL-C concentrations that correlate with the severity of inflammation and poor outcomes.[8,9] It was also shown that HDL-C concentration decreases in septic patients, and the low level of HDL-C is associated with a poor prognosis.[11]

There are few studies that have examined the role of HDL-C levels in CAP patients. Thus, in this study, we aimed to evaluate HDL-C levels in CAP and to determine the predictive value of disease severity in CAP.

Materials and Methods

Study Design and Patient Selection

This single-center, prospective study was conducted in the Department of Chest Diseases in September 2017 and September 2018. The study was approved by the local ethical committee. Informed consent was obtained from all participants.

One hundred twenty-five newly diagnosed adult patients with CAP were included in the study. CAP was defined as an acute condition characterized by at least one respiratory symptom together with two or more of the following clinical signs: fever, chills, cough, sputum production, shortness of breath, pleuritic chest pain, and

one auscultation sign in conjunction with newly developing infiltration in chest X-ray.[12] The patients with CAP were assigned into three groups as follows: Group 1; outpatients, Group 2; hospitalized patients and Group 3; patients requiring intensive care unit. CRP, PCT and HDL-C levels were evaluated at baseline, 7th and 30th days in all CAP patients. The relationship between CRP, PCT and HDL-C levels was investigated. Demographic data, clinical and laboratory parameters of all CAP patients were recorded.

Exclusion criteria were age under 18 years, presence of mental disability, pregnancy, hyperlipidemia and use of anti-lipid drugs, end-stage cancer, those receiving parenteral nutritional support and unwillingness to participate in the study.

CRP (Siemens BN II System, Munich, Germany), HDL-C (Roche Cobas 8000, Mannheim, Germany) and PCT levels (Roche Cobas 6000, Tokyo, Japan) were measured using commercial kits. Normal levels based on the kit used were: CRP 0-5 mg/L, HDL-C in male > 40 mg/dL, in female > 50 mg/dL, PCT < 0.01 ng/mL.

Statistical analysis

The distribution of the continuous variables was examined by both Shapiro-Wilk's test and normality plots. Normally distributed variables were expressed by the mean and standard deviation (mean ± SD), while other continuous and discrete variables were summarized by median (minimum-maximum). Frequency (%) was given for categorical variables. Three patient groups were compared in terms of demographic characteristics by one-way analysis of variance (ANOVA), Kruskal-Wallis test or Chi-square tests. Bonferroni correction and Bonferroni-Dun correction were performed as posthoc tests for ANOVA and Kruskal-Wallis test, respectively. Column proportions were compared by z test in the case chi-square test resulted significantly.

The interaction effect of group and time on serum CRP, PCT, and HDL-C levels was examined with the F1-LD-F1 design for nonparametric analysis of longitudinal data since the two-way mixed ANOVA assumptions were not met. P values of ANOVA-type statistics were given for group-time interaction effect and time effect in each group. LD-F1 design and Bonferroni correction were applied to obtain pairwise comparisons within each group. The diagnostic performances of baseline HDL-C levels discriminating Group 3 from Group 2 and Group 2 from Group 1 were examined by ROC curve analysis. The area under the curve (AUC) and its standard error (SE) were given. The optimal cut-off point was determined by Youden's index. 95% "exact" Clopper-Pearson confidence interval (CI) were calculated for sensitivity, specificity and accuracy, as 95% CI of the predictive values were the standard logit confidence intervals given by Mercaldo et al.[13]

F1-LD-F1 design and LD-F1 design were performed by nparLD package in RStudio (Version 1.1.456). All other analyses were performed via IBM SPSS Statistics 21.0 (IBM, Armonk, NY, USA). A p-value < 0.05 was accepted as statistically significant.

Results

A total of 125 subjects with CAP were included in the study. There were 40 patients in Group 1, 42 in Group 2, and 43 in Group 3. The mean age in these three groups was 42.31 ± 16.78 years (min-max: 18-86), 63.14 ± 14.83 years (30-85), and 70 ± 17.86 years (19-93), respectively. There were significant age differences between in three groups (p< 0.001). In Group 1, 45.20% of the patients (n= 17) were male, and the proportion of male patients in Group 1 was smaller as compared to the other two groups (p= 0.004). The demographic data general clinical manifestations are shown in Table 1.

Table 1. Demographic data and clinical characteristics in patients with community-acquired pneumonia

Variables	Group 1 (n=40)	Group 2 (n=42)	Group 3 (n=43)	p
Age (mean ± SD)	42.31 ± 16.78	63.14 ± 14.83	70 ± 17.86	< 0.001*
Gender (n, %)				
Male	17 (42.50)[1,2]	30 (71.41)[1]	32 (74.43)[2]	0.004
Female	23 (50)[1,2]	12 (26.12)[1]	11 (23.91)[1]	
BMI (normal< 25 kg/m²) (n, %)	25 (62.50)	20 (47.64)	21 (48.82)	0.327
Smoking status (n, %)	18 (45)	26 (61.95)	24 (55.81)	0.299
SpO_2 (mean ± SD)	95.69 ± 2.61	91.28 ± 4.21	88.11 ± 4.14	< 0.001*
Systolic blood pressure mmHg (mean ± SD)	112.16 ± 11.57	116.51 ± 14.89	115.91 ± 14.50	0.341
Bilateral lung infiltration on chest X-ray (n, %)	7 (17.50)[1]	15 (35.71)[2]	32 (74.41)[1,2]	< 0.001
Comorbidities (n, %)				
Diabetes mellitus	4 (10)[1]	14 (33.33)[1]	11 (25.58)	0.039
Chronic heart disease	5 (12.50)	19 (45.24)	35 (81.39)	< 0.001*
Chronic lung disease	4 (1)[1]	11 (26.19)	17 (39.53)[1]	0.009
Chronic liver disease	0 (0)	3 (7.14)	1 (2.32)	–
Cerebrovascular disease	0 (0)	1 (2.38)	3 (6.98)	–

*All groups were significantly different from each other.
[1,2]: Corresponding groups were significantly different.
BMI: Body mass index, SpO_2: Oxygen saturation.

Table 2 shows the serial CRP, PCT, and HDL-C results measured at baseline and at days 7 and 30 of the study. There was a significant decline in CRP and PCT from baseline to day 30 in all groups (p< 0.001), while HDL-C levels increased significantly from baseline to day 30 (p< 0.001). However, the difference between HDL-C at

baseline and HDL-C at day 7 were not significantly different in Group 1. HDL-C levels were significantly higher in Group 1 patients compared to Group 2 and 3 patients at baseline, 7th and 30th days.

A strong positive and linear correlation between baseline PCT and CRP levels was found (Spearmen's r= 0.722, p< 0.001). A moderately strong, negative linear correlation between HDL-C and CRP (Figure 1) and PCT (Figure 2) was found (Spearman's r= -0.557, r= -0.841, p< 0.001). A significant change was observed in serial CRP, PCT, and HDL-C levels in all groups. The extent of change was similar in Groups 2 and 3 (p> 0.05), while it was significantly different as compared to Group 1 (Table 3, Figure 3).

Baseline HDL-C was able to differentiate Group 2 from Group 1, with a cut-off of 21.35 mg/dl. HDL-C levels did not provide statistical significance for differentiating Group 3 from Group 2. The sensitivity and specificity of HDL-C cut-off value were 0.738 (95% CI: 0.580-0.861) and 0.875 (95% CI: 0.732-0.958), with an overall accuracy of 0.861 (95% CI: 0.728-0.935) (Figure 4).

Table 2. Serial CRP, PCT and plasma HDL-C measurements in study groups

Variables	**Group 1**	**Group 2**	**Group 3**	
	Median (min-max)	**Median (min-max)**	**Median (min-max)**	**p***
CRP (mg/L)				
CRP1	77.10 (7.50-343)	192 (44.57-51)	226 (47.11-17)	**< 0.001†**
CRP7	7.50 (3-110)	24 (4.33-104)	38.12 (3.27-139)	**< 0.001†**
CRP30	3.50 (3-27)	5.90 (3-24)	7.51 (3.13-47)	**< 0.001†**
p-value**	**< 0.001‡**	**< 0.001‡**	**< 0.001‡**	
PCT (ng/mL)				
PCT1	0.09 (0.02-25)	0.76 (0.04-39)	1.58 (0.09-89)	**< 0.001†**
PCT7	0.05 (0.01-0.85)	0.11 (0.03-2.94)	0.12 (0.03-1.92)	**< 0.001†**
PCT30	0.03 (0.01-1)	0.04 (0.03-0.23)	0.04 (0.01-2.11)	0.162
p-value**	**< 0.001‡**	**< 0.001‡**	**< 0.001‡**	
HDL-C (mg/dL)				
HDL-C1	34 (4.21-72)[1]	16 (2.82-56)	14.89 (2.91-52)	**< 0.001†**
HDL-C7	34.37 (12-70)[2]	25.71 (10.36-56)	28 (9-54)	**< 0.001†**
HDL-C30	47 (25-82)[1,2]	40.28 (26-68)	42 (27-73)	**0.043§**
p-value**	**< 0.001**	**< 0.001‡**	**< 0.001‡**	

* Between-group comparison result, ** Within-group comparison result
† Group1 was significantly different compared to the other two groups
‡ All time points were significantly different from each other
§ Group1 was significantly different compared to Group3
[1,2] p< 0.05
CRP: C-Reactive protein, PCT: Procalcitonin, HDL-C: High-density lipoprotein cholesterol.

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Table 3. Group-time interaction for PCT, CRP, and HDL-C

	Group-time interaction			
	All Groups	**Group 1-Group 2**	**Group 1-Group 3**	**Group 2-Group 3**
	p	**p**	**p**	**p**
CRP	0.005	0.006	0.012	0.299
PCT	< 0.001	0.007	< 0.001	0.243
HDL-C	< 0.001	< 0.001	< 0.001	0.780

CRP: C-Reactive protein, PCT: Procalcitonin, HDL-C: High-density lipoprotein cholesterol

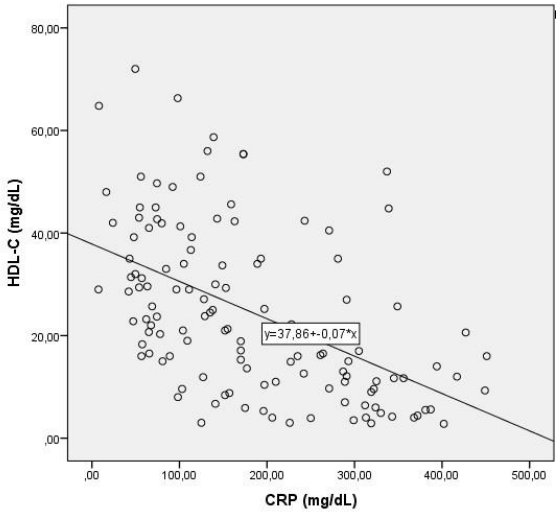

Figure 1. The relationship between HDL-C (mg/dL) and the CRP (mg/L) (r=-0.557, p<0.001). (CRP: C-Reactive protein, HDL-C: High-density lipoprotein cholesterol.)

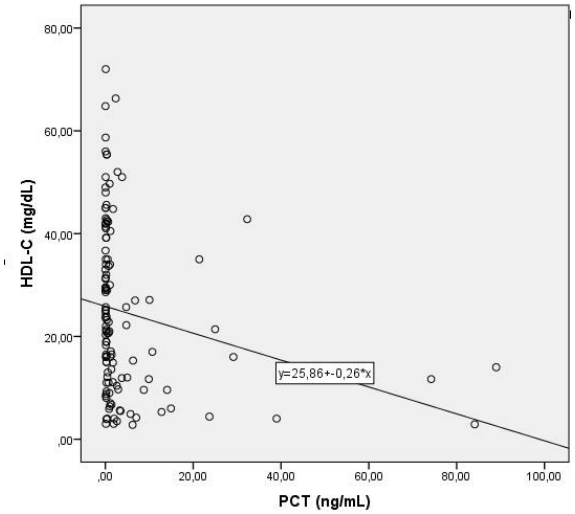

Figure 2. The relationship between HDL-C (mg/dL) and the PCT (ng/mL) (r=-0.841, p<0.001). (PCT: Procalcitonin, HDL-C: High-density lipoprotein cholesterol.)

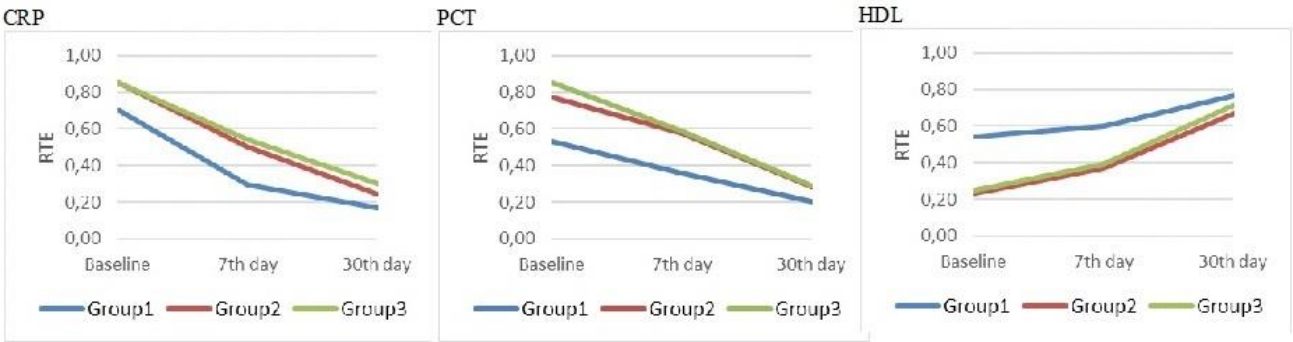

Figure 3. Change in serum CRP, PCT and HDL-C over time in study groups.
(CRP: C-Reactive protein, PCT: Procalcitonin, HDL-C: High-density lipoprotein cholesterol.)

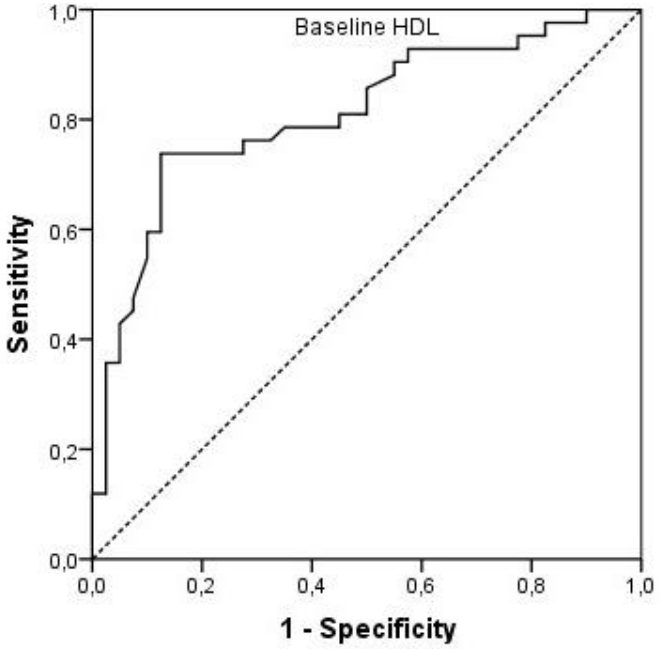

Figure 4. The discriminative power of ROC curves for baseline PCT and HDL-C in Groups 2 and 1. (HDL-C: High-density lipoprotein cholesterol.)

Discussion

In this study, we found a significant reduction in HDL-C during the acute course of CAP. Also, HDL-C levels were found to be significantly lower in more severe patients such as Groups 2 and 3 than outpatients in Group 1. In the follow-up of the patients, it increased compared to the baseline on the 7th and 30th days. HDL-C cut-off value was 73% sensitive and 87% specific in distinguishing cases requiring outpatient treatment and hospitalization. There were significant negative correlations between HDL-C levels and PCT, CRP levels.

Biomarkers are any substances, structures, or processes that can be measured within the body and that can impact or predict the incidence or outcome of a disease.[14] In pneumonia, biomarkers are utilized to assist in diagnosis to determine the disease severity, risk category, triage, administering antibiotherapy, and predicting the prognosis. Several studies have examined potential biomarkers with high sensitivity and specificity as well as high with positive and negative predictive values that can be measured simply and reliably in pneumonia patients.[15]

In recent years, HDL-C particles have been reported to possess anti-inflammatory, antioxidant, and immunomodulatory properties. HDL-C has significant functions in normal lung physiology and plays a role in triggering a pulmonary immune response against lung injury and infections.[16] During the acute phase response in humans, HDL-C and its parent apolipoprotein (ApoA-I) levels decrease with changes in the protein content of HDL-C associated proteins. Ultimately, this leads to a decline in serum paraoxonase levels and in the antioxidant properties of HDL-C.[17] In adult lungs, ApoA-I is released from the alveolar epithelial cells and

alveolar macrophages. It is neutralized by binding to lipopolysaccharides produced by the cell wall of gram-negative bacteria and to lipoteichoic acid, which is a component of the cell wall of gram-positive bacteria. Also, HDL-C modulates innate cellular immunity and prevents the release of inflammatory cytokines. In sepsis, it transports cholesterol to adrenal glands for steroid synthesis.[17,18] On the other hand, HDL-C is oxidized during acute or chronic inflammation, becoming dysfunctional and pro-inflammatory. Dysfunctional HDL is not only devoid of its protective properties but also may be associated with the spread of tissue injury and infection.[19,20] HDL-C and ApoA-I also affect the pathogenesis of influenza A infections. HDL-C derived from mice infected with influenza A virus exhibit reduced anti-inflammatory, antioxidant, paraoxonase and platelet-activating capacity.[21]

Changes in lipid metabolism have been studied in only a few studies in patients with CAP. Rodriguez Reguero et al. found a significant reduction in total cholesterol, HDL-C, apolipoproteins A1 and B during the acute phase of CAP. They only reported a significant increase in HDL-C levels after 15 days of follow-up.[22] Deniz et al. observed a significant negative correlation between HDL-C levels and the radiological extent of the disease in 97 patients. Also, a similar correlation was reported for erythrocyte sedimentation rate, while other biomarkers such as CRP and PCT have not been investigated.[23] In another study in patients with lower respiratory tract infections, a reduction in serum total cholesterol, LDL cholesterol, and HDL-C was observed among those diagnosed with CAP.[24] Our findings confirm the data of the authors who reported a decrease in HDL-C levels in the acute process in CAP. In this present study, a decrease was observed in the acute process in cases with high baseline HDL-C values. In Group 2 and Group 3 patients, HDL-C levels were observed to be lower than the Group 1 patients. Since Group 3 patients are the patients who absolutely need to be hospitalized, it may be useful to evaluate HDL-C levels to make the decision for hospitalization among Group 1 and 2 patients.

In a study by Chien et al., the prognostic value of serum lipid levels was examined in severe CAP patients requiring ICU. The CRP, LDL, and HDL cholesterol levels at admission did not differ significantly between those who did and did not survive, although a significant decline in HDL-C at day seven was observed among those who subsequently died. Accordingly, HDL-C levels of ≥ 17 mg/dL and an LDL cholesterol level of ≤ 21 mg/dL were reported to be predictors of in-hospital mortality.[5] In a retrospective study by Sabalis et al., mean HDL-C levels in patients developing shock was 16.25 mg/dL, while it was 23.66 mg/dL in those admitted to intensive care.[4] In the current study, the cut-off value for HDL-C to differentiate outpatients from those requiring hospitalization was 21.35 mg/dL. Serial measurements (i.e., baseline, day 7, and day 30) showed a trend toward decline in CRP and PCT in Groups 1, 2, and 3, while HDL cholesterol levels increased in response to treatment. These observations are in line with previous studies, supporting the inverse association between HDL-C and inflammatory serum markers such as CRP and PCT. HDL-C serves as an effective inflammatory modulator during infection. In another study with sepsis patients, baseline HDL-C was found to be correlated with albumin and CRP, suggesting that HDL-C serves as an acute phase reactant.[25]

The present study had certain limitations. One of the limitations of our study is that the lipid profiles of most of the participants were not known before they became ill. The duration and change of antibiotic treatments during this study were not recorded. Also, the association between HDL-C levels and mortality was not explored, and the duration of ICU stay in patients in Group 3 was not assessed. Another limitation of our study relates to the fact that due to the low number of patients in whom a causative organism could be identified, the association between HDL-C and possible pathogens was not assessed.

In conclusion, HDL-C levels can be used to identify acute phase reactions in patients with CAP and to evaluate disease severity. In this study, HDL-C was found to be particularly useful in distinguishing outpatients from those requiring hospitalization. Low HDL-C levels may be a warning to healthcare professionals for closer follow-up in outpatient cases. Also, we believe that HDL-C levels in CAP patients may be a useful marker for monitoring response to therapy, such as CRP and PCT.

Ethical Considerations: The study procedure was established in compliance with the basis of the Helsinki Declaration and confirmed by the local ethics board (Decision number: 115, Date: 13.04.2016)

Conflict of Interest: The authors declare no conflict of interest.

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