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Hypoalbuminemia as an early predictor of severe COVID-19 infection: A retrospective observational study

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***Abstract*---**Objectives: Several unique characteristics have been found in severe COVID19, such as lymphopenia, old age, high CRP level, elevated D dimer levels and underlying comorbid diseases. Serum albumin, being a negative acute phase reactant has been found to be associated with inflammatory response and poor outcomes in infectious diseases. The aim of the study was to analyse whether the serum albumin levels on admission might reflect the severity of systemic inflammation in COVID 19 infection and thus serve as an early predictive factor for COVID 19 outcomes. Materials and Method: This retrospective observational study included 185 COVID-19 positive patients. Laboratory data was recorded from blood samples

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collected at admission and analyzed by standard methods in the laboratory. Hypoalbuminemia was defined as serum albumin levels <3.5g/dl. $p < 0.05$ was considered statistically significant. Results: In the 185 COVID 19 patients studied, average age was 51.29 (±15.68) years. The study population had a male predominance (68.11%). 85 (45.95%) individuals were found to have hypoalbuminemia on admission. 18 (9.73%) deaths were reported amongst the study population and a significant association was found between low serum albumin levels on admission and mortality.($p < 0.001$). Age, TLC, NLR and HRCT Thorax CT severity scores were significantly higher in patients with hypoalbuminemia while PaO2/FiO2 ratio was found to be significantly lower in patients with hypoalbuminemia ($p<0.001$). It was also observed that hypoalbuminemia was significantly associated with the presence of comorbidities like hypertension, diabetes mellitus, and ischemic heart disease. Analysis of the area under the receiver operating characteristic curve (AUROC) for serum albumin levels for predicting survival was 0.768 (95% CI). It also suggested that serum albumin levels of ≥ 3.05 mg/dl have 71.9% sensitivity and 72.8% specificity to predict survival in these COVID 19 patients. Multivariate regression analysis showed that high NLR (>3.13) (OR, 11.010; 95% CI, 1.304-92.967) and presence of at least one comorbidity (OR, 3.930; 95% CI, 1.133-13.629), independently predicted mortality. However, hypoalbuminemia was not found to be an independent predictor of death (OR,1.578; 95% CI, 0.375-6.644) after adjusting for age, NLR and presence of comorbidities, Conclusion: Hypoalbuminemia on admission was associated with severe COVID 19 infection in this study population. Although significantly associated with mortality, we did not find hypoalbuminemia to be an independent predictor of death in COVID 19. Further studies are required to assess the therapeutic value of albumin in severe COVID-19.

***Keywords*---**COVID-19, SARS-CoV 2, serum albumin, hypoalbuminemia.

Introduction

The World Health Organization (WHO) declared COVID 19 as a pandemic on 11 March 2020. Caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2), the first case of COVID 19 was reported in Wuhan, in the Hubei province in China in December 2019. Since then, a total of around 258 million cases of this deadly disease have been reported worldwide, leading to more than 5 million deaths.[1] In India, the novel coronavirus has led to more than 34 million cases with around 4.6 million deaths.[1] The spectrum of this disease ranges from being asymptomatic to life threatening acute respiratory distress syndrome.

Hypoalbuminemia, often seen in hospitalized or critically ill patients occurs due to reduced production of albumin or due to increased losses via the kidney, gastrointestinal tract, skin, or extravascular loss; or because of increased

breakdown of albumin. Low serum albumin levels have also been reported in patients with severe COVID 19.[2] However this has not been found to run parallel with hepatocellular injury in these patients, suggesting some other mechanism for hypoalbuminemia.[3] It has been hypothesized that the lower serum albumin levels in COVID 19 patients could be explained by the systemic inflammatory response and the cytokine storm seen in severe disease. Due to the dysregulated inflammatory response, vascular permeability is increased, leading to loss of albumin from the vascular compartment into the interstitial space.

Severe COVID 19 has been significantly associated with lymphopenia, older age, high C reactive protein, elevated D dimer and underlying comorbidities [2,4,5,6]. The role of serum albumin levels in the severity of COVID 19 is still under evaluation. To address this question, we analyzed the serum albumin levels of hospitalized COVID 19 patients on hospital admission, and studied the correlation of hypoalbuminemia with outcomes, in terms of mortality.

Methodology

This was a retrospective observational study conducted among adult patients hospitalized for COVID 19 in Krishna Hospital, Karad during the period July 2021 to September 2021. The approval of the Ethics Committee of the Krishna Institute of Medical Sciences 'Deemed to be University' was obtained before the initiation of the study. 185 patients who were ≥ 18 years age and hospitalized with a diagnosis of COVID-19, confirmed by a positive result of real-time reverse transcription-polymerase chain reaction (RT-PCR) for the presence of SARS- CoV-2 in nasopharyngeal swab specimens, were enrolled into the study. Patients who refused to participate and those treated for COVID 19 on an outpatient basis were excluded.

Data was collected by reviewing the case sheets and daily patient notes entered into a semi-structured pre-tested questionnaire. We also collected comorbidity data in terms of the presence of hypertension, diabetes mellitus, obesity, chronic kidney disease, chronic obstructive pulmonary disease, chronic lung disease, immunocompromised state, or malignancy.

Laboratory data was recorded from blood samples collected at admission and analyzed by standard methods in the laboratory. This included a complete hemogram with differential counts, renal function tests, liver function tests and serum albumin. The neutrophil-to-lymphocyte ratio (NLR) value was measured by dividing the neutrophil count by the lymphocyte count. D dimer, Ferritin, CRP, ESR, and wherever applicable, procalcitonin, IL6 values were also recorded. PaO2/FiO2 ratio was calculated from arterial blood gas analysis on admission. HRCT Thorax CT severity scores of subjects were also recorded. Hypoalbuminemia was defined as serum albumin levels <3.5g/dl based on previous studies. [1]

Statistical Analysis

Data collected was entered in Microsoft Excel 2013. It was represented in frequencies and percentages. Mean ± standard deviation of quantitative variables

was calculated. Appropriate statistical tests were applied using IBM SPSS version 23.1 (Trial version) for analysis. Chi-square test was used for association and student's t-test for comparison between the study variables. The area under the receiver operating characteristic curve (AUROC) analysis was used to predict the serum albumin cut off for evaluating mortality in the patients. Statistical significance was considered at $p < 0.05$ at 95% confidence interval.

Results

185 patients hospitalised for COVID 19 fulfilling the inclusion criteria, were enrolled in the study. The mean age of the study population was 51.29 (±15.68) years with a range of 16 to 92 years. The most commonly affected age group was 41 to 60 years with 78 participants (42.16%) followed by 61 to 80 years with 56 participants (30.27%). There were a total of 126 males (68.11%) and 59 females (31.89%) participants, with a male: female ratio of 2.14:1. 116 out of 185 had comorbidities as given in table no. 1; out of which majority had hypertension (27.57%) followed by diabetes mellitus (23.24%)

Table 1: Presence of Comorbidities

Comorbidity	n	Percentage
Hypertension	51	27.57%
Diabetes Mellitus	43	23.24%
Chronic Obstructive Pulmonary Disease	6	3.24%
Ischemic Heart Disease	4	2.16%
Cerebrovascular Accident	2	1.08%
Chronic Kidney Disease	2	1.08%
Obesity	2	1.08%
Chronic Lung Disease	1	0.54%
Malignancy	0	0 %
Other	5	2.70%

Mortality analysis

There were a total of 18 deaths amongst the study population with a mortality of 9.73%. 42 out of 185 cases (22.70%) required intensive care for the management of disease. The association of mortality with select study parameters has been illustrated in table no 2. A higher age, lower haemoglobin, higher total leukocyte count (TLC), and higher serum creatinine were significantly associated with mortality. Additionally, significant mortality was also associated with higher ferritin levels, elevated C reactive protein (CRP), lower Pao2/FiO2 ratio, and higher HRCT Thorax CT severity score assessed on the day of hospital admission in these COVID 19 patients.

Table 2: Comparison of baseline characteristics in survivors and non-survivors

Variable	Outcome	Mean	± SD	*p*
Age	Non- survivors (18)	62.44	8.81	0.001*
	Survivor (167)	50.08	15.80	

D dimer	Non- survivors(18)	1.17	1.81	0.754
	Survivor (167)	10.90	131.35	
Ferritin	Non- survivors(18)	604.04	533.39	<0.001*
	Survivor (167)	298.38	296.09	
CRP	Non- survivors (18)	2.78	1.85	0.584
	Survivor (167)	4.21	11.04	
P/F Ratio	Non- survivors(18)	144.50	105.12	<0.001*
	Survivor (167)	306.22	106.45	
Hb	Non- survivors (18)	11.04	1.89	<0.001*
	Survivor (167)	12.91	1.63	
TLC	Non- survivors(18)	13205.56	8576.06	<0.001*
	Survivor (167)	7311.35	3601.49	
N/L Ratio	Non- survivors (18)	7.43	2.06	0.540
	Survivor (167)	4.72	5.89	
Serum bilirubin	Non- survivors(18)	0.73	0.47	0.946
	Survivor (167)	0.72	0.83	
Serum Creatinine	Non- survivors (18)	1.57	0.72	<0.001*
	Survivor (167)	1.04	0.32	
HRCT	Non- survivors (18)	14.17	4.57	<0.001*
	Survivor (167)	8.14	4.21	

*Significant

The presence of comorbidities like hypertension, diabetes mellitus, and chronic lung disease was also associated with higher mortality as shown in table no. 3.

Table 3: Comparison of comorbidities in survivors and non-survivors

Comorbidities	Non-survivors (18)	Survivors (167)	*p*
Hypertension	11	40	0.001*
Diabetes Mellitus	12	31	<0.001*
Chronic Obstructive Pulmonary Disease	0	6	0.414
Ischemic Heart Disease	1	3	0.297
Cerebrovascular Accident	1	1	0.053
Chronic Kidney Disease	1	1	0.053
Obesity	1	1	0.053
Chronic Lung Disease	1	0	0.002*
Malignancy	0	0	-
Other	0	5	0.281

*Significant

Association of serum albumin levels with mortality. Out of total of 185 patients, there were 85 cases of hypoalbuminemia (45.95%) with serum albumin levels less than 3.5 on admission and the rest 100 cases with normal albumin levels (54.05%). 4 cases were excluded from mortality analysis for hypoalbuminemia since they had confounding factors like pre-existing chronic liver disease, chronic kidney disease, and sepsis. Out of these 4 cases, 3 patients died. Amongst the other 15 deaths in the study population, 13 patients (86.67%) had

hypoalbuminemia while only 2 (13.33%) had normal serum albumin levels. Thus a significant association was seen between low serum albumin levels on admission and mortality in these COVID 19 patients ($p < 0.001$).

Table 4: Association between the serum albumin levels and death

	Non- survivors	Survivors	Total
Normal albumin	2	97	99
Hypoalbuminemia	13	69	82
Total	15	166	181

$X^2 = 11.29$, df = 1, $p < 0.001$, Significant

Comparison of study parameters in patients with hypoalbuminemia and normal albumin: The study parameters were compared in the patients with normal albumin and those with hypoalbuminemia, as illustrated in table 5 and 6. Age, TLC, leukocyte count, NLR and HRCT Thorax CT severity scores were significantly higher in patients with hypoalbuminemia while PaO2/FiO2 ratio was significantly lower in patients with hypoalbuminemia ($p<0.001$). No significant difference was seen in the CRP, D- dimer, and ferritin levels in the COVID 19 patients with and without hypoalbuminemia.

Table 5: Comparison of quantitative study parameters in hypoalbuminemia and normal albumin groups

		n	Mean	± SD	*p*
Age	Hypoalbuminemia	85	52.76	14.28	<0.001*
	Normal Albumin	100	41.8	15.89	
TLC	Hypoalbuminemia	85	9312.5	5718.7	<0.001*
	Normal Albumin	100	6614.05	3018.76	
P/F	Hypoalbuminemia	85	263.62	124	<0.001*
	Normal Albumin	100	324.66	98.43	
HRCT Thorax CT Severity Score	Hypoalbuminemia	85	11.7	5.28	0.001*
	Normal Albumin	100	9.12	5.11	
D dimer	Hypoalbuminemia	85	1.08	2.02	0.360
	Normal Albumin	100	18.55	173.32	
Ferritin	Hypoalbuminemia	85	388.48	403.11	0.061
	Normal Albumin	100	295.37	263.68	
CRP	Hypoalbuminemia	85	2.64	5.69	0.952
	Normal Albumin	100	2.71	13.6	
N/L ratio	Hypoalbuminemia	85	6.31	6.14	0.002*
	Normal Albumin	100	3.84	2.54	

It was also observed that hypoalbuminemia was significantly associated with the presence of comorbidities like hypertension, diabetes mellitus, and ischemic heart disease.

Table 6: Comparison of comorbidities in the hypoalbuminemia and normal albumin groups

Comorbidities	Hypoalbuminemia	Normal albumin	*p*
Hypertension	31	20	0.012*
Diabetes Mellitus	27	16	0.011*
Chronic Obstructive Pulmonary Disease	5	1	0.062
Ischemic Heart Disease	4	0	0.028*
Cerebrovascular Accident	1	1	0.910
Chronic Kidney Disease	1	1	0.910
Obesity	2	0	0.123
Chronic Lung Disease	1	0	0.277
Malignancy	0	0	-
Other	4	1	0.121

*Significant

Multivariate analysis for mortality

Multivariate regression analysis was carried out to assess the predictors of death outcomes. We found that high NLR (>3.13) (OR, 11.010; 95% CI, 1.304-92.967) and presence of at least one comorbidity (OR, 3.930; 95% CI, 1.133-13.629), independently predicted mortality. However, on controlling age, NLR and presence of comorbidities, hypoalbuminemia was not found to be an independent predictor of death (OR,1.578; 95% CI, 0.375-6.644)

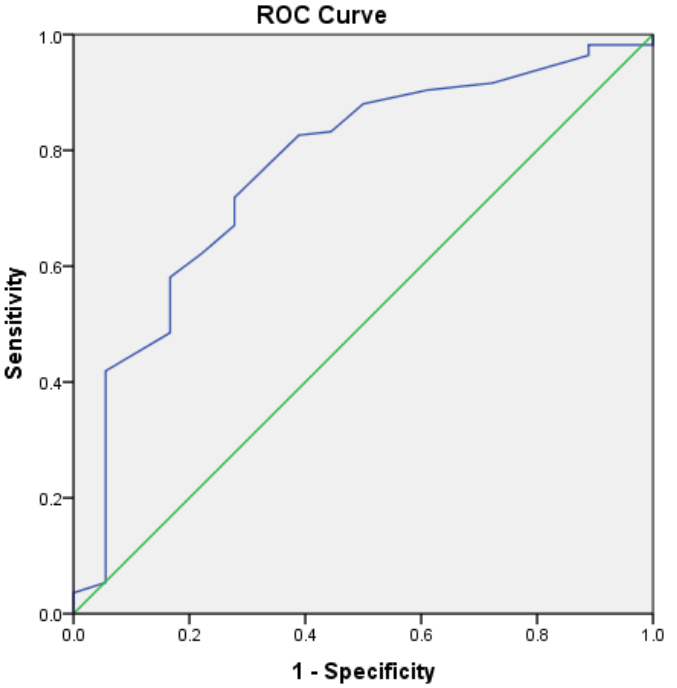
Table 7: Multivariate analysis of parameters for risk of death

Variables	Sig.	Exp(B)	95% C.I.for EXP(B)	
			Lower	Upper
Age	.065	1.041	.997	1.087
NLR	.028	11.010	1.304	92.967
Presence of at least 1 comorbidity	.031	3.930	1.133	13.629
Hypoalbuminemia	.534	1.578	.375	6.644

ROC analysis for serum albumin levels predicting survival

Analysis of the area under the receiver operating characteristic curve (AUROC) for serum albumin levels for predicting survival was 0.768 (95% CI). It also suggested that serum albumin levels of ≥ 3.05 mg/dl have 71.9% sensitivity and 72.8% specificity to predict survival in these COVID 19 patients.

Fig1: ROC analysis of serum albumin levels and survival



Discussion

Critical illness and mortality have been associated with hypoalbuminemia over a large spectrum of diseases and clinical settings. Hypoalbuminemia has also been reported in cases of severe COVID 19 in several studies present in the literature. However, the predictive value of serum albumin levels for the outcomes of COVID 19 has not been adequately assessed, especially in the Indian population. Hypoalbuminemia, as defined by serum albumin level <3.5 g/dl, was significantly associated with mortality in the present study. Lower serum albumin levels were also present with individuals who were older, comorbid, had a higher total leucocyte count, higher neutrophil: lymphocyte ratio, higher HRCT thorax CT severity score as well as a lower Pao2/FiO2 ratio. This was indicative that lower serum albumin levels on admission were associated with severe COVID 19 in the study population.

A systematic review and meta-analysis done by Aziz et al[8] confirmed the association between low albumin levels and COVID 19. Yuan Xu[9], in a study conducted in China, identified the presence of hypoalbuminemia in severe and non-severe COVID 19 patients. In a multi-point assessment of serum albumin levels in week 1, week 2, and week 3 or 4 of illness, they also found serum albumin levels to increase with recovery from disease. This suggested the importance of dynamic monitoring of serum albumin level as a predictor of outcomes in COVID 19.

Huang et al[7] also reported that serum albumin levels on admission could predict the outcomes in COVID 19 independent of other parameters like age and presence of comorbidities. In the study done by Viana-Llamas et al[10], hypoalbuminemia (serum albumin < 34g/L) was associated with mortality. It was also identified by multivariate regression analysis, as a predictor for mortality, independent of other parameters like Charlson-Age Index, sex, lymphopenia, creatinine, high-sensitivity C- reactive protein >8 mg/L, lactate dehydrogenase >250 U/L, bilateral infiltration on chest X-ray and q-SOFA ≥2. This was in contrast with present study results, which did not find hypoalbuminemia to be an independent predictor of mortality after adjusting for age, NLR and presence of comorbidity. However, this may be a result of a relatively smaller sample size and a more comorbid study population.

Hypoalbuminemia in disease is caused by a variety of mechanisms- increased capillary permeability due to systemic inflammatory response, reduced protein synthesis in liver dysfunction or in catabolic states, decreased half-life of serum albumin leading to reduced serum albumin total mass in inflammatory states, increased volume of distribution, and increase expression of vascular endothelial growth factor.[11] However, in COVID 19, the mechanism of hypoalbuminemia is still under speculation. Yafei Zhang et al[3] found that more than 50% of the COVID 19 patients enrolled in the study had hypoalbuminemia (serum albumin <40g/L), while it was present in approximately 90% of patients in the severe category. In spite of this, markers of hepatic injury like AST, ALT, total bilirubin, GGT and LDH were not significantly elevated in the COVID 19 patients as compared to the control group (cases of community-acquired pneumonia). In other studies as well, serum albumin levels have not been found to run in parallel with hepatic dysfunction or hepatocellular injury.[7]

Hypoalbuminemia in COVID 19 could be explained by the inflammatory response and resultant cytokine storm in severe illness- by increasing capillary permeability and leading to accumulation of albumin in the interstitial spaces. The cytokines released into the circulation also are said to down regulate the album synthesis in the liver at a pre-translational level. [12] In our study as well, we found hypoalbuminemia to be associated with other inflammatory markers like elevated NLR and TLC. Hence, serum albumin level could potentially be used as a marker of inflammation in COVID 19 to predict outcomes. Our study found serum albumin levels of ≥ 3.05 mg/dl to have 71.9% sensitivity and 72.8% specificity to predict the survival in COVID 19 patients.

The present study had certain shortcomings and limitations. It was restricted to a single tertiary care centre and had a retrospective design with a limited sample size. Majority of the study participants (62.7%) has underlying comorbidities. Serum albumin levels were only measured on admission, and the predictive value of these baseline levels was assessed. Changes in the serum albumin levels during the course of the illness were not documented. Further studies are required to analyze whether the changes in serum albumin levels at various points in the course of the disease have an association or a predictive value with outcomes. Further trials are also required to evaluate the utility and efficacy of albumin infusions in the management of severe COVID 19.

Conclusion

In conclusion, hypoalbuminemia on admission was associated with severe COVID 19. Hence, lower serum albumin levels may be utilised as an early predictor of severe disease to allow risk stratification in patients infected with SARS- CoV 2 in this pandemic situation. Although associated significantly with mortality, we did not find low serum albumin levels to independently predict death outcomes. Further studies are required to assess the therapeutic value of albumin in severe COVID 19.

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References

1. WHO Coronavirus (COVID-19) Dashboard [Internet]. [cited 2021 Nov 25]. Available from: https://covid19.who.int
2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 28;395(10229):1054–62.
3. Zhang Y, Zheng L, Liu L, Zhao M, Xiao J, Zhao Q. Liver impairment in COVID-19 patients: A retrospective analysis of 115 cases from a single centre in Wuhan city, China. Liver Int. 2020 Sep;40(9):2095–103.
4. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020 Jul 28;71(15):762–8.
5. He X, Yao F, Chen J, Wang Y, Fang X, Lin X, et al. The poor prognosis and influencing factors of high D-dimer levels for COVID-19 patients. Sci Rep. 2021 Jan 19;11(1):1–7.
6. Ejaz H, Alsrhani A, Zafar A, Javed H, Junaid K, Abdalla AE, et al. COVID-19 and comorbidities: Deleterious impact on infected patients. J Infect Public Health. 2020 Dec;13(12):1833–9.
7. Huang J, Cheng A, Kumar R, Fang Y, Chen G, Zhu Y, et al. Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. J Med Virol [Internet]. [cited 2021 Oct 27]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7273060/
8. Aziz M, Fatima R, Lee-Smith W, Assaly R. The association of low serum albumin level with severe COVID-19: a systematic review and meta-analysis. Crit Care. 2020 May 26;24(1):255.
9. Xu Y, Yang H, Wang J, Li X, Xue C, Niu C, et al. Serum Albumin Levels are a Predictor of COVID-19 Patient Prognosis: Evidence from a Single Cohort in Chongqing, China. IJGM. 2021 Jun 24;14:2785–97.
10. Viana-Llamas MC, Arroyo-Espliguero R, Silva-Obregón JA, Uribe-Heredia G, Núñez-Gil I, García-Magallón B, et al. Hypoalbuminemia on admission in COVID-19 infection: An early predictor of mortality and adverse events. A retrospective observational study. Med Clin . 2021 May 7;156(9):428–36.

11. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: Pathogenesis and Clinical Significance. JPEN J Parenter Enteral Nutr. 2019 Feb;43(2):181–93.
12. Ramadori G. Hypoalbuminemia: an underestimated, vital characteristic of hospitalized COVID-19 positive patients? Hepatoma Research. 2020 Jun 3;6:28.