

## Original Research Article

# Study of serum albumin as a marker of severity in COVID-19 positive SARI and COVID-19 negative SARI patients

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## ABSTRACT

**Background:** COVID-19 a pandemic caused by SARS CoV-2 has caused a wide impact globally. Clinical spectrum of COVID-19 ranges widely including asymptomatic infection, mild upper respiratory tract infection, severe pneumonia, ARDS, MODS and even death. Hypoalbuminemia in COVID-19 indicates severe disease. The aim of the study was to determine incidence of hypoalbuminemia and correlation of severity of hypoalbuminemia with COVID-19 positive SARI and COVID negative SARI patients.

**Methods:** A study was conducted on 265 SARI patients who were admitted in hospitals attached to BMCRI. History was taken, general physical examination and a detailed systemic examination was done. Patients were categorized into mild, moderate and severe illness. RT-PCR for COVID-19 patients done using throat and nasal swab. Total WBC counts and differential counts, platelet counts were estimated. Serum albumin levels were correlated with pneumonia severity and compared between COVID-19 positive and Negative SARI. And also, correlation with comorbidities was done.

**Results:** The study included 265 SARI patients, of which 135 were COVID-19 positive patients and 130 were COVID-19 negative. Patients categorized into moderate and severe SARI. Mean age of subjects with COVID-19 positive (severe) was higher-  $58.70 \pm 15.598$  followed by COVID-19 positive (moderate)-  $55.13 \pm 14.480$ . About 30% (N=90) were belong to severe SARI group, Chi-square test showed statistical significant association with respect to age. Chi-square test showed no statistical significant association with respect to gender. Independent sample t test showed statistical difference with respect to S. albumin levels between COVID positive and COVID negative subjects. In COVID positive subjects, S. albumin levels showed statistical significant difference between moderate and severe sub groups whereas there was no statistical significant difference seen in COVID negative sub groups.

**Conclusions:** The relationship between hypoalbuminemia and reduced survival in COVID-19 may have several explanations. First, acting as an anti-inflammatory and antioxidant protein, albumin may protect against cytokine storm. Second, albumin encompasses anticoagulant properties and inhibits oxidative stress-related clotting and platelet activation that occurs in severe COVID-19. Third, albumin is an inverse acute phase reactant. In our present study hypoalbuminemia was more significant in severe COVID-19 positive SARI patients compared to COVID-19 negative SARI patients hence, we could say that hypoalbuminemia is inversely related with COVID-19 severity and also more significant hypoalbuminemia in COVID-19 positive SARI.

**Keywords:** Severe pneumonia, Hypoalbuminemia, Antioxidant, Acute phase reactant

## INTRODUCTION

A novel coronavirus (CoV) named '2019-nCoV' by the WHO is in charge of the current outbreak of pneumonia

that began at the beginning of December 2019 near in Wuhan City, Hubei Province, China. COVID-19 is a pathogenic virus. From the phylogenetic analysis carried out with obtainable full genome sequences, bats occur to

be the COVID-19 reservoir, but the intermediate host(s) has not been detected till now.<sup>1</sup> The Wuhan city was locked down on January 23<sup>rd</sup> 2020 whereas WHO declared a ‘public health emergency of international concern’ on 30<sup>th</sup> January 2020.<sup>2</sup> Initially the disease started with zoonotic transmission but soon it occurred to spread through human to human transmission. Transmission of the virus causing COVID-19 i.e.; SARS-CoV-2, is considered to be via droplets rather than aerosols, but strong directional airflow may support the spread by droplet upto more than 2 m.<sup>3</sup> COVID-19 presents a wide spectrum of clinical manifestations, that go from an asymptomatic infection to a severe pneumonia accompanied by multisystemic failure leading to patient’s death. The immune response to SARS-CoV-2 is known to involve all the components of the immune system that all together appear responsible for viral elimination and recovery from the infection. Nonetheless, such immune response is implicated in the progress of the disease to a more severe and lethal process. There is a need for reliable indicator to assess the severity of the disease.

Several unique characteristics have been found in severe COVID-19, such as lymphopenia, old age, high CRP level and underlying comorbid diseases. Significantly decreased albumin level is common in severe COVID-19. But the change in albumin does not parallel the severity of hepatocellular injury in COVID-19. This suggests that there may be mechanisms other than a hepatocellular injury that explains the profound hypoalbuminemia seen in COVID-19. One of the possible mechanisms is the intense systemic inflammation being reported in severe COVID-19. Hypoalbuminemia is common in many inflammatory diseases because increased capillary permeability can result in the escape of albumin to the interstitial space. The role of albumin in the progression of COVID-19 remains unknown. We hypothesised that serum albumin levels at admission might reflect the severity of systemic inflammation and thus can serve as a predictive factor for COVID-19 outcomes.<sup>4</sup> The main objective of this study is to estimate serum albumin levels in patients with severe acute respiratory illness and to correlate with severity of severe acute respiratory illness and also to compare serum albumin levels in COVID-19 positive and negative SARI patients.

**METHODS**

This is a cross sectional study conducted on 265 SARI patients who were admitted in hospitals attached to BMCRI between April 2019 to December 2019. History

was taken, general physical examination and a detailed systemic examination was done. Patients were categorized into mild, moderate and severe illness. RT-PCR for COVID-19 patients done using throat and nasal swab. Total WBC counts and differential counts, platelet counts were estimated. Serum albumin levels were correlated with pneumonia severity and compared between COVID-19 positive and negative SARI. And also, correlation with comorbidities was done.

**Objectives**

The objectives of this study were (a) to estimate serum albumin levels in patients with severe acute respiratory illness; (b) to correlate between SARI severity and serum albumin levels; and (c) to compare serum albumin levels in COVID-19 positive and negative SARI patients.

**Type design**

The study was a cross sectional study.

**Inclusion criteria**

Patients with following criteria’s were included in this study- (a) patients/attender willing to give informed consent; (b) patient of either sex with age more than 18 years; and (c) patients admitted in COVID-19 suspect hospital and diagnosed with SARI.

**Exclusion criteria**

Patients not willing to give informed consent and who were less than 18 years of age were excluded.

Ethical committee approval was sought and clearance was given.

**Statistical method**

Data was analyzed by descriptive statistics. Correlation between severity of COVID-19 infection and serum potassium levels was measured using Chi square test.

**Statistical analysis**

The statistical software used for data analysis were namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 and Microsoft word and excel had been used to generate tables and graphs etc (Table 1).

**Table 1: Age distribution of the patients.**

COVID-19	Severity	N	Minimum	Maximum	Mean	SD
Negative	Moderate	69	20	86	46.90	17.132
	Severe	61	19	91	52.56	15.988
Positive	Moderate	54	25	80	55.13	14.480
	Severe	81	24	96	58.70	15.598

Mean age of subjects with COVID positive (severe) was higher- 58.70±15.598 followed by COVID positive (moderate)- 55.13±14.480.

**RESULTS**

Table 2 shows distribution of the subjects based on age. Subjects was higher above 65 years- 80 (30.2%) followed by age group of 36 to 45 years- 51 (19.2%). Chi-square test was applied to associate the age with severity. Chi-square test showed statistical significant association with respect to age ( $\chi^2=35.15$ ;  $p=0.002$ ).

Graph shows distribution of the subjects based on gender. Males were higher- 174 (65.7%) as compared to females- 91 (34.3%).

Chi-square test was applied to associate the gender with severity. Chi-square test showed no statistical significant association with respect to gender ( $\chi^2=3.16$ ;  $p=0.78$ ).

Table 3 shows the mean and standard deviation of albumin levels among COVID positive and negative patients.

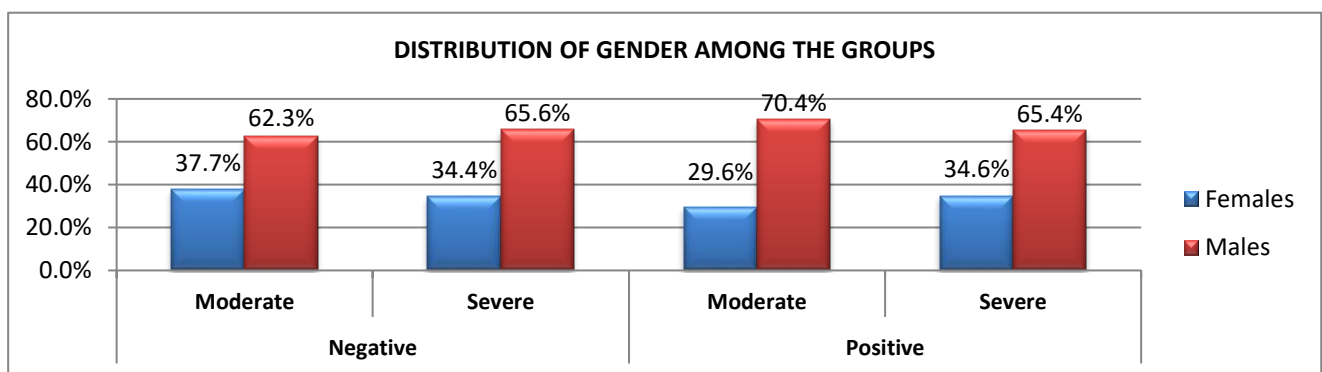
Independent sample t test showed statistical significant difference with respect to S. albumin levels ( $p=0.00$ ) between COVID positive and negative subjects.

In COVID positive subjects, S. albumin levels showed statistical significant difference ( $p=0.00$ ) between moderate and severe sub groups whereas there was no statistical significant difference seen in COVID negative sub-groups.

**Table 2: Distribution of age among the groups.**

Age (years)		Negative		Positive		Total
		Moderate	Severe	Moderate	Severe	
Less than 25	Count	9	4	1	1	15
	%	13.0	6.6	1.9	1.2	5.7
26 to 35	Count	9	5	5	7	26
	%	13.0	8.2	9.3	8.6	9.8
36 to 45	Count	22	12	8	9	51
	%	31.9	19.7	14.8	11.1	19.2
46 to 55	Count	7	13	13	11	44
	%	10.1	21.3	24.1	13.6	16.6
56 to 65	Count	9	10	9	21	49
	%	13.0	16.4	16.7	25.9	18.5
Above 65	Count	13	17	18	32	80
	%	18.8	27.9	33.3	39.5	30.2
Total	Count	69	61	54	81	265
	%	100.0	100.0	100.0	100.0	100.0

Chi square value=35.15, p value=0.002\*Significant.



**Figure 1: Distribution of gender among the groups.**

**Table 3: Distribution of albumin levels.**

COVID-19	Severity	N	Minimum	Maximum	Mean	SD
Negative	Moderate	69	1.8	4.8	3.296	0.6127
	Severe	61	1.4	4.7	3.161	0.6798
Positive	Moderate	54	2.3	4.2	3.359	0.4289
	Severe	81	1.5	4.1	2.836	0.4817

**Table 4: Comparison between COVID negative and COVID positive groups using independent sample t test.**

Albumin	COVID negative vs COVID positive	
	Mean difference	P value
	0.18	0.01*

\*Significant p value=0.002.

**Table 5: Comparison between moderate and severe subgroups using independent sample t test.**

Albumin	Moderate vs severe	
	COVID negative	COVID positive
	0.13	0.23
	0.52	0.00*

\*Significant p value=0.002.

## DISCUSSION

In our study demographic characteristics of the study subjects studied showed that males were higher as compared to females which was similar to Huang et al having majority male subjects and Violi et al where 58% were males.<sup>5</sup>

In the present study mean age of subjects with COVID positive (severe) was higher- 58.70±15.598 followed by COVID positive (moderate)- 55.13±14.480, distribution of subjects based on age showed subjects was higher above 65 years 80 (30.2%) followed by age group of 36 to 45 years- 51 (19.2%). According to Rica et al study the mean age (SD) was 66 (18) years for COVID-19 (+) patients and 62 (14) for COVID-19 (-) patients, with difference being not statistically significant also no significant difference between gender distribution. In the study Huang et al, they studied patients with the mean age of 53.4±16.7 years. They also cited that 20% cases had severe disease where as 80% were non-severe cases. Mean age was 66.1±17.5 years in study Violi et al.<sup>6</sup>

We also studied distribution of diabetes and hypertension among the groups and out of 265(100%) subjects, 99(37.4%) had diabetes of which majority were severe COVID-19 positive followed by moderate COVID-19 positive SARI with statistically significant association with respect to diabetes. 102 patients had hypertension, which was more common with severe COVID-19 negative patients and then with severe COVID positive patients, however association with hypertension was not statistically significant. Similarly, Violi et al majority of COVID-19 patients had associated comorbidities most common being hypertension and diabetes and most of them had statistically significant association with severe COVID-19. The relationship between hypoalbuminemia and reduced survival in COVID-19 may have several explanations. First, acting as an anti-inflammatory and antioxidant protein, albumin may protect against cytokine storm. Second, albumin encompasses anticoagulant properties and inhibits oxidative stress-related clotting and platelet activation that occurs in severe COVID-19. Third, albumin is an inverse acute phase reactant. In our present study hypoalbuminemia was more significant in severe COVID-19 positive SARI patients compared to COVID-

19 negative SARI patients hence, we could say that hypoalbuminemia is inversely related with COVID-19 severity and also more significant hypoalbuminemia in COVID-19 positive SARI.

Similar results were seen in Huang et al study, serum albumin level was inversely correlated with severity in COVID-19 and hypoalbuminemia is important predictors of mortality. Kheir et al study showed higher albumin levels on admission were associated with significantly fewer adverse outcomes in COVID-19 patients.<sup>7</sup> A meta-analysis done by Panagiotis et al demonstrated the presence of significantly lower serum albumin concentrations in COVID-19 patients with high disease severity or poor outcome which is supporting the results of our study.<sup>8</sup>

Regarding the association with comorbidities, our study found that serum albumin levels was significantly lower in severe COVID-19 patients with diabetes and hypertension. Violi et al stated that hypoalbuminemia in severe COVID-19 patients were mostly associated with comorbidities. Similarly, in the study by et al on severe COVID-19 positive and hypoalbuminemia 70% had HTN followed by dyslipidemia, cardiovascular disease and diabetes.<sup>9</sup>

## Limitations

The limitations of the study were that sample size was small. Serial monitoring of serum albumin levels with disease progression could not be done as this was a cross-sectional study. Association of serum albumin levels with mortality could not be established.

## CONCLUSION

The relationship between hypoalbuminemia and reduced survival in COVID-19 may have several explanations. First, acting as an anti-inflammatory and antioxidant protein, albumin may protect against cytokine storm. Second, albumin encompasses anticoagulant properties and inhibits oxidative stress-related clotting and platelet activation that occurs in severe COVID-19. Third, albumin is an inverse acute phase reactant. In our present study hypoalbuminemia was more significant in severe COVID-19 positive SARI patients compared to

COVID-19 negative SARI patients hence, we could say that hypoalbuminemia is inversely related with COVID-19 severity and also more significant hypoalbuminemia in COVID-19 positive SARI.

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