Original Article

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Prognostic Effect of Hypoalbuminaemia on Severity and Outcome in COVID-19: A Retrospective Cohort Study

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ABSTRACT

Introduction: Severe Acute Respiratory Disease-Coronavirus-2 (SARS-CoV-2) is a novel virus first detected in December 2019 causing the Coronavirus Disease-2019 (COVID-19) which has evolved into a pandemic rapidly. In patients who become symptomatic, 5% require oxygen and 15% develop severe disease ranging from respiratory failure to sepsis and septic shock. Severe COVID-19 infection is associated with high mortality. Hypoalbuminaemia is a negative acute phase reactant which has been associated with inflammatory response and poor outcome in infectious diseases. Hypoalbuminaemia is found in patients with severe COVID-19 disease.

Aim: To assess the prognostic value of hypoalbuminaemia on severity and mortality of patients with COVID-19 infection.

Materials and Methods: The present retrospective cohort study analysed data of 200 consecutive patients, with confirmed diagnosis of COVID-19 admitted, discharged or diseased between the period of April 2021 to June 2021. They were further classified as severe and non severe, survivors and non survivors based on Oxygen Saturation (SpO_2) levels as per World Health Organisation (WHO) criteria and based on survival status of the patients. Hypoalbuminaemia was defined as serum albumin <3.5 g/dL. Demographic characteristics, previous co-morbidities, clinical findings and laboratory findings were collected. Analytical variables were compared using the Chi-square test, level of significance was set at p-value <0.05.

Results: Hypoalbuminaemia was more frequent in patients with severe disease than in patients with non severe disease (28% vs 15%, Ch-square value was 34.54, p<0.001), also hypoalbuminaemia was more frequent in non survivors than survivors (23.5% vs 19.5%. Chi-square value was 43.794, p<0.001). A binary logistic regression analysis was performed to attribute the true association between hypoalbuminaemia and severity and survival status of the patients with 95% CI for OR and it was found statistically significant (p-value <0.001). Hence, hypoalbuminaemia was found to be an independent predictor of severity and mortality in the study subjects.

Conclusion: Hypoalbuminaemia may serve as an independent prognostic marker and may be used to identify patients at risk of severity and death in COVID-19 patients.

Keywords: Albumin, Coronavirus disease-2019, Marker, Mortality, Pandemic

INTRODUCTION

Coronavirus Disease-2019 (COVID-19) is caused by SARS-CoV-2, a novel virus, first recognised in December 2019 in Wuhan, Hubei province, China. Out of the total people infected, some remain asymptomatic and among the symptomatic patients, 15% develop severe disease and 5% have critical disease with complications such as respiratory failure, Acute Respiratory Distress Syndrome (ARDS), sepsis and septic shock, thromboembolism and/or multiple organ failure, including acute kidney injury and cardiac injury [1]. However there is currently no effective treatment for COVID-19 [2]. Several unique characteristics have been found in severe COVID-19 such as lymphopenia, old age, high C-Reactive Protein (CRP) level and underlying co-morbid diseases significantly decreased albumin level [2].

Albumin, a small protein is synthesised by the liver, is a free oxygen radical scavenger, has antioxidant effects therefore, it plays a vital role in inflammation. Current literature supports the idea that clinical severity in patients with COVID-19 infection may be due to virally driven hyperinflammation as suggested by Huang J et al., [2]. During critical illness, inflammatory mediators decrease albumin synthesis in order to prioritise synthesis of other acute phase reactants [3]. Additionally, these mediators increase vascular permeability allowing albumin to escape to the extravascular space, which may also lead to low serum albumin levels. Moreover, low serum albumin concentrations in critical illness have been associated with poor outcomes [3].

A meta-analysis of 90 cohort studies with acutely ill patients by Vincent JL et al., showed odds of mortality by 137%, morbidity by 89%, and prolonged hospital stay by 71% [4].

Although the field of COVID-19 research is rapidly growing, few studies have examined the association between hypoalbuminaemia and COVID-19 disease severity and outcome in terms of mortality [5].

Therefore, this retrospective study was conducted to further evaluate the association of hypoalbuminaemia on the severity and outcome of patients with COVID-19.

MATERIALS AND METHODS

The present study was a retrospective study conducted on 200 patients, who were diagnosed with COVID-19 infection and admitted in Kempegowda Institute of Medical Sciences and Research Centre, Bangalore from April 2021 to June 2021 for a duration of two months. Approval for the study was taken from the Institutional Ethics Committee (IEC number KIMS/IEC/A001/M/2022).

Sample size calculation: Sample size estimation was done as follows:

$$n = \frac{Z^2_{(1-\alpha)} \times PQ}{\delta^2}$$

$Z_{(1-\alpha)}$=1.96 (for 95% Confidence Interval)

P=0.50 (Based on the probability, that 50% of the COVID non survivor patients will have hypoalbuminaemia as per the previous literature) [3]

Q=1-P

δ (Margin of Error)=0.10

n=96.04, rounded off to 100

Due to the random characteristics among COVID-19 patients, a design effect of 2 was used and the sample size was inflated to 200.

Inclusion criteria: Patients with COVID-19 infection confirmed by Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) and age more than 18 years were included in the study.

Exclusion criteria: Patients with congestive heart failure, coronary artery disease, malignancy, nephrotic syndrome, chronic liver disease, anaemia, chronic obstructive pulmonary disease, chronic infections like pulmonary tuberculosis and cerebrovascular disease were excluded from the study.

Study Procedure

The severity of COVID-19 was defined according to WHO clinical management guidance of COVID-19 [1]. Severe type was defined as SpO_2 <90% on room air as per WHO criteria [1]. Patients who survived were defined as survivors and patients who died were defined as non survivors for the period of hospital stay between April 2021 to June 2021.

Hypoalbuminaemia was defined as any albumin value <3.5/dL, normal laboratory range in laboratory being 3.5-5.2 g/dL. The primary outcome was to study the severity of the disease and its association with hypoalbuminaemia and secondary outcome was to study the mortality of the disease and its association with hypoalbuminaemia.

The retrospective study was conducted based on patients medical records and study variables were extracted which included age, sex, mean clinical variables and laboratory variables such as Oxygen Saturation (SpO_2) and albumin concentration was noted.

STATISTICAL ANALYSIS

Statistical Package for Social Sciences (SPSS) for Windows version 22.0 Released 2013. Armonk, NY: IBM Corp., was used to perform statistical analysis. Descriptive analysis of all the explanatory and outcome parameters were done using frequency and proportions for categorical variables, whereas in mean and Standard Deviation (SD) for continuous variables. Analytical variables were compared using the Chi-square test, level of significance was set at p<0.05. A binary logistic regression analysis was performed to know the true association between hypoalbuminaemia and severity and survival status of the patients with 95% Confidence Interval (CI) for Odds Ratio (OR).

RESULTS

A total of 200 patients with a confirmed diagnosis of COVID-19 by RT-PCR positivity were included in the final analysis after applying all the exclusions. Age, vital parameters were non parametrically distributed.

The mean age of the patients was 53.2 years SD 16.1. The total number of males were 112 (56%) and females were 88 (44%) [Table/Fig-1].

Variables	Category	Frequency (n)	Percentage (%)
Age (years) (Mean±SD) (53.2±16.1) Range (18-89 years)	18-20 years	4	2.0%
	21-40 years	41	20.5%
	41-60 years	88	44.0%
	61-80 years	60	30.0%
	>80 years	7	3.5%
Gender	Male	112	56.0%
	Female	88	44.0%

[Table/Fig-1]: Age and gender distribution among study patients.

The distribution of co-morbidities among study patients has been shown in [Table/Fig-2].

[Table/Fig-3] shows the distribution of patients based on the clinical severity and outcome, 82 patients (41%) had severe COVID-19 infection and 59 patients (29.5%) were non survivors.

Co-morbidities	Present		Absent	
	n	%	n	%
HTN	51	25.5%	149	74.5%
DM	73	36.5%	127	63.5%

[Table/Fig-2]: Distribution of co-morbidities among study patients.
HTN: Hypertension; DM: Diabetes mellitus

Variables	Category	Frequency (n)	Percentage
Severity	Severe	82	41.0%
	Non severe	118	59.0%
Survival	Survivor	141	70.50%
	Non survivor	59	29.50%

[Table/Fig-3]: Distribution of patients based on the clinical severity and Outcome.

Based on the severity among COVID-19 patients, 56 patients (68.3%) with severe disease had hypoalbuminaemia which was statistically significant with a p-value <0.001, as shown below [Table/Fig-4].

Hypoalbuminaemia	Severe		Non severe		χ^2 value	p-value
	n	%	n	%		
Present	56	28%	30	15%	34.547	<0.001**
Absent	26	13%	88	44%		

[Table/Fig-4]: Comparison of presence of Hypoalbuminaemia based on the severity among COVID-19 patients using Chi-square test.
**Statistically significant

And based on the outcome among COVID-19, out of 200 patients 59 did not survive out of which 47 patients had hypoalbuminaemia which is statistically significant with a p-value of <0.001, as shown below [Table/Fig-5].

Hypoalbuminaemia	Survivor		Non survivor		χ^2 value	p-value
	n	%	n	%		
Present	39	19.5%	47	23.5%	43.794	<0.001**
Absent	102	51%	12	12%		

[Table/Fig-5]: Comparison of presence of hypoalbuminaemia based on the Outcome among COVID-19 patients using Chi-square test.
**Statistically significant

Various co-morbidities like hypertension, diabetes mellitus and age of the patient were compared with hypoalbuminaemia and the statistical significance was found with hypoalbuminaemia [Table/Fig-6].

Variables	OR	95% CI for OR		p-value
		Lower	Upper	
HTN	1.08	0.423	2.779	0.87
DM	2.43	1.018	5.782	0.05
Age	1.02	0.99	1.048	0.20
Hypoalbuminaemia	7.90	3.37	18.522	<0.001**

[Table/Fig-6]: Comparison of co-morbidities with hypoalbuminaemia.
OR: Odds ratio; 95% CI indicates 95% Confidence Interval for OR

A binary logistic regression analysis was performed to attribute the true association between hypoalbuminaemia and survival status of the patients and the results are presented below [Table/Fig-7].

Condition	Severity	Mean	SD	Mean Diff	p-value
Severity	Severe	3.50	0.42	-0.39	<0.001**
	Non severe	3.89	0.44		
Survival status	Survivor	3.88	0.40	0.50	<0.001**
	Non survivor	3.37	0.43		

[Table/Fig-7]: Comparison of mean Albumin levels based on the Severity and Survival Status of the patients using Mann-Whitney test.
**Statistically significant

DISCUSSION

The results of the present study showed a statistically significant association between hypoalbuminaemia upon initial presentation and mortality in the group of patients included in our study, 56 patients (28%) with severe COVID-19 disease had hypoalbuminaemia with a statistically significant p-value <0.001 and 47 patients (23.5%) who did not survive had hypoalbuminaemia with a statistically significant p-value <0.001. The results of the present study are consistent with prior studies that demonstrate a correlation between hypoalbuminaemia and COVID-19 severity [2-5].

The mean albumin levels in patients with severe disease and non survivors of COVID-19 patients was significantly lesser, mean of 3.5 and 3.37 respectively which was statistically significant with a p-value <0.001, as compared to non severe disease and survivors of COVID-19 infection, mean of 3.89 and 3.88 respectively. The mean difference was statistically significant at p<0.001.

Aziz M et al., performed a meta-analysis of four studies that demonstrated an increased risk for severe COVID-19 with hypoalbuminaemia [6]. In a retrospective cohort study of 299 patients, Huang J et al., showed that hypoalbuminaemia was an independent predictor for mortality in COVID-19 patients [2]. Abdeen Y et al., in a retrospective study, showed a statistically significant association between hypoalbuminaemia upon initial presentation and mortality in the group of patients included in their study [3]. The above findings are consistent with our study.

In this study, it was found that lower albumin levels on admission can predict the outcome of COVID-19 independent of other known indicators such as lymphocyte count or co-morbidities [3,5]. Hypoalbuminaemia was seen predominantly in severe COVID-19 cases compared with mild cases in previous studies and the present study [3-14].

Albumin infusion has therapeutic efficacy in conditions such as sepsis and cirrhosis through its modulatory effect on inflammation and oxidative stress in addition to plasma expansion [3-14]. Improvement in oxygenation in adult respiratory distress syndrome has been shown in a meta-analysis [10]. Albumin treatment could be a potential approach with low side-effect in patients with severe COVID-19 disease, however as majority of patients with severe COVID-19 are elderly with cardiovascular co-morbidities, efficacy and safety of albumin as therapy should be verified in prospective studies [15].

Limitation(s)

The present study was limited by certain factors. Firstly, it was a single-centre study and hence, the results could not be generalised. Secondly, albumin therapy was not used at this centre.

CONCLUSION(S)

Hypoalbuminaemia was associated with severity and mortality in our study population and could be considered a strong predictor for mortality in hospitalised patients with COVID-19. Hence, initial screening of patients for hypoalbuminaemia and early stratification into low risk and high risk groups and aggressive treatment could prevent COVID-19 severity and mortality.

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