Original Research Article

Association of Serum Albumin and Lipoproteins as strong predictor of severity in patients with COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) has been proclaimed to be one of the deadliest and most infectiouspandemic of the modern times which is caused by the SARS-CoV-2 (severe acute respiratory syndrome corona virus 2). The aim of this study was to establish an association, if any, between serum albumin and serum lipoproteins (mainly HDL and LDL) and COVID-19 severity and adverse outcomes. In this study, we extracted data from 500 clinically confirmed and hospitalized COVID-19 patients (>= 18 years of age) between June 2020 to February 2021 at the associated hospital of Rajarshi Dashrath Autonomous State Medical College (RDASMC), Ayodhya, Uttar Pradesh, India. The patients were divided into two groups- mild to moderate and severe groups according to the Centers for Disease Control and Prevention (CDC). Serum albumin, Serum globulin, A/G ratio, high density lipoproteins (HDL) and lowdensity lipoprotein (LDL) concentrations were measured and compared amongst these groups. The median age of these 500 patients was 59 years (IQR: 47-66). Out of the total 500 patients hospitalized and enrolled in this study, 79.7% (n= 398) were mild to moderately affected while 20.3% (n=102) were severely affected. Significant hypoalbuminemia was observed in 53.3% and 83.5% in mild to moderate and severely affected groups respectively. We also found out a significantly low concentrations of serum LDL and HDL levels in severely affected group as compared to the mild to moderately affected group.Thus, with severity of disease, a drastic reduction in serum albumin as well as serum LDL and HDL levels is indicative of a possible hepatotoxicity that may exacerbate survival chances in severely affected patients.

Keywords: COVID-19, Albumin, HDL, LDL, severity

Introduction

Coronaviruses are a large family of enveloped positive sense RNA viruses known to cause clinical symptoms ranging from the common cold to severe respiratory infections, such as severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS). Coronavirus disease 2019 (COVID-19) has recently been identified as a deadly communicable disease caused by a novel strain of severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) and it has shown to represent one of the deadliest pandemic outbreaks in modern times affecting almost 50 million people and causing more than 21.2 million deaths globally so far. The spectrum of COVID-19 illness ranges from being asymptomatic or experiencing mild symptoms to important clinical manifestations such as severe pneumonia, which can further progress to acute respiratory distress syndrome (ARDS), multiple organ failure and potentially death[1-3].Human serum albumin (HSA) is an acute phase reactant with antioxidant property. Thus, under normal physiologic conditions, plasma albumin provides an abundant source of free thiols that are able to scavenge reactive oxidant species (ROS).Hypoalbuminemia (<32g/L) is amongst the most frequently observed laboratory abnormalities in patients with SARS-CoV-2 infection[4-8].and it was more pronounced in severe than mild-moderate cases.High density and low density lipoproteins are complex protein molecules which transport lipid molecules around the body. Numerous studies have stated a decrease in LDL and HDL levels in patients with COVID-19 infections. Most of these studies indicated a greater fall in lipid levels with an increase in the severity of the illness.The general consensus regarding plasma lipid levels (mainly HDL and LDL) along with serum albumin levels is that they progressively decrease with an increase in the severity of coronavirus disease.

Material and Methods

This study involved 500 COVID-19 patients hospitalized with mild to moderate and severe symptoms between June 2020 and February 2021in the associated hospital of RDASMC, Ayodhya, Uttar Pradesh, India after ethical approval from the institutional ethical committee. Adults>=18 years of age with laboratory confirmed COVID-19 diagnosed and classified into mild to moderately affected and severely affected groups on the basis of Centers for Disease Control and Prevention (CDC)[9] were selected. Oropharyngeal and Nasopharyngeal swabs for laboratory diagnosis of COVID-19 were taken and RT-PCR for E and S gene were performed. At the time of admission to the hospital, routine analyses were carried out and demographic and clinical data were collected. The laboratory results including serum albumin, globulin and lipoproteins (HDL and LDL) were extracted during admission and on the third day after admission (second testing). Patients younger than 18 years of age and having

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atleast one month history of hepatitis and with renal or liver dysfunction were excluded from the study. All the patients were divided into two subgroups according to CDC: mild to moderately affected i.e. those with absence of viral pneumonia and hypoxia and severely affected i.e. those with pneumonia, ARDS, sepsis and septic shock, cardiomyopathy, arrhythmia and acute kidney injury.

Results

Table 1: shows clinical and demographic features of study patients according to severity

	Mild to moderate group	Severe group	p value
n	398	102	
Age	55.1±18.5	64.8±14.1	<0.001
Male gender	59%	72%	0.074
Hypertension	49%	63%	0.256
Diabetes	24%	32%	0.112
Smoking habit	8%	16%	0.511
COPD	12%	26%	0.014
Cardiovascular disease	12%	18%	0.297

Data are expressed in mean±standard deviation

COPD: chronic obstructive pulmonary disease

Table 1 shows some of the demographic and clinical features of mild to moderate and severely affected subgroups. Compared with the mild to moderately affected group, the severely affected had more prevalence of COPD (26%), Diabetes (32%), cardiovascular diseases (18%) and smoking habit (16%)

Table 2: shows laboratory characteristics of study patients according to severity

		Mild to moderate group	Severe group	*P*
ALB(IQR)	At admission test	35.70 (32.17, 39.30)	31.10 (28.56, 34.70)	<0.001
	At second test	34.50 (31.40, 37.50)	30.30 (27.80, 33.52)	<0.001
GLO (IQR)	At admission test	30.70 (27.60, 34.40)	33.40 (29.55, 37.55)	<0.001
	At second test	30.00 (26.80, 33.30)	32.00 (28.35, 36.70)	<0.001
ALB/GLO (IQR)	At admission test	1.16 (0.96, 1.38)	0.93(0.79, 1.10)	0.558
	At second test	1.15 (0.97, 1.34)	0.94 (0.79, 1.10)	<0.001
HDL	At admission test	0.94 (0.79, 1.15)	0.85 (0.72, 1.04)	<0.001
	At second test	0.98 (0.82, 1.19)	0.91 (0.73, 1.11)	<0.001
LDL	At admission test	2.43 (1.95, 2.96)	2.08 (1.59, 2.67)	<0.001
	At second test	2.49 (2.01, 2.94)	2.28 (1.67, 2.82)	<0.001

Data are expressed in median(IQR). *P* values are calculated by Kruskal- Wallis rank-sum test.

The plasma concentrations of albumin (ALB), globulin (GLO), ALB/GLO, HDL and LDL levels were recorded upon admission and on the third day after admission. *P* values were comparedamong mild to moderate and severely affected groups.Table 2 shows a decrease in plasma albumin levels in mild to moderate group median of 35.70 (IQR, 32.17,39.30) and in severe group median of 31.10 (IQR, 28.56, 34.70) at the time of admission. After adjustment for multivariable like age, sex and comorbidities, every 1g/L decrease in albumin was found to be associated with a higher risk of progression to severe group. The odds ratio (OR) adjusted was 1.16; 95% confidence interval (CI) 1.13- 1.18; *P*= 0.005. After second test, albumin levels significantly decreased to a median of 34.50 (IQR, 31.40, 37.50) in mild to moderate and to a median of 30.30 (IQR, 27.80, 33.52) in severe group respectively. The OR after adjustment was found to be 1.21 (1.17-1.26; *P*= 0.018). This progressive decline is suggestive of poor prognosis. However, the Globulin levels shows a statistically significant increase in severely affected group to a median of 33.40 (IQR,29.55, 37.55) as compared to the mild to moderately affected group to a median of 30.00 (IQR,26.80, 33.30). Interestingly, the A/G ratio shows a significant reduction in severe group to a median of 0.94 (IQR,0.79, 1.10) than the mild to moderate group to a median of 2.49 (IQR,2.01, 2.94) after second test probably because of an increase in globulin and decrease in albumin levels. Table 2 also shows a marked difference in lipoprotein levels in the two groups. At the time of admission, the mild to moderate group showed a higher HDL level to a median of 0.94 (IQR,0.79, 1.15) than the severe group to a median of 0.85 (IQR, 0.72, 1.04). Even after second test, HDL levels were higher in mild to moderate, median 0.98 (IQR, 0.82, 1.19) than the severe group, median 0.91 (IQR, 0.73, 1.11). Similarly, LDL levels in mild to moderate group was significantly higher, median 2.43 (IQR, 1.95, 2.96) than the severe group, median 2.08 (IQR, 1.59, 2.67) both at the time of admission and after second test, median of 2.49 (IQR, 2.01, 2.94) and median of 2.28 (IQR, 1.67, 2.82) in mild to moderate and severe groups respectively.

Discussion

Coronavirus disease 2019 (COVID 2019) is a pandemic associated with high risk of morbidity and mortality.It has been reported to be one of the worst pandemics of modern times. Due to lack of information regarding its pathophysiology and clinical progress, proper institution and implementation of appropriate health care needs was hampered. Several studies have elaborated an alteration in the routine laboratory tests in COVID-19 patients, including a decrease in serum albumin levels, an increase in serum globulin levels, A/G ratio and also an increase in serum LDL and HDL levels.Albumin is a protein that plays a crucial role in maintaining the homeostasis like perpetuating colloidal osmotic pressure, intravascular transport of molecules, lipid metabolism, thrombosis and inflammation and has been considered as an important biomarker for malnutrition and poor health state for long. Hypoalbuminemia, has been shown to be associated with disease severity of many conditions like chronic inflammatory diseases, inflammatory bowel disease and diabetes mellitus[10] as well as with cirrhosis and with severity of surgical trauma, acute diseases and sepsis.In addition, during the previous SARS epidemic, hypoalbuminemia has been shown to be associated with disease severity and increased hospital mortality[12-15].The mechanism involved in hypoalbuminemia in COVID-19 patients is not clearly known but possibly it could be due to presence of a systemic inflammatory state in COVID-19 patients as suggested by Huang et al[16] which leads to extravasation of serum albumin in the interstitial space due to increased capillary permeability. However, Veering and his associates stated that serum albumin concentrations decreaseswith advancing age in both males and females[17].Hence, the in between groups showing higher severity of disease due to hypoalbuminemia, in part, may be related

to advancing age. An alternative pathophysiology was also suggested by Huang et al who attributed hypoalbuminemia to hepatic dysfunction considering the fact that there was a marked and significant decrease in LDL and HDL levels as the disease exacerbated. Notably, Sun et al[18] suggested that cytokine storm develops in COVID-19 patients. Imaeda et al[19] stated that the levels of inflammatory cytokines are inversely correlated to albumin concentrations. Hence, a possible upsurge in cytokines perhaps causes an inhibition in protein synthesis in hepatocytes causing hypoalbuminemia.Meanwhile, Globulin concentration, unlike, albumin showed a significant increase with disease severity which was observed to be higher in severely affected group, median 32.00 (IQR, 28.35, 36.70) as compared to the mild to moderately affected group, median 30.00 (IQR, 26.80, 33.30) after second testing on third day of admission to the hospital. This observation was in accordance with the study conducted by Huang et al[20] which also showed a significant reduction in A/G ratio which was found to be more apparent in death and critically ill group as compared to the non-critically ill group.The A/G ratio in our study was found to significantly decrease in the severe group, median0.94 (IQR, 0.79, 1.10) than the mild to moderate group, median 1.15 (IQR,0.97,1.34). This can be explained by the fact that there has been a significant decrease in albumin concentration as against a rise in globulin concentration with an increase in the severity of the disease. This observation was again in accordance with the study conducted by Feketea et al[21]who also reported a decrease in A/G ratio and attributed it mainly to hypoalbuminemia with an increase in the severity of disease.On the other hand, the serum lipoproteins viz. LDL and HDL evinced marked differences between mild to moderately affected and severely affected patient groups. LDL concentrations showed a significant decrease in severe group, median 2.28 (IQR,1.67, 2.82)as compared to the mild to moderate group, median 2.49 (IQR, 2.01, 2.94) while HDL levels also showed a significant decrease in severe group, median 0.91 (IQR, 0.73, 1.11) than the mild to moderate group, median 0.98 (IQR,0.82, 1.19) which is probably suggestive of an impaired lipoprotein synthesis in COVID-19 patients exhibiting a significant decrease as disease exacerbates. Our results were found quite similar with those in the study conducted by Roccaforte et al[22] who also recorded a significant decrease in HDL and LDL levels in COVID-19 patients and concluded that lipids probably play an important role in viral replication, internalization and immune activation in COVID-19 patients. They also concluded that lipid abnormalities can be used for indirectly assessing the response to clinical treatment.

Conclusion

To conclude, we can say that albumin levels and A/G ratio can be used in the prognosis of COVID-19 patients. The lower the albumin levels, the worse the prognosis. Critical hypoalbuminemia is shown to be associated with poor prognosis and deserves greater and more careful clinical intervention.On the other hand, HDL and LDL levels can also be used for indirectly assessing the response to clinical treatment in COVID-19 patients.

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