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Original Research Article

Association of Interleukin-6 (IL-6) and High-Density Lipoprotein Cholesterol (HDL-C) with Disease Severity of Coronavirus Disease 2019 (COVID-19)

B.Uma Maheswari[1], R. Thamarai[2], A. Velayutharaj[3], Balaji.K[4], K. Sivakumar[5]

[1]Final Year Postgraduate, Department of Biochemistry, Trichy SRM Medical College Hospital and Research Centre, Irungalur, Trichy.
[2]Professor, Department of Biochemistry, Trichy SRM Medical College & Research Centre, Irungalur, Trichy, Tamilnadu, India
[3]Professor & HOD, Department of Biochemistry, Trichy SRM Medical College & Research Centre, Irungalur, Trichy, Tamilnadu, India.
[4]Professor, Department of Biochemistry, Trichy SRM Medical College & Research Centre Irungalur, Trichy, Tamilnadu, India.
[5]Professor & HOD, Department of Medicine, Trichy SRM Medical College & Research Centre, Irungalur, Trichy, Tamilnadu, India.

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Corresponding author: Dr B.Uma Maheshwari
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Abstract

Introduction: IL-6 is the key molecule of cytokine storm in COVID -19. Dyslipidemia is a common complication in patients with Coronavirus disease 2019 (COVID-19), but the association of dyslipidemia with the severity of COVID-19 is still unclear. In this study, we aimed to investigate the biochemical alterations of High-Density Lipoprotein Cholesterol (HDL-C), and Interleukin-6 (IL-6) in COVID-19 patients and their relationships with the disease severity.

Materials and Methods: We conducted a retrospective single-institutional study of 99 consecutive confirmed cases of COVID-19. Serum IL-6 and HDL-C concentrations, demographic and clinical profile were collected during hospital stay. Duration of study was from September 2020 to August 2021. Descriptive statistics were applied to summarize the demographic data. Results are reported as mean with standard deviation. Receiver operating characteristic curve (ROC) analysis was used to compare biochemical markers.

Results: Serum HDL-C levels had a significant positive correlation with SpO_2 with correlation coefficient r = 0.589. Serum IL-6 had a negative correlation with SpO_2 with correlation coefficient r = -0.632. The AUC for IL6 and HDL-C in predicting COVID severity is 0.982 and 0.985 respectively.

Conclusion: HDL-C is decreased and IL-6 is increased with the disease severity.

Keywords: Coronavirus, Dyslipidemia, High-Density Lipoprotein Cholesterol, Interleukin-6.

Introduction

Coronavirus disease 2019 pandemic has become a global challenge [1]. Several studies have indicated a "Cytokine Storm" with the release of interleukin-1 (IL-1), IL-6, and IL-8, along with tumor necrosis factor alpha (TNFα) and other inflammatory mediators [2,3]. IL-6 - better predictor of disease progression and it has been positively correlated with disease stages and radiologic changes [2]. Some previous studies have already explored the predictive value of IL-6 on several clinical aspects of COVID-19. The level of IL-6 at admission is useful to predict the risk of patients needing mechanical ventilation or high-flow oxygen during hospitalization [4]. Baseline interleukin-6 (IL-6) was found to be associated with COVID-19 severity [5]. Indeed, the significant increase of baseline IL-6 was positively correlated with the maximal body temperature during hospitalization and with the increased baseline of CRP, LDH, ferritin, and D-dimer [5]. High baseline IL-6 was related with more significant progressed chest computed tomography (CT) findings [5]. Many studies had mentioned that the dynamic change in IL-6 can be used as a marker for disease monitoring in patients with severe COVID-19.

Dyslipidemia is associated with damage to the immune, respiratory, and cardiovascular systems, along with high levels of pro-inflammatory cytokines [6]. Dyslipidemia is a common complication in patients with COVID-19 [7]. Reduction in total cholesterol and low-density lipoprotein cholesterol (LDL-C) in patients with COVID-19 has been reported. Very few studies studied the relationship between the Interleukin-6 (IL-6) and High-Density Lipoprotein Cholesterol among covid-19 patients. This study aimed to study the biochemical alteration of High-Density Lipoprotein Cholesterol (HDL-C) and Interleukin-6 (IL- 6) in COVID-19 patients and to analyze the potential association of dyslipidemia and Interleukin-6 with the severity of COVID-19.

Materials and Methods

We conducted a retrospective single-institutional study of 99 consecutive confirmed cases of COVID-19. Serum IL-6 and HDL-C concentrations, demographic and clinical profile were collected during hospital stay. The sampling technique followed was convenience sampling. A total of 99 hospitalized patients (admitted from September 2020 to August 2021), who were clinically diagnosed and laboratory confirmed to have a COVID-19 infection, were preliminarily involved in this study. The patients excluded were those who are under lipid lowering drugs such as statins. Patients were classified into mild, moderate and severe groups based on the coronavirus pneumonia diagnosis and treatment guidelines. The patients with COVID-19 who met any of the following three criteria were defined as severe patients: (1) respiratory distress ≥30 breaths per minute; (2) oxygen saturation (SpO2) at rest less than or equal to 93%. Treatment and outcome data for each patient was also obtained from the electronic medical record system IL-6 was estimated using electrochemiluminescence method in fully automated analyzer Roche Cobas C311 Biochemistry Analyzer. Serum HDL was estimated using enzymatic colorimetric method.

Descriptive statistics were applied to summarize the demographic data. Results are reported as mean with standard deviation. Univariate and multivariable analyses were conducted to examine the associations between lipids and IL-6 and disease severity. Receiver operating characteristic curve (ROC) analysis was used to compare biochemical markers. Spearman tests were used to analyze the correlations between lipids and IL 6. Statistical analyses were performed using SPSS software ver. 23.0

Results

The mean age among the subjects was 47.87 (± 17.34) ranging from 14 to 82 years. Among the subjects, 58 (58.59%) were males and 41 (41.41%) were females. Among the study population with COVID-19, 89 (89.9%) had mild COVID followed by 7 (7.07%) had severe COVID and least 3 (3.03%) had moderate COVID. The mean IL-6 among the subjects was 16.77 (± 36.02) ranging from 3 to 244 IU/L. The mean HDL-C among the subjects was 50.08 (± 14.37) ranging from 22 to 78 mg/dl (Table 1). Table 2 shows the comparison of IL-6 with COVID severity. The mean IL-6 among severe was 101.21 which is higher than mean among moderate which was 53.33 followed by mild with a mean of 8.22 and the difference was statistically significant ($p < 0.05$).

The mean HDL-C among severe was 27.8 which is lower than mean among moderate which was 34 and mild with a mean of 55.4 and the difference was statistically significant ($p < 0.05$) as shown in Table 2. The mean LDL-C among severe was 130 which is higher than mean among mild which was 93.89 followed by moderate with a mean of 89.33, but the difference was not statistically significant ($p > 0.05$) as given in Table 2. IL-6 had a significant negative correlation with SpO2 with correlation coefficient $r = - 0.632$. HDL- C had a significant positive correlation with SpO2 with correlation coefficient $r = 0.589$ as given in Table 3. The cutoff of IL-6 for predicting COVID severity is 31.9 (sensitivity 80% and specificity 98.8%). After adjusting for age and gender, binomial regression using IL-6 and HDL-C for predicting COVID severity was assessed separately. For each unit increase in IL-6, the risk of COVID severity increases by 1.17 times from mild to moderate or severe pneumonia. For each unit increase in HDL-C, the risk of COVID severity increases by 0.71 times from mild to moderate or severe pneumonia or the severity decreases by 1.414 times from moderate or severe to mild pneumonia.

The area under the curve for IL6 in predicting COVID Severity is tabulated in Table 5 & 6. The cutoff of IL-6 for predicting COVID severity is 31.9 which had a sensitivity of 80%, specificity of 98.8%, positive predictive value of 95.01%, negative predictive value of 94.53% and a diagnostic accuracy of 94.62%. The area under the curve for HDLC in predicting COVID Severity is 0.985 (0.953 - 1).The cutoff of HDLC for predicting COVID Severity is 31 which had a sensitivity of 62.5%, specificity of 96.7%, positive predictive value of 84.4%, negative predictive value of 90.03% and a diagnostic accuracy of 89.1%.

Table 1: Mean of serum IL6, HDL-C LDL-C

Parameters	N	Mean	Std. Deviation	Minimum	Maximum
IL6	92	16.77	36.02	3.0	244.0
HDL-C	38	50.08	14.37	22.0	78.0
LDL-C	45	97.60	33.99	56.0	210.0

Table 2: Comparison of IL-6, HDL-C, LDL-C with COVID severity

Parameters	COVID severity	N	Mean	Std. Deviation	p value
IL6	Severe	7	101.21	93.48	
	Moderate	3	53.33	2.08	
	Mild	82	8.22	8.38	0.000
HDL-C	Severe	5	27.80	5.26	

	Moderate	3	34.00	5.29	
	Mild	30	55.40	10.77	0.000
LDL-C	Severe	5	130.00	62.27	
	Moderate	3	89.33	57.74	
	Mild	37	93.89	25.11	0.073

Table 3: Correlation of IL6 & HDL-C with SpO_2

Spearman's rho correlation with SpO_2	Correlation coefficient "r"	p value
IL6	-0.632	0.001
HDLC	0.589	0.001

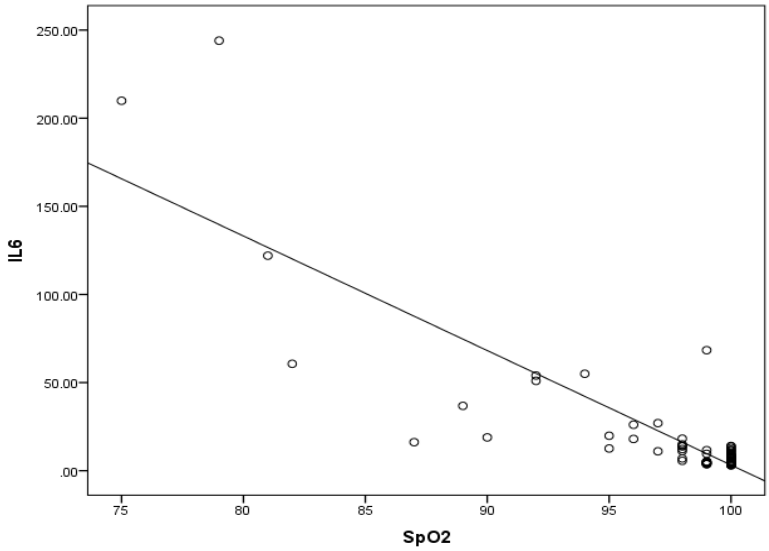

Figure 1: Correlation of IL6 with SpO_2

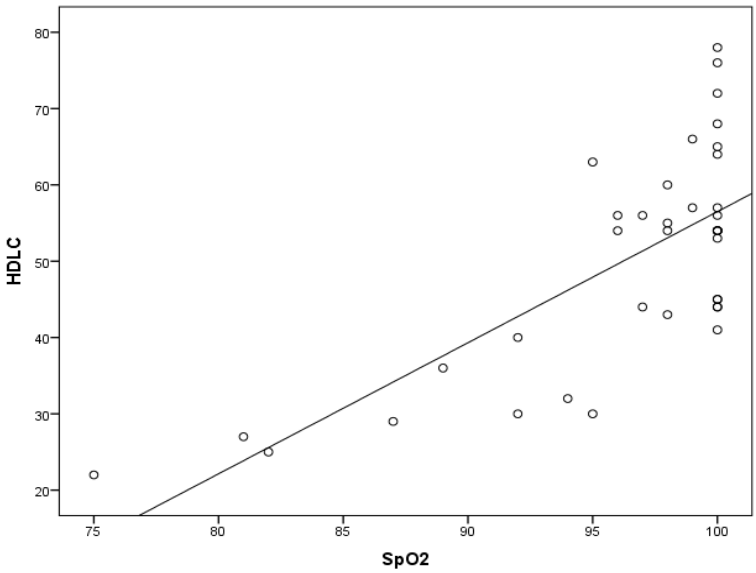

Figure 2: Correlation of HDL-C with SpO_2

Table 4: Binomial Regression for predicting COVID severity

Variables	B	Std. Error	Adjusted Odds Ratio (95% C.I.)	p value
IL6	0.155	0.056	1.17 (1.05 - 1.3)	0.006
HDLC	-0.346	0.159	0.71 (0.52 - 0.97)	0.03

Table 1:ROC curve for predicting COVID severity with IL6

Test Result Variable(s)	Area under the curve	95% Confidence Interval		p value
		Lower Bound	Upper Bound	
IL6	0.982	0.957	1.000	0.001

Table 2: ROC curve for predicting COVID severity with IL6

Test Result Variable(s)	Cut off	Sensitivity	Specificity	PPV	NPV
IL6	31.90	80.00%	98.80%	95.01%	94.53%

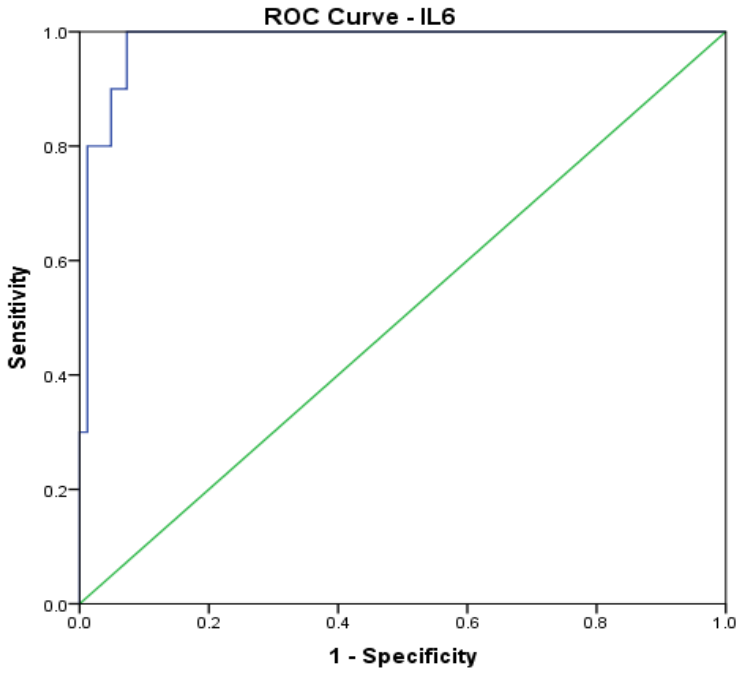

Figure 3: ROC curve for predicting COVID severity with IL6

Table 7: ROC curve for predicting COVID severity with HDL-C

Test Result Variable(s)	Area under the curve	95% Confidence Interval		p value
		Lower Bound	Upper Bound	
HDLC	0.985	0.953	1.000	0.001

Table 8: ROC curve for predicting COVID severity with HDL-C

Test Result Variable(s)	Cut off	Sensitivity	Specificity	PPV	NPV
HDLC	31.00	62.50%	96.70%	84.40%	90.03%

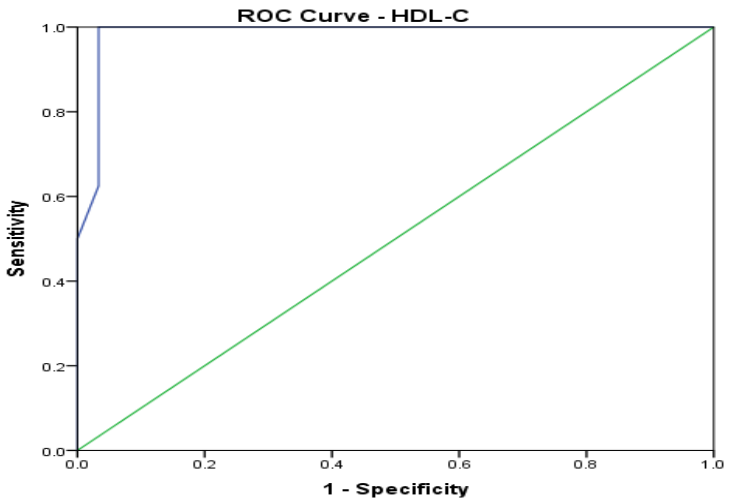

Figure 4: ROC curve for predicting COVID severity with HDL-C

Discussion

This study had been chosen to study the relationship of IL - 6 and HDL among Covid-19 patients. This study includes 99 Covid-19 patients. The patients were categorized into mild, moderate and severe cases. The mean age among the subjects was 47.87 ± 17.34. Among the study population, 58.59% were males and 41.41% were females. Among the study population with COVID-19, 89.9% had mild COVID followed by 7.07% had severe COVID and least 3.03% had moderate COVID. In this study, the mean IL - 6 among the subjects was 16.77 ± 36.02 ranging from 3 to 244 IU/L.Herold T *et al* [8] stated that the cutoffs for IL-6 level (>35 pg/mL at presentation and maximal value >80 pg/mL) among covid patients [8].

IL-6 level is useful marker to predict impending respiratory failure with high accuracy and can help physicians correctly allocate patients who might benefit from early treatment escalation. An important trait of IL-6 upregulation in Covid-19 is that it precedes the development of acute lung injury that implicates its usability as an early marker of severe disease [9]. However, there is controversy if excessive IL-6 synthesis is true a cornerstone of the pathogenesis of respiratory failure in Covid-19 or is just an epiphenomenon of increased IL-1β and TNFα in the cytokine storm [10]. A study by Giamarellos-Bourboulis *et al* [10,11]. suggests that patients with severe respiratory failure in Covid-19 suffer from distinct types of immune dysregulation which are mediated by IL-6 upregulation.

This dysregulation is characterized by high production of proinflammatory cytokines by monocytes and macrophages and CD4 lymphocyte depletion that contributes to the progression of inflammation of lung parenchyma. In this study, the area under the curve for IL6 in predicting COVID Severity is 0.982 (0.957 - 1).

In our study, the cutoff of IL-6 for predicting COVID severity is 31.9 which had a sensitivity of 80%, specificity of 98.8%, positive predictive value of 95.01%, negative predictive value of 94.53% and a diagnostic accuracy of 94.62%.

In the study, HDL-C, levels were lower in covid patients which correlates with chidambram *et al* [12] study. Among the various serum lipoprotein fractions, pre-clinical evidence suggests that HDL-C is an

important modulator of inflammation, including interference with viral fusion, reduction in the rate of bacterial complications, and neutralization of exaggerated immune responses. Viral infection triggers a specific lipid profile of the host which could serve as a potential biomarker to aid diagnostics [13]. COVID-19 patients develop abnormalities, such as lymphocytopenia, progressive increase in pro-inflammatory cytokine levels.

HDL-cholesterol and ApoA1 play protective roles in the maintenance of health and have beneficial effects on the lungs and various other disease states as per Evo kocar study [14,15]. Therefore, blood lipids and serum IL-6 should be included in diagnostic work-up to stratify disease severity. This study highlights the significant association of dyslipidemia and Il-6 with the severity of disease. This study recommends that based on the biochemical markers it is easy to administer active management in COVID-19 patients to reduce the severity and mortality. We hope that this study can still give early insight into further risk stratification for COVID-19 infections.

This study has several limitations. First, the presence of confounding factors such as age and other diseases like diabetes, Hypertension patients that can affect the relationship between dyslipidemia and the severity of COVID-19 shall still be considered. Second, this study included only 99 patients, if the sample size is large it could be clearly hypothesized the causal relationship between dyslipidemia and inflammation among Covid 19.

Conclusion

High IL-6 and low HDL-C levels on admission exhibited predictive value in discriminating disease severity and mortality during hospitalization. Our study examined COVID-19 in regard to lipid metabolism, and thus provides new insights into the disease. The results proved that dyslipidemia and increased inflammatory marker (IL-6) is associated with increased severity and mortality of COVID-19.

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