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To Correlate Serum Lipid Parameters with Clinical Outcome in COVID-19 Patients

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Abstract **Original Research Article**

Background: COVID-19 has disrupted many countries worldwide; its high mortality and spread has overwhelmed the healthcare systems. Hence it has become important to identify reliable predictors of disease severity and morbidity which would streamline healthcare resources into improving efficiency of management and thus improving the clinical burden and overall outcome. Since dyslipidemia in COVID-19 has been associated with worse outcomes, it can be determined by lipid parameters at admission and its trends. ***Aim:*** To correlate serum lipid parameters levels in COVID-19 patients, admitted in an Indian setting, with clinical outcome. ***Methods:*** A single-center, observational cross-sectional study was conducted in COVID-19 positive patients admitted from April1st, 2021 to May 1st, 2021. The diagnosis was confirmed by Real-Time Polymerase Chain Reaction (RT-PCR). Each serum lipid parameter was compared to clinical outcomes and checked for statistical association. ***Results:*** A total of 157 COVID-19 patients were studied. By the Mann-Whitney test TC median values were 109.5 in the Non survivors and 138 in survivor group (p value <0.05), HDL was 13 in non survivors and 33 in survivors. LDL was 18 in the non-survivor group and 46 (p-value <0.05 for both). The median TG in the group that succumbed to death was 48 as compared to the survivor group which was 138 (p value <0.05). HDL/LDL ratio was 0.14 in non-survivor group and 0.29 in survivors. However, the VLDL-C levels and TC/HDL showed a significant increase in the group that succumbed to death as compared to the group that survived (p=0.003 and p<0.05). ROC curve showed that HDL-C has maximum AUC of 9.77 and least standard error 0.013. ***Conclusion*:** Hypolipidemia was seen among many COVID-19 patients and had a strong association with the outcome of the disease. Most sensitive being the levels of HDL-C cholesterol at admission, which could be potentially be used as a cost-free test at the time of triaging patients based on prognosis prediction.

Keywords: COVID-19, Lipid Profile, HDL.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a highly contagious infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has rapidly grown into a pandemic after the first cases of this predominantly respiratory viral illness were first reported in Wuhan, Hubei Province, China. In late December 2019, SARS-CoV-2 rapidly disseminated across the world in a short span of time [1]. As per the WHO report on 14th June, 2021, the total number of cases have amounted to 175,306,598 and the number of confirmed deaths to 3,792,777 [2]. With the advent of the second wave, India has been burdened with increasing cases, which have now crossed the 30 million mark and the Health Ministry has confirmed 377,031 deaths according to the data published on June 16th, 2021 [3].

COVID-19 has disrupted many countries worldwide, overwhelming their healthcare systems. It has been associated with a death rate higher than any other respiratory viral infection. Hence it has become important to identify reliable predictors of disease severity and morbidity which would streamline healthcare resources into improving efficiency of management and thus improving the clinical burden and overall outcome.

Various biomarkers are being investigated for their role in the determination of outcome and prognosis of COVID-19. Evidence suggests that an impaired immune function and hyper-inflammatory responses are characteristics of COVID-19 severity and mortality. Proteosome analysis have also suggested that patients with severe COVID-19 display dysregulated lipid metabolism [4]. HDL is considered an anti-inflammatory, anti-thrombotic, anti-oxidative, anti-apoptotic lipoprotein and has endotheliocyte protective effects. Decreased HDL concentrations have been reported to be closely associated with poor prognosis in patients with sepsis, pneumonia, and other infections [5]. Dyslipidemia can lead to a sustained chronic inflammatory state, which leads to a high cardiovascular (CVD) risk which is strongly interlinked with the morbidity and mortality associated with COVID-19 [6]. In this study, we aimed to assess the correlation between different serum lipid parameters with the clinical outcome of COVID-19 positive patients.

METHODS

This was an observational cross-sectional study conducted among patients admitted between April 1st, 2021 and May 1st, 2021 under the Internal Medicine Department in Victoria Hospital, Bangalore Medical College and Research Institute, Bangalore, Karnataka, India. Approval and clearance were obtained from the institutional Ethics Committee (BMCRI/PS/02/2020-21). The patients included in the study were aged ≥18 years of both genders, diagnosed with COVID-19 infection by RT-PCR technique using ABI/Thermofischer-Taqpath technique. The study excluded patients <18 years of age and those not willing to provide signed informed consent prior to the study.

Case record forms with follow up charts were used to record demographic data, duration, clinical features and incidence of comorbidities like hypertension, diabetes, renal, cardiac and respiratory disorders were noted. All participants were followed up to the outcome. Laboratory results at admission, including routine blood tests, liver function, kidney function, coagulation function, and C-reactive protein, were collected and evaluated. Venous blood samples were collected from each subject after at least 12 h of fasting for evaluation of serum lipid parameters. A Beckman Coulter DXH 800 was used for routine blood parameter analysis. The blood biochemistry indexes and lipid profiles were measured using the Cobas B 101 POC system. All laboratory data were tested in the same laboratory with standardization and certification procedures.

The Guidelines for Management of COVID-19 – A point of Care Approach (version 4.0) April 2021, given by the Government of Karnataka was used for the management and to discharge patients. According to the guidelines, asymptomatic patients who remained asymptomatic during their stay in the hospital were discharged 10 days after the positive RT-PCR test. There was no requirement of a negative test before discharge of the patient. The patients were advised to follow home isolation for further 7 days and were followed up through tele counselling.

The symptomatic, mild to moderate cases were discharged after 10 days of onset of symptoms only if they exhibited no symptoms for the last 3 consecutive days before discharge and would maintain saturation (>95%) for the last 4 consecutive days without oxygen support and if there was resolution of breathlessness and other clinical signs / symptoms and the repeat inflammatory markers at the time of discharge were either of normal range or showed a decreasing trend. Failing this criterion, the patients were kept in-patient till they achieved a 3 consecutive symptom free period before discharge. Again, there was no requirement of a negative test report before discharge and patient was advised home isolation for further 7 days. For severe cases, a three consecutive day complete symptom-free period post maintenance of saturation without oxygen and a negative RT-PCR report were considered for discharge and advised a 7-day home isolation and tele counselled follow up.

Statistical analysis was carried out using SPSS (Statistical Package for Social Sciences) version 20. [IBM SPASS statistics 9IBM corp. Armonk, NY, USA released 2011)]. Continuous variables were expressed as mean and standard deviation and categorical variables were presented as counts and percentages. Patients were categorized based on outcome, group A being the patients that survived and were discharged and group B containing the patients who succumbed to death, different parameters were compared between these groups using Chi-square test for categorical variables and a non-parametric test, Mann-Whitney test was applied to non-normal distributed data. P value of <0.05 was considered statistically significant.

RESULTS

The study was conducted with 157 patients, who were admitted into Victoria Hospital, Bangalore, under the Internal Medicine department and were diagnosed to be COVID-19 positive. The study population was divided into two groups based on outcome, Group A were discharged from the hospital and Group B succumbed to death. A total of 133(84.7%) were discharged from the hospital and twenty-four (15.3%) patients died during hospitalization, with maximum deaths seen among the middle age groups, 46 years to 65 years who contributed 6.4% of the total 15.3% of deaths. When plotted with a Chi-square test, it was seen that there was no statistical association of age with outcome (χ^2 =7.48 and p value =0.27) (Table-1). 65.0% (n=120) of the patients were men and the male to female ratio of 1.85. Sex of the patient also showed no association with the

outcome (χ^2 = 0.067 and p value =0.78) (Table-2 and Figure-1).

Out of 157 subjects 19.1% (n=30) of them were asymptomatic, and of which only 1.3% (n=2) of them succumbed to death (Table-3). The rest 127 of them were symptomatic, with fever, cough and breathlessness being the most common symptoms overall as well as in the mortality group (Table-4).

Out of the 157 subjects, 27.4% (n=43) of them had no pre-existing comorbidities at admission. In the rest, the most common comorbidity was Type 2 Diabetes Mellitus, which 48.40% (n=76) patients had. Other common comorbidities were hypertension (38.9%) and ischemic heart disease (8.9%) (Table-5). The patients with chronic kidney disease showed the highest mortality rates. (79%) (Figure-2).

Table-1: Distribution of the Subjects Based On Age

Age		OUTCOME		Total
		DEATH	DISCHARGE	
26 to 35 yrs.	Count	3	25	28
	%	1.9%	15.9%	17.8%
36 to 45 yrs.	Count	4	36	40
	%	2.5%	22.9%	25.5%
46 to 55 yrs.	Count	5	20	25
	%	3.2%	12.7%	15.9%
56 to 65 yrs.	Count	5	22	27
	%	3.2%	14.0%	17.2%
66 to 75 yrs.	Count	3	11	14
	%	1.9%	7.0%	8.9%
Above 75 yrs.	Count	3	4	7
	%	1.9%	2.5%	4.5%
Less than 25 yrs.	Count	1	15	16
	%	.6%	9.6%	10.2%
Total	Count	24	133	157
	%	15.3%	84.7%	100.0%
Chi-square value- 7.48				
p value- 0.27				

Table-2: Distribution of the Subjects Based On Gender

Gender		OUTCOME		Total
		DEATH	DISCHARGE	
FEMALE	Count	9	46	55
	%	5.7%	29.3%	35.0%
MALE	Count	15	87	102
	%	9.6%	55.4%	65.0%
Total	Count	24	133	157
	%	15.3%	84.7%	100.0%
Chi-square value- 0.076				
p value- 0.78				

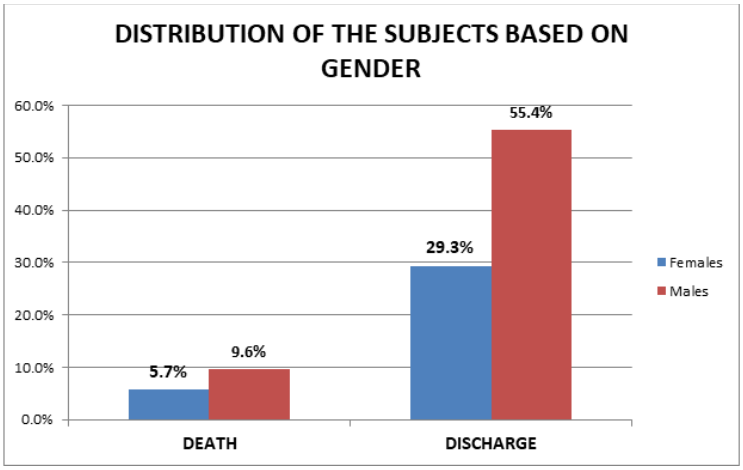

Figure-1: Sex of the patient and Clinical outcome

Table-3: Distribution of the Subjects Based on Presence or Absence of Symptoms

Symptoms		**OUTCOME**		**Total**
		DEATH	**DISCHARGE**	
Symptomatic	Count	22	105	127
	%	14.0%	66.9%	80.9%
Asymptomatic	Count	2	28	30
	%	1.3%	17.8%	19.1%
Total	Count	24	133	157
	%	15.3%	84.7%	100.0%
Chi-square value- 2.12				
p value- 0.14				

Table-4: Distribution of the Subjects Based on Presenting Complaints

Presenting complaints		**OUTCOME**		**Total**	**Chi-square value**	**p value**
		DEATH	**DISCHARGE**			
FEVER	Count	14	62	76	1.11	0.29
	%	8.9%	39.5%	48.4%		
COUGH	Count	10	57	67	0.012	0.91
	%	6.4%	36.3%	42.7%		
BREATHLESSNESS	Count	8	29	37	1.5	0.22
	%	5.1%	18.5%	23.6%		
MYALGIA	Count	5	18	23	0.86	0.35
	%	3.2%	11.5%	14.6%		
FATIGUE	Count	2	21	23	0.9	0.34
	%	1.3%	13.4%	14.6%		
DIARRHEA	Count	0	1	1	0.18	0.67
	%	0.0%	0.6%	0.6%		
ANOSMIA	Count	0	16	16	3.21	0.07
	%	0.0%	10.2%	10.2%		

Table 5: Distribution of the Subjects Based on Co-Morbidities

CO -MORBIDITIES		**OUTCOME**		**Total**	**Chi-square value**	**p value**
		DEATH	**DISCHARGE**			
DIABETES MELLITUS	Count	13	63	76	0.37	0.54
	%	8.30%	40.10%	48.40%		
HYPERTENSION	Count	13	48	61	2.79	0.09
	%	8.30%	30.60%	38.90%		
IHD	Count	2	12	14	0.012	0.91
	%	1.30%	7.60%	8.90%		
CKD	Count	3	9	12	0.94	0.33
	%	1.90%	5.70%	7.60%		
HYPOTHYROIDISM	Count	2	11	13	0	0.99
	%	1.3%	7.0%	8.3%		
NIL	Count	6	37	43	0.08	0.77
	%	3.8%	23.6%	27.4%		

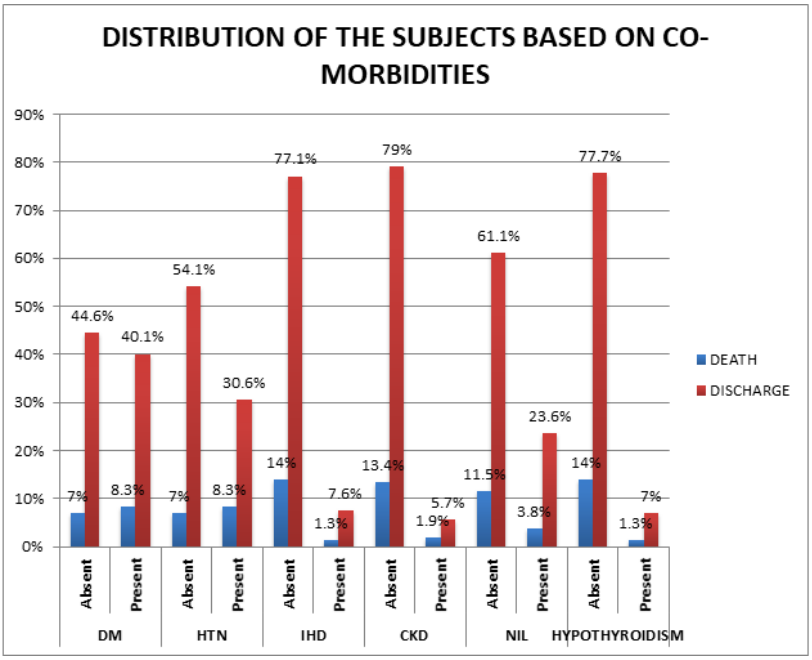

Figure-2: Comorbidities and Clinical Outcome

Lipid profile parameters were analyzed based on outcome using the Mann-Whitney Test (Table-6).

According to the statistical test we found that the median value of all parameters of the lipid profile were significantly decreased in the group that succumbed to death than the values amongst the group which was discharged. The Total cholesterol values 109.5 in the Non survivors as compared to 138, the median level in the survivor group with p value = 0.00. Similarly, HDL-C and LDL-C showed a significant decrease in the population that did not survive. HDL was as low as median of 13 in them as compared the survivor group median which was 33. LDL levels were 18 in the non-survivor group and 46 in the group which got discharged p-values for both being 0.00. HDL/LDL ratio was also significantly lower in the group that didn't survive.

The median triglyceride levels (TG) in the group that succumbed to death was 48 as compared to the survivor group which was 138, which was statistically significant with p value =0.00. However, the VLDL-C and TC/HDL levels showed a significant increase in the group that succumbed to death as compared to the group that survived (p=0.003 and p=0.00)

Table-6: Comparison Of The Lipid Profile Based On Outcome Using Mann-Whitney Test

Lipid Profile	Outcome	N	Minimum	Maximum	Median	IQR	p value
TC	Death	24	58	187	109.5	16	0.00*
	Discharge	133	70	253	138	48.5	
LDL	Death	24	23	81	45	18	0.00*
	Discharge	133	15	168	74	46	
HDL	Death	24	8	27	13	6	0.00*
	Discharge	133	12	82	33	15	
VLDL	Death	24	14	114	47.5	31	0.003*
	Discharge	133	8	81	28	21	
TG	Death	24	11	95	48	35	0.00*
	Discharge	133	40	404	138	98	
HDL / LDL	Death	24	0.16	0.86	0.29	0.14	0.00*
	Discharge	133	0.15	2.6	0.43	0.29	
TC /HDL	Death	24	4.5	11.7	8.55	3.1	0.00*
	Discharge	133	1.9	9.7	4.3	2.1	

*Significant

In order to evaluate the prognostic value and to determine the best cut-offs of the Lipid Prolife parameters for predicting in-hospital mortality among severe COVID-19 patients, receiver operating characteristic (ROC) curves were obtained. All these

parameters were shown statistically to have an association with the outcome of the patient (Figure-3).

The AUCs was 0.977 (95% CI: 0.952 –1.00, p <0.001) for HDL-C. Hence HDL has the highest AUC and is the best of the parameters to assess the outcome, followed by TG, whose AUC was 0.947 (95% CI: 0.912–0.983, p<0.001).

These were closely followed by LDL, AUC was 0.817 (95% CI: 0.743–0.892, p<0.001) and TC with AUC 0.773 (95% CI: 0.683–0.864, p<0.001). For HDL/LDL ratio the AUC was 0.759 (95% CI: 0.655–0.863, p<0.001).

VLDL had an AUC 0.311(95% CI: 0.185–0.437, p=0.003) and TC/HDL it was 0.071 (95% CI: 0.019–0.124, p<0.001). These were the least sensitive investigations as shown but the ROC curve (Table-7).

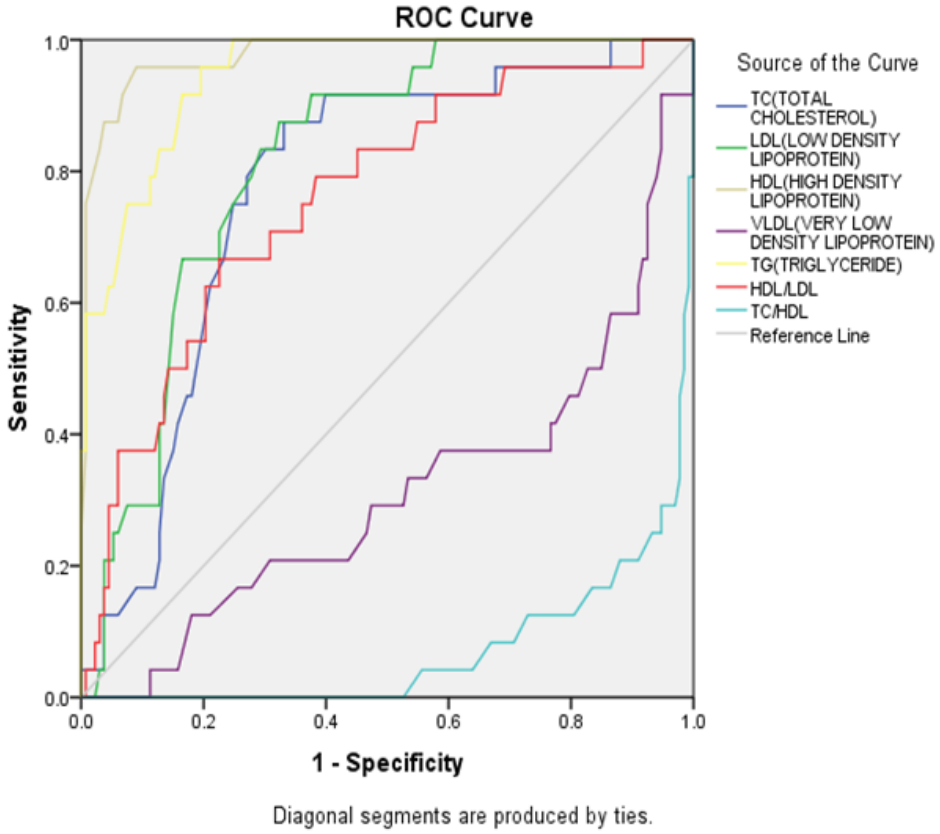

Figure-3: Receiver Operating Curve (ROC) for AUC of Lipid parameters

Table-7: Area Under the Curve (AUC) for various Lipid parameters.

Area Under the Curve					
Test Result Variable(s)	**Area**	**Std. Error**	**P value**	**Asymptotic 95% Confidence Interval**	
				Lower Bound	**Upper Bound**
TC	.773	.046	.000*	.683	.864
LDL	.817	.038	.000*	.743	.892
HDL	.977	.013	.000*	.952	1.000
VLDL	.311	.064	.003*	.185	.437
TG	.947	.018	.000*	.912	.983
HDL/LDL	.759	.053	.000*	.655	.863
TC/HDL	.071	.027	.000*	.019	.124

*Significant

DISCUSSION

In this study, we found dyslipidemia in patients with COVID-19 infection and demonstrated that low concentrations of TC, HDL-C, LDL-C, TG, HDL/LDL ratio and TC/HDL ratio and an increase in VLDL-C at admission were significantly associated with the outcome of the patients. The non-survivors with COVID-19 showed lower values of all parameters except VLDL concentrations, which showed a

significant increase in them, compared to those survivors.

As we reviewed many studies are findings are consistent with the studies done by Yi Li, Yan Zhang, Rongli Lu, Minhui Dai., in China, which concluded that low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-I (apoA-I) showed an increasing trend in survivors, but showed a downward trend in non-survivors [5]. A similar study by Alexander V. Sorokin, Sotirios K. Karathanasis, concluded that the "cytokine storm" underlying COVID- 19 produces immune- mediated inflammatory Dyslipoproteinemia, leading to low HDL- C and LDL- C levels, elevated triglycerides, increased lipoprotein oxidation, low ApoE levels, and impaired inflammation resolution due to decreased SPMs biosynthesis [6]. There were very few studies commenting about the triglyceride levels, a study by Kenneth R. Feingold commented that the triglyceride levels were variable depending on the diet of the patient [7]. There have also been studies that show serum triglyceride levels were elevated in patients with mild or severe infections but not in patients with critical illness [8]. In contrast, other studies reported that triglyceride levels were higher in patients that died from COVID-19 compared to patients that were critically ill or non-critically ill [9]. Our study has showed that triglyceride levels have significantly decreased in the non-survivor population as compared to the group that got discharged.

Since HDL and LDL are the most common parameters that are considered and most sensitive. There are numerous studies outlining the magnitude of lipoprotein level reduction during the acute-phase response may be associated with the severity and mortality of sepsis and that HDL cholesterol may have a protective effect against sepsis [10]. Acute inflammation caused by many other viral infections have resulted in dyslipidemia in patients, and lipid metabolism is known to play an important role in the host immune response. Clinical observations have shown that patients with acute Epstein-Barr virus (EBV) infection, cytomegalovirus (CMV) infection, even dengue-positive patients have shown lower HDL-C and LDL-C concentrations when profiled [11-13].

In a SARS-CoV-2 infection, the decrease in lipid parameters could be explained by couple of hypotheses. There's evidence of dysregulation of multiple apolipoproteins including APOA1, APOA2, APOH, APOL1, APOD, and APOM. Most of them are associated with macrophage functions and were downregulated. As shown by Proteomic and Metabolomic Characterization given by Bo Shen [4]. Other mechanisms to understand the dyslipidemia include the effect of liver dysfunction caused by SARS-CoV2 infection or potential drugs affect lipid synthesis. It was reported that 14%-53% of patients with COVID-19 had hepatic dysfunction, especially in severe and critical patients. Therefore, the synthesis of apolipoproteins and lipoproteins would be affected by hepatic dysfunction in patients with severe COVID-19 [14]. One more major explanation could be that acute inflammation caused by SARS-CoV-2 releases excessive pro-inflammatory cytokines, such as IL-1, IL-6, IL-12, IFN-γ and TNF-α, as the disease progresses over time and gradually worsens [15, 16]. It was shown that tumor necrosis TNF-α, IL-1β and IL-6 could decrease the synthesis and/or secretion of apolipoproteins in hepatic cell lines in a dose-dependent manner [17]. Furthermore, a severe inflammatory response could also cause capillary leakage, thus resulting in the leakage of lipoproteins and apolipoproteins particles from intravascular to extravascular compartments. This is seen as exudates that have been found evidently in the early phase of COVID-19 lung pathology [18].

Additional mechanisms leading to the dysfunction of HDL involve inflammation- induced oxidative modification of ApoA- I which reduces Reverse cholesterol transport [19]. An antioxidant enzyme present in HDL, paraoxonase 1 (PON1), is also inactivated under inflammation- induced oxidative stress, which further compromises HDL function [20]. Impaired HDL antioxidant activity further results in lipid oxidation, specifically generating oxidized LDL (oxLDL). oxLDL and oxidized HDL (oxHDL) are potent activators of the oxidized LDL scavenge receptor (LOX- 1), inducing further inflammation and aggravating tissue damage and could explain the worser prognosis with lower levels of these parameters [6].

A reduced HDL, LDL and TC have been accepted to be reduced as shown in our study and all the studies that we have reviewed [4-8]. Our study has showed us that HDL is most sensitive investigations to extrapolate clinical outcome, followed by TG levels, LDL levels and TC levels. In our study we also aimed to show the use of HDL/LDL ratio could be used as a fairly sensitive investigation with statistically significant association with the prognosis of the patient and deciding the outcome. Hence the present study holds significance for reviewing the hypolipidemic status of COVID-19 patients and also the statistical confirmation of the usage of new lipid biochemical markers as a prognostic determinant of outcome of the disease. In reviewing the hypolipidemic status and the pleiotropic effects of HDL, it would definitely be a promising direction in searching for novel treatments for patients with COVID-19 and it would also be potential to use novel biochemical parameters at admission and follow-up to gauge on the outcome of the disease in a cost-free manner.

CONCLUSION

In conclusion, decreased levels of HDL-C, TG, LDL-C and TC were seen among many COVID-19 patients and were statistically shown to have an association with the outcome of the disease. Most sensitive being the levels of HDL-C cholesterol at admission, which could be potentially used at the time of triaging patients based on prognosis prediction. As it is a relatively affordable investigation, therefore it can help the overburdened healthcare systems of all countries alike. More studies would be required to put forth a universally accepted criterion for future guidelines for using this as a triaging tool.

DECLARATIONS

Ethical Approval: Approved – BMCRI/PS/02/2020-21

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Conflict of interest: None

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