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ORIGINAL ARTICLE

Hypoalbuminemia in COVID-19 patients: A Predictor of Poor Outcome

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ABSTRACT

Background: The coronavirus disease 2019 (COVID-19) has quickly spread to become a pandemic. Most studies demonstrate that increased liver enzymes in COVID-19 have little clinical relevance. In severe COVID-19, lower albumin levels are seen.
Aim: To see how hypoalbuminemia levels affect the COVID-19 patients.
Study design: Retrospective cohort study.
Place and duration of study: Services Institute of Medical Sciences Lahore and Bahria International Hospital, Lahore from 10th January 2021 to 17th September 2021.
Methodology: Sixty-seven confirmed cases of COVID-19 on RT-PCR were recruited. They were further divided into two groups. Group N (normal albumin levels) had thirty-six participants whereas group HA (hypoalbuminemia) contained thirty-one participants. Both males and females of all age groups, having complete medical records were included. Biochemical variables were noted from the medical record within 48 to 72 hours after admission. Twenty eight days follow up was done to note the mortality. Patients having incomplete medical records who expired within 2 days after admission were excluded.
Results: A significantly higher number of deaths, lymphopenia, hypertensive, diabetics, and asthmatic participants were found in Group HA as compared to Group N. Hypoalbuminemia is mostly seen in older age and biochemical variables such as total leukocyte count and, neutrophils were elevated, whereas lower levels of lymphocytes were found in group HA. Lower lymphocytes and higher creatinine levels are the most prevalent predictors of mortality. The Pearson's correlation of albumin with lymphocytes showed a positive correlation and inverse correlation with TLC, Neutrophil counts, CRP levels
Conclusion: The group HA is associated with higher mortality and increased levels of prognostic factors of mortality.
Keywords: Hypoalbuminemia, SARS-CoV-2, Mortality, Predictive importance, Therapeutic benefits, Inflammatory markers

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has been declared a pandemic by the World Health Organization, with much greater fatality rates than SARS and Middle East respiratory illness.[1] However, there is currently no effective therapy for this rare disease.[2] Lymphopenia, ageing, elevated CRP levels, and underlying co-morbid conditions have all been found as separate indications of severe COVID-19[3]. Although albumin levels drop significantly in severe COVID-19 cases, the drop is not related to the severity of hepatocellular lesions.[4] This suggests that COVID19's substantial hypoalbuminemia might be related to causes other than liver injury. The considerable systemic inflammation associated with severe COVID-19 might be a contributing factor[5]. Because increased capillary permeability causes albumin to seep into the interstitial space, hypoalbuminemia is frequent in many inflammatory disorders[6,7].

Serum albumin concentrations were expected to indicate the severity of systemic inflammation and could therefore be used to predict the outcomes of COVID-19. To find an answer to this question, we undertook the study to examine patient outcomes, with and without hypoalbuminemia and to study the function of altered albumin levels in the prognosis of COVID-19.

The objective of the study was to see how hypoalbuminemia levels affect the COVID-19 patients.

MATERIALS AND METHODS

This is a retrospective analysis conducted at Services Institute of Medical Sciences Lahore and Bahria International Hospital Lahore from 10th January 2021 to 17th September 2021. A total of 67 study participants had full medical records and a COVID-19 positive RT-PCR was included. The study received approval from the Institutional Review Committee of hospital. The study population was further divided into groups. The first group had low albumin levels (less than 35g/l) labelled as Group HA (hypoalbuminemia) and the second group had normal albumin levels (35-55 g/l) named as Group N. Both men and women, aged 18-70, were recruited for the study. Comorbid conditions such as high blood pressure, diabetes, asthma and chronic obstructive pulmonary disease (COPD) and ischemic heart disease (IHD) have been noted. Biochemical variables, total leukocyte count (TLC), C-reactive protein (CRP), D. Dimer, procalcitonin, albumin, AST, ALT and creatine were also noted in groups. The 28 days death rate was also noted in both groups. Continuous variable with normal distribution has been reported as mean and standard deviation. Percentages were used to express categorical variables. The student t-test (for normally distributed data) and the Mann-Whitney U test (for non-normally distributed variables) were applied to see the statistical variance. The difference between categorical variables was investigated using the x2 test or Fisher's exact test, where appropriate. Pearsons's correlation was applied to determine the relationship of albumin levels with other biochemical variables. Binary logistic regression for the prediction of mortality whereas Pearsons's correlation to analyze the relationship between the parametric variables with albumin levels. A statistically significant *P* value of 0.05 was used.

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RESULTS

A total of 67 participants were included in the study. They are divided into normal albumin (Group N) and hypoalbuminemia (Group HA) groups. 54.7% of the participants were males. The death ratio was significantly greater in the HA group as compared in Group N (8.3% vs 32.3% respectively p=0.014). Similarly, the lymphopenia significantly differed between the groups (25% vs 67.7% respectively p<0.01). The Group HA contained more diabetics and hypertensive patients as compared to the group N (p=0.028 and p= 0.045 respectively). The other comorbid

conditions such as ischemic heart disease, COPD, and asthma did not differ significantly between the groups (*p*=0.326 and *p*=0.326 and p=0.054 respectively) [Table 1].

In group HA the age of the patients was significantly greater (p=0.005). Similarly, the TLC neutrophil count was found to the signifying higher in the HA group as compared to the group N (P= 0.006 and 0.004 respectively). However, we did not find any differences in creatine levels between the two groups (Table 2). It was significantly elevated levels of CRP, procalcitonin, D. Dimer and LHD levels in Group HA (Table 3).

The variation in lymphocytes and creatinine was shown to have a big impact on mortality (OR, 22.02; 95% CI, and OR, 10.88; 95% CI, respectively). The biochemical variables such as albumin (OR, 1.884; 95% CI, 0.845- 4.199), TLC, CRP, and LDH also have some impact on mortality (Table 4). The Pearson's correlation of albumin with lymphocytes showed a positive correlation and inverse correlation with TLC, neutrophil counts, CRP levels, and procalcitonin. LDH and D. Dimer are shown in Table 5.

Table 1: Comparing of gender, comorbid conditions, and deaths between the groups

Variable		Normal albumin (n=36)		Hypoalbuminemia (n=31)		P value
		No.	%	No.	%	
Gender	Male	16	44.4	18	58.1	0.266
	Female	20	55.6	13	41.9	
Deaths	Non-survivors	3	8.3	10	32.3	0.014
	Survivors	33	91.7	21	67.7	
Lymphocytopenia	No	27	75%	10	32.3	0.001
	Yes	9	25%	21	67.7	
HTN	No	29	80.6	18	58.1	0.045
	Yes	7	19.4	13	41.9	
DM	No	33	91.7	22	71.0	0.028
	Yes	3	8.3	9	29.0	
IHD	No	33	91.7	26	83.9	0.326
	Yes	3	8.3	5	16.1	
Asthma	No	33	91.7	23	74.2	0.054
	Yes	3	8.3	8	25.8	
COPD	No	33	91.7	26	83.9	0.326
	Yes	3	8.3	5	16.1	

Table 3: Comparison of non-normally distributed biochemical variable between the groups

Variable	Normal			Hypoalbuminemia			P value
	Median	95.0% Lower CL	95.0% Upper CL	Median	95.0% Lower CL	95.0% Upper CL	
CRP	23.60	18.67	28.51	32.80	31.00	51.23	0.008
Procalcitonin	0.21	0.19	0.23	0.57	0.36	0.79	0.00
Dimer	1.42	0.86	1.78	8.78	6.20	10.01	0.00
LDH	208.16	165.46	231.41	501.89	454.52	614.78	0.00

Man-Whitney u Test (non-normal)

Table 5: Pearson's correlation of Albumin with other parametric biochemical variables

Parameter	Albumin	TLC	Lymphocytes	Neutrophils	CRP	Procalcitonin	D. Dimer	LDH	Creatinine
Albumin	1	-	-	-	-	-	-	-	-
TLC	-.348**	1	-	-	-	-	-	-	-
Lymphocytes	.588**	-.288*	1	-	-	-	-	-	-
Neutrophils	-.247*	0.096	-0.106	1	-	-	-	-	-
CRP	-.296*	-0.048	-.243*	.368**	1	-	-	-	-
Procalcitonin	-.524**	0.199	-.366**	.334**	.439**	1	-	-	-
D. Dimer	-.629**	0.213	-.514**	0.206	0.146	.484**	1	-	-
LDH	-.657**	.262*	-.548**	.406**	.383**	.458**	.631**	1	
Creatinine	0.080	0.207	-0.047	-0.054	-0.086	-0.004	0.010	-0.111	1

**Correlation is significant at the 0.01 level (2-tailed) *Correlation is significant at the 0.05 level (2-tailed)

Table 2: Comparison of normally distributed biochemical variable between groups

Variable	N Group	HA Group	P value
Age (years)	52.79±12.23	61.33±11.82	0.005
TLC (×10^9/L)	4.40±1.27	5.41±1.62	0.006
Neutrophil count (10/L)	2.95±0.91	4.05±1.97	0.004
Lymphocytes (×10/L)	1.31±0.25	0.92±0.26	0.000
AST (U/L)	25.64±6.70	26.48±7.92	0.64
ALT (U/L)	29.33±8.81	30.03±10.80	0.77
Creatinine (mg/dl)	1.16±0.45	1.11±0.34	0.622

Table 4: Binary logistic regression of factors for risk of death

Variables	Sig.	Exp (B)	95% C.I. for EXP (B)	
			Lower	Upper
TLC	0.619	1.435	0.346	5.947
Neutrophils	0.308	0.323	0.037	2.838
Lymphocytes	0.470	22.023	0.005	96679.261
CRP	0.224	1.075	0.957	1.209
Procalcitonin	0.541	0.162	0.000	55.605
D. Dimer	0.110	0.507	0.221	1.167
Albumin	0.121	1.884	0.845	4.199
LDH	0.086	1.045	0.994	1.099
Creatinine	0.327	10.877	0.092	1283.605

DISCUSSION

The most notable conclusion of our research is that the amount of albumin and the risk of mortality in COVID-19 patients are associated with each other. A blood albumin level of 35 g/L after 48 to 72 hours of admission elevated the probability of mortality in COVID-19 by at least 2 times, according to this retrospective analysis. The literature has consistently noted and mentioned hypoalbuminemia in severe COVID19[8-11]. The prognostic usefulness of albumin, however, has been reported in few studies. One study also reported hypoalbuminemia increased the risk of mortality almost 6 times[9]. We also discovered that lower albumin levels can predict COVID-19 prognosis irrespective of other known indications like lymphocyte count or comorbidities in this study[12,13].

This finding is following a recent study that found that hypoalbuminemia, or a decrease in albumin, is linked to the severity of ARDS or acute renal damage[14].

Hypoalbuminemia was connected to prognosis and outcome in 80.4 percent of COVID-19 patients with decreased liver function, according to a meta-analysis[15]. The reasons for COVID-19 hypoalbuminemia have not been well investigated or explained. The liver produces albumin, which has a serum half-life of roughly

21 days. ALT and AST values increased modestly in COVID-19 patients but were not predictive[16]. Hypoalbuminemia was found more frequently in severe COVID19 patients than in mild COVID19 patients in prior research also. Hepatocellular dysfunction or liver injury alone cannot explain this behaviour[17]. Furthermore, the research found that the median time from onset of illness to admission was only three days, much smaller than the serum albumin half-life, showing that hypoalbuminemia in severe COVID19 was less likely to be caused by decreased albumin synthesis[18]. We identified a relationship between albumin levels and inflammatory indicators in our investigation such as CRP, WBC, and LDH. Systemic inflammation might be the cause of hypoalbuminemia in those with severe COVID-19. Higher levels of inflammatory markers are seen in severe instances of COVID-19[19]. As a result of increased capillary permeability caused by inflammation, serum albumin can escape into the interstitial space, increasing albumin volume distribution[20]. Therefore, it is clear from our results that hypoalbuminemia in COVID-19 is caused by systemic inflammation.

Albumin's therapeutic efficacy in sepsis and cirrhosis reveals that it may modulate inflammation and oxidative stress in addition to expanding plasma volume[21]. A meta-analysis revealed that albumin therapy enhances oxygenation in patients with ARDS[22]. Due to the lack of a particular therapy for COVID-19 related systemic inflammation, albumin treatment with low side effects may be a potential alternative. The effectiveness and safety of albumin in COVID-19 must be validated in prospective studies, however, because the majority of patients with severe COVID-19 are older and have cardiovascular and hypertensive comorbidities. There are several limitations to this study as well. We did a retrospective analysis based on a single Centre. The prediction of mortality in our study was measured after 48 to 72 hours of admission.

In our data set the progressive changes and their association were not considered. Moreover, for better understanding, a prospective clinical trial is needed with controls and intervention groups with albumin levels correction therapeutically.

CONCLUSION

The group HA is associated with higher mortality and increased levels of prognostic factors of mortality. So, we should consider albumin infusions to analyze the therapeutic effects in Covid-19 patients. Albumin possible can provide therapeutic benefit in COVID-19, but it needs further investigation.

Conflict of interest: Nil

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