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Original Article

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Lipid profile as a predictor of severity in COVID-19

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Abstract

***Background & Aims*:** Accounting for wide variations in clinical manifestations, many variants of the SARS-CoV-2 virus have evolved since the start of the COVID-19 pandemic in 2020. The cause of death in COVID-19 varied from pulmonary involvement to abnormalities in coagulation and thromboembolism. In recent years, the role of lipids and lipoproteins in cardiovascular complications due to thromboembolic disturbances has been brought to light. Hence we conducted a study to evaluate the association between lipid profile and the severity of COVID-19 and their correlation with inflammatory markers.

***Materials & Methods*:** The retrospective-observational study included 320 subjects who were confirmed cases of COVID-19. Clinical history including intensive care unit admission, mechanical ventilation requirement, duration of hospital stay, mortality, CT score, CORAD classification scores, along with laboratory investigations comprising of lipid profile and inflammatory markers like C-reactive protein, ferritin, procalcitonin, lactate dehydrogenase, and interleukin-6 were evaluated. Data was analyzed using Mann Whitney U test and Spearman correlation test with R software version 4.1.2, considering p value < 0.05 statistically significant.

***Results*:** It was observed that 61.56% of the subjects needed intensive care unit admission while only 8.13% required mechanical ventilation and 12.81% were non-survivor patients. A statistically significant association of total cholesterol with mortality ($p = 0.0181$), low-density lipoprotein-cholesterol (LDL-c) with mortality ($p = 0.0237$), and mechanical ventilation ($p = 0.0211$); triglycerides with intensive care unit admission ($p = 0.0359$) and mechanical ventilation ($p = 0.0085$) was observed. LDL-c and total cholesterol showed an inverse correlation with duration of hospital stay, while inflammatory markers CRP, ferritin, LDH, and IL 6 had a negative correlation with TC,HDL-c and LDL-c (all p values below 0.05).

***Conclusion*:** From the present study, it is evident that the lipid profile is linked to both severity and mortality in COVID-19 patients. Primary information from the lipid profile of a COVID-19 patient can help physicians to anticipate the prognosis of the disease and help in instituting preemptive treatment, thereby decreasing complications and any resultant mortality.

***Keywords*:** Biomarkers, Cholesterol, COVID-19, Lipids, SARS-CoV-2

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Introduction

The coronavirus disease (COVID-19), a potentially fatal condition, was discovered towards the end of 2019 (1). It is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Although WHO declared an end to the COVID global health emergency, the virus has not been completely eradicated, necessitating further research. During the pandemic, the clinical presentation of the disease varied from asymptomatic to catastrophic. In more extreme cases, it led to pneumonia, requiring respiratory support and even death. Apart from respiratory illness, the other causes for mortality include venous thromboembolism, coagulopathy, multi-organ dysfunction and shock (1). Old age, male gender, obesity, cardiovascular diseases, hypertension, and diabetes mellitus were some of the key factors responsible for COVID-19 mortality (2). Even though several studies have elaborated on various pathophysiological aspects of COVID-19, there is not enough data on how the metabolic pathways are affected.

SARS-CoV-2 is an RNA virus with a higher mutation rate and frequency of recombination. In contrast to DNA viruses, RNA viruses control host metabolism through post-transcriptional regulation, to keep up with the replication (3). SARS-CoV-2 requires four major structural proteins namely spike, envelope, membrane, and nucleocapsid to complete the virion assembly and host cell infection (4).

Lipids, especially cholesterol enriched lipid rafts play a crucial role in activation, incorporation, and cell-to-cell infection spread of SARS-CoV-2 virus (5). The spike protein of SARS-CoV-2 virus binds with the cholesterol of HDL-c and when the scavenger receptor binding protein B1 (SRB1) uptakes HDL-c, it enters the host cell. The cytosolic phospholipase A2 also plays a role in the assembly of SARS-CoV 2 replication organelles (6).

The above examples emphasize the importance of lipids in the life cycle of the virus, leading us to theorize that harnessing the pathways of lipid metabolism for therapeutic intervention might yield prolific results. The most challenging task in any such antiviral agent development is that it requires a profound knowledge of lipid metabolism alteration by SARS COV-2 infection. Hence, the present descriptive study was carried out on COVID-19 patients to observe if there was an association between lipid profile with inflammatory markers, disease severity, and duration of hospital stay.

Materials & Methods

This retrospective observational study was conducted in a tertiary care hospital in Coimbatore, India, after the approval from the Institutional Human Ethics Committee. The study included subjects admitted between March-2020 and July-2021 with RT-PCR positive COVID-19 tests as per WHO's interim guidance (7). By convenient sampling, the study involved 320 participants of either gender in whom lipid profile testing was done.

For all subjects, demographic data comprising of age, gender, clinical history including CT score, CO-RADS scores, ICU admission, mechanical ventilation requirement, duration of hospital stay, and mortality were sourced from patients' medical records. The Laboratory Information System (LIS) was used to obtain lipid profile data including total cholesterol (TC), triglycerides (TGL), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c). In addition, data of inflammatory markers such as lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin, procalcitonin (PCT), and interleukin-6 (IL-6) were also obtained. The laboratory parameters were analyzed in Roche Cobas auto-analyzers using dedicated kits and reagents.

Data was analyzed using R software version 4.1.2 and MS Excel. Categorical variables were stated as a frequency table. Mann Whitney U test was applied to compare distributions of lipid profile with indicators of disease severity like ICU admission, mechanical ventilation, and mortality. Spearman's correlation test analyzed the correlation of CT score, CO-RADS score, duration of hospital stay, and inflammatory markers of COVID-19 with lipid profile. A p-value <0.05 was considered statistically significant.

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Results

In the present study, among 320 subjects with age ranging from 18 to 91 years, the mean age was 55.14 ± 14.84 years. Among the study participants, 216 (67.5%) were male and 104 (32.5%) were female with a female-to-male ratio of 1: 2.08 (Table 1). While 197 (61.56%) subjects needed ICU admission, 26 (8.13%) required mechanical ventilation, and 41 (12.81%) were non-survivor patients (Table 1).

Table 1. Descriptive statistics of categorical variables

Variables		Number of Subjects (%)
Age (years)	<20	5 (1.5%)
	21-40	51 (15.9%)
	41-60	139 (43.4%)
	61-80	118 (36.8%)
	81-100	7 (2.1%)
	Mean ± SD	55.14 ± 14.84
	(Median)	56
Gender	Female	104 (32.5%)
	Male	216 (67.5%)
ICU Admission	No	123 (38.4%)
	Yes	197 (61.5%)
Mortality	No	279 (87.1%)
	Yes	41 (12.8%)
Mechanical ventilation	No	294 (91.8%)
	Yes	26 (8.1%)

Among the lipid profile parameters, TG showed a significant association among patients requiring ICU admission (p = 0.0359) and mechanical ventilation (p = 0.0085). In case of non-survivor patients, there was a significant difference in distribution of TC (p = 0.0181) and LDL-c (p = 0.0237). Furthermore, a significant association of LDL-c was observed in patients requiring mechanical ventilation (p = 0.0211). There was no significant difference in the distribution of HDL-c among patients who required ICU admission, mechanical ventilation, or non-survivor patients (Table 2).

Table 2. Comparison of lipid profile with ICU admission, mortality and mechanical ventilation

Lipid profile	Variables								
	ICU admission			Mortality			Mechanical Ventilation		
	YES	No	p-value	YES	NO	p-value	YES	NO	p-value
TC mg/dL (Ref: <200)	135.05 ± 40.59	139.79 ± 36.55	0.2345[MW]	126.02 ± 49.92	138.46 ± 37.09	0.0181[MW*]	133.12 ± 42.63	137.2 ± 38.83	0.4468[MW]

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Lipid profile	Variables								
	ICU admission			Mortality			Mechanical Ventilation		
	YES	No	p-value	YES	NO	p-value	YES	NO	p-value
Mean ± SD	130	135		115	135		128	132.5	
Median									
HDL-c mg/dL (Ref: 40-60) Mean ± SD	30.42 ± 9.92	32.3 ± 9.03	0.118[MW]	30.76 ± 13	31.2 ± 9.04	0.7632[MW]	32.38 ± 11.39	31.03 ± 9.46	0.4989[MW]
Median	29	31		28	30		32	30	
LDL-c mg/dL (Ref: <100) Mean ± SD	81.28 ± 38.08	88.25 ± 34.01	0.0670[MW]	74.2 ± 43.48	85.4 ± 35.42	0.0237[MW]*	69.77 ± 38.07	85.22 ± 36.34	0.0211[MW]*
Median	79	84		63	82		66	82	
TG mg/dL (Ref: <150) Mean ± SD	142.25 ± 84.48	137.52 ± 129.09	0.0359[MW]*	142.83 ± 105.54	140.08 ± 103.67	0.5764[MW]	171.62 ± 91.24	137.68 ± 104.47	0.0085[MW]*
Median	120	110		109	117		152.5	112	

*Abbreviation: MW – Mann Whitney U test, * indicates statistical significance*

From the Spearman's rank correlation, no significant correlation was found between the lipid profile and CO-RADS score. However, there was a significant inverse correlation of TC, HDL-c and LDL-c with CT score and also TC and LDL-c with duration of hospital stay (Table 3). Where the inflammatory markers were considered, a significant inverse correlation of TC, HDL-C and LDL-C with LDH, CRP, ferritin and IL6 was found. However, there was no significant correlation of lipid profile with PCT (Table 4).

Table 3. Correlation of lipid profile with CT score, CORADS score, and duration of hospital stay

Lipid profile	CT score		CO-RADS score		Duration of hospital stay	
	Correlation Coefficient	p-value [SP]	Correlation Coefficient	p-value [SP]	Correlation Coefficient	p-value [SP]
TC	-0.2536	< 0.001*	-0.1051	0.1137	-0.2102	< 0.001*
HDL –c	-0.1765	0.0138*	-0.0785	0.2377	-0.1011	0.071
LDL-c	-0.3137	< 0.001*	-0.0934	0.1597	-0.2626	< 0.001*
TG	0.0476	0.5099	0.0546	0.4121	0.0789	0.1591

*Abbreviation: SP – Spearman's rank correlation test, * indicates statistical significance*

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Table 4. Correlation of lipid profile with biochemical markers of COVID-19

Biochemical markers of COVID-19		Lipid profile			
		TC	HDL-c	LDL-c	TG
LDH	Correlation Coefficient	-0.1845	-0.1870	-0.2403	0.0366
	p-value SP	0.0016*	0.0014*	< 0.001*	0.534
CRP	Correlation Coefficient	-0.2919	-0.1361	-0.3654	-0.0083
	p-value SP	< 0.001*	0.0318*	< 0.001*	0.8962
Ferritin	Correlation Coefficient	-0.1949	-0.2253	-0.2911	0.0776
	p-value SP	< 0.001*	< 0.001*	< 0.001*	0.1825
PCT	Correlation Coefficient	-0.1015	-0.0568	-0.155	0.0678
	p-value SP	0.3053	0.5668	0.1162	0.4941
IL6	Correlation Coefficient	-0.2703	-0.1721	-0.2847	0.0252
	p-value SP	< 0.001*	0.0027*	< 0.001*	0.6632

*Abbreviation: SP – Spearman's rank correlation test, * indicates statistical significance*

Discussion

It has been found that lipids and lipoproteins as part of the innate immune system play a vital role in host defense against viral infections (8). On the other hand, it is established that the viruses target the cellular metabolism by reprogramming the lipid synthesis, signaling, and metabolism, thereby creating an environment ideal for replication (6,9). Viral infections cause a variety of alterations in lipid metabolism like decrease in serum HDL-c, TC, and LDL-c, and increase in TGL (10). Hence this study was designed to evaluate the lipid profile of COVID-19 patients and their correlation with disease severity, duration of hospital stays, and inflammatory markers.

In the present study, it has been found that TG was elevated in patients who required mechanical ventilation and ICU admission, but LDL-c was decreased significantly in mechanically ventilated and non-survivor patients. TC was also found to be decreased in the non-survivor patients. These findings were substantiated by the studies by Sun et al., (11), Masanaet al., (12) and Rezaei et al., (13) where there was a downward trend in LDL-c and TC in non-survivor COVID-19 groups. Similarly, a Saudi Arabian study reported high TG levels and low LDL-c levels in the patients with severe COVID-19 infection (14).

Meanwhile, Spearman's rank correlation showed an inverse correlation between TC and LDL-c with duration of hospital stay. Lower levels of TC and LDL-c levels were related to increased severity; the higher the severity the longer the hospital stay, recovery, and infection spread. This was in line with a study by Rezaei et al. (13). On contrary, Sun et al., opined no significant difference in hospitalization considering mild or severe COVID cases (11). Our investigation of CT score established an inverse correlation with TC, LDL-c and

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HDL-c, but there is no direct studies to link CT score association with lipid profile distribution. However, there are studies that positively associate CT score to inflammatory markers like CRP, D-dimer, and IL-6, which alter the lipid metabolism in COVID-19 patients (15).

The markers of inflammation, LDH, CRP, ferritin, and IL6 have negative correlations with TC, HDL-c and LDL-c. Similar findings were noticed in majority of the studies, which explained that the severity was determined by increased levels of the pro-inflammatory cytokines CRP and IL-6 and their inverse relationship to HDL-c and LDL-c (16). A study by Masana et al. also observed high levels of ferritin in mild and severe COVID-19 patients (12). A meta-analysis of biomarkers has shown inverse association of lipid profile with elevated LDH and CRP (17).

The changes in TG and LDL-c could be attributed to the inflammatory cytokines released during infection, which leads to decreased lipoprotein lipase synthesis in adipose tissue and muscles. As a sequel there is a decrease in the clearance of triglyceride rich lipoproteins and decrease in LDL-c levels. Apart from this, the increase in hepatic VLDL synthesis also contributes to elevated TGL (10). While the mechanism by which the HDL-c is decreased is uncertain, some of the proposed hypotheses include decrease in Cholesteryl Ester Transfer Protein (CETP) activity, decreased synthesis of Apo A1, and increase in the clearance of HDL-c (1).

The findings of our study suggest that derangement in lipid profile must prompt us to look beyond cardiovascular health, since it indicates the degree of inflammation in infectious disease like COVID-19 probably due to its underlying role in pathophysiology. Hence, lipid profile can be used as a biomarker to predict the prognosis of a patient in COVID-19.

Nevertheless, the present study does have a smaller sample size as lipid profile was a lesser requested investigation in patients with COVID 19. Also, the study cohorts were not categorized for mild/severe/acute symptoms, co-morbidities, or underlying therapy affecting the severity of the disease.

Conclusion

During the COVID-19 pandemic, the cardiovascular complications due to thromboembolic disturbances could be attributed to increase in TGL, LDL-c and decrease in HDL-c, as these alterations are pro-atherogenic in nature. From the present study, it is evident that the lipid profile is linked to both severity and mortality in COVID-19 patients. Because lipid profile analysis is inexpensive and widely available in all laboratories, it may be useful in determining the severity and prognosis of COVID-19 in resource-constrained locations. There are studies which suggest that these alterations in lipoprotein metabolism persist in COVID-19 patients even after they have recovered from the infection. These findings advocate the importance of carrying out longitudinal studies in COVID-19 patients to evaluate the duration of dysregulation in lipoprotein metabolism and their effects on the long-term sequel of COVID-19 infection.

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Conflict of interests

The authors declare that they have no conflicts of interest

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Data Availability

The raw data supporting the conclusions of this article are available from the authors upon reasonable request.

Ethical Statement

Ethical clearance was obtained from the Institutional Human Ethics Committee Institutional Ethics Board reference no: PSG/IHEC/2021/Appr/Exp/209

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References

1. Kumari A, Agarwal Y, Singh SB, Mahajan S, Sharma V.Correlation of Lipid Profile with Inflammatory Markers among COVID-19 Positive Patients: A Retrospective Study. J Clin of Diagn Res 2022;16: BC19-BC23. https: //doi.org/10.7860/JCDR/2022/55477.16744
2. Feingold KR. The bidirectional link between HDL and COVID-19 Infections. J Lipid Res 2021;62: 100067. https: //doi.org/10.1016/j.jlr.2021.100067
3. Abu-Farha M, Thanaraj TA, Qaddoumi MG, Hashem A, Abubaker J, Al-Mulla F. The Role of Lipid Metabolism in COVID-19 Virus Infection and as a Drug Target. Int J Mol Sci 2020;21: 3544. https: //doi.org/10.3390/ijms21103544
4. Wang MY, Zhao R, Gao LJ, Gao XF, Wang DP, Cao JM. SARS-CoV-2: Structure, Biology, and Structure-Based Therapeutics Development. Front Cell Infect Microbiol 2020;10: 587269. https: //doi.org/10.3389/fcimb.2020.587269
5. Levin MG. Circulating Lipids and COVID-19: Insights From Mendelian Randomization. Arterioscler Thromb Vasc Biol 2021;41: 2811-3. https: //doi.org/10.1161/ATVBAHA.121.316940
6. Theken KN, Tang SY, Sengupta S, FitzGerald GA. The roles of lipids in SARS-CoV-2 viral replication and the host immune response. J Lipid Res 2021;62: 100129. https: //doi.org/10.1016/j.jlr.2021.100129
7. WHO. Clinical management of COVID-19: interim guidance, 27 May 2020. World Health Organ 2020;1-10.
8. Feingold KR, Grunfeld C. Lipids: a key player in the battle between the host and microorganisms. J Lipid Res 2012;53: 2487-9. https: //doi.org/10.1194/jlr.E033407
9. Heaton NS, Randall G. Multifaceted roles for lipids in viral infection. Trends Microbiol 2011;19: 368-75. https: //doi.org/10.1016/j.tim.2011.03.007
10. 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: 1169-96. https: //doi.org/10.1194/jlr.R300019-JLR200
11. Sun JT, Chen Z, Nie P, Ge H, Shen L, Yang F, et al. Lipid Profile Features and Their Associations With Disease Severity and Mortality in Patients With COVID-19. Front Cardiovasc Med 2020;7: 584987. https: //doi.org/10.3389/fcvm.2020.584987
12. Masana L, Correig E, Ibarretxe D, Anoro E,Arroyo J A, Jericó C, et al. Low HDL and high triglycerides predict COVID-19 severity. Sci Rep 2021;11: 1-9. https: //doi.org/10.1038/s41598-021-86747-5
13. Rezaei A, Neshat S, Heshmat-Ghahdarijani K. Alterations of Lipid Profile in COVID-19: A Narrative Review. Curr Probl Cardiol2022 ;47: 100907. https: //doi.org/10.1016/j.cpcardiol.2021.100907
14. Mohammedsaeed W, Alahamadey Z, Khan SM. Alteration of Lipid Profile in Covid-19 Saudi Patients At Al-Madinah Al-Munawarah. Eur J Biomed Pharm Sci 2020;7: 63-7.
15. Saeed GA, Gaba W, Shah A, Al Helali AA, Raidullah E, Al Ali AB, et al. Correlation between Chest CT Severity Scores and the Clinical Parameters of Adult Patients with COVID-19 Pneumonia. Radiol Res Pract 2021;2021: 6697677. https: //doi.org/10.1155/2021/6697677
16. Hu X, Chen D, Wu L, He G, Ye W. Declined serum high density lipoprotein cholesterol is associated with the severity of COVID-19 infection. Clin Chim Acta 2020;510: 105-10. https: //doi.org/10.1016/j.aca.2020.01.026
17. Malik P, Patel U, Mehta D, Patel N, Kelkar R, Akrmah M,et al. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. BMJ Evid Based Med 2021;26: 107-8. https: //doi.org/10.1136/bmjebm-2020-111536

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