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Medicine

HYPOALBUMINEMIA–A RISK FACTOR IN COVID 19 PATIENTS ADMITTED AT ACPM MEDICAL COLLEGE DURING SECOND WAVE OF EPIDEMIC.

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ABSTRACT **Background:** Hypoalbuminemia is amongst the most frequently observed laboratory abnormalities in patients with SARS-CoV-2 infection. Profound hypoalbuminemia seen in COVID-19 may be due to intense systemic inflammation. Hypoalbuminemia is common in many inflammatory diseases. Present study was aimed to study the value of hypoalbuminemia on admission as a predictor of mortality and adverse events in COVID 19 patient. **Material and Methods:** Present study was single-center, Retrospective Cross-sectional study, conducted from case records of patients with clinical manifestations like fever and pulmonary symptoms and RT-PCR positive for SARS-CoV-2. **Results:** In present study 100 case-records satisfying study criteria were considered for this study. The male predominant was observed 63(63.0 %) than female 37(37.0%). The mean age of present study patients were 62.37 ± 14.02 year. Majority of 69% of patients required respiratory support during COVID-19. Majority cases had moderate COVID (50 %) as compared to severe COVID (31.82 %) & mild COVID (18.18 %). Mortality was 14.77 %. The mean Serum Albumin level was significantly lower in Severe COVID cases 2.09 ± 0.94 g/dl as compared to Moderate 3.01 ± 1.03 g/dl & Mild 4.93 ± 1.59 g/dl COVID disease severity. There was statistical significant difference in mean Serum Albumin in Disease Severity of COVID-19 (p=0.001). The mean Serum Albumin level of died patients was 1.89±0.95 g/dl, which was comparatively lower as compared to live (discharged) patients 3.87±1.78 g/dl. There was statistical significant difference in mean Serum Albumin level in clinical outcome of COVID-19 patients (p<0.001). **Conclusion:** The low albumin is associated with disease severity and poor outcomes in terms of worse respiratory failure due to alveolar endothelial damage in COVID-19.

KEYWORDS : Coronavirus Disease; Covid-19; Hypoalbuminemia, albumin

Introduction:

Coronaviruses are enveloped, RNA viruses which belong to the family Coronaviridae. The World Health Organization has officially announced coronavirus disease 2019 (COVID-19) as pandemic and its death toll far exceeded severe acute respiratory syndrome and Middle East Respiratory syndrome.[2,3] The high prevalence of the disease followed by long incubation periods of the virus yields an un-precedented pandemic with an increasing number of cases across countries making COVID-19 the worst pandemic outbreak in modern history.[4]

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.[5] Utilizing biomarkers especially that are regularly measured to the patients is paramount to access risks and allocate resources efficiently.

Cytokines and chemokines play an important role in inflammatory response during virus infections. However, some viruses like HCoVs can induce an excessive cytokines/chemokine response known as "cytokine strom".[6] The release of cytokine and chemokine induces an increase in capillary leakage which alters the distribution of albumin between intravascular and extravascular compartments.[7] Albumin level has been studied extensively of its association with inflammatory process.[8] Decrease albumin level is common in severe COVID 19.

COVID-19 can cause flu like symptoms including fever, cough, dysponea, myalgia and fatigue. More serious forms can cause severe pneumonia, respiratory failure, multi organ dysfunction and death. Gastrointestinal symptoms such as diarrhoea, nausea and vomiting have also been described along with loss of sense of taste and smell.[9] Individuals with underlying morbidities, such as cardiovascular disease, hypertension, obesity, diabetes, pulmonary disease, and immunocompromising conditions, are especially susceptible to this severe disease course. Male gender and advanced age are also established risk factors.

Several biological markers have been found to correlate with the severity of COVID19 including high C-Reactive Protein (CRP) level, high erythrocyte sedimentation rate (ESR) and low level of serum albumin (hypoalbuminemia).[9,10]The normal range of serum albumin is 3.4-5.4g/dL. We define hypoalbuminemia as less then 3.4g/dL. Hypoalbuminemia is amongst the most frequently observed laboratory abnormalities in patients with SARS-CoV-2 infection.

Profound hypoalbuminemia seen in COVID-19 may be due to intense systemic inflammation. Hypoalbuminemia is common in many inflammatory diseases because increased capillary permeability can result in the escape of albumin to the interstitial space. We hypothesized 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.

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). Under conditions of oxidative stress, the Cys34 of HSA may undergo irreversible oxidation, which impairs the HSA antioxidant property and eventually elicits cell and tissue damage. It is interesting, at this regard, that albumin oxidation triggers neutrophil extracellular traps through ROS accumulation within neutrophils, which eventually accumulate within lungs.[11]

There is a growing body of evidence to suggest that ROS are implicated in platelet and clotting activation, thereby it is plausible that in case of albumin degradation/oxidation, both compartments are overactivated. In fact, hypoalbuminemia consequence to oxidative stress/inflammation is associated with thrombosis tendency and poor survival.[11]

Second wave of Covid -19 started in middle of March 2021 with variable presentations with involvement of other system along with respiratory system. Characteristic features of second wave were as follows with newer symptoms involving gastrointestinal, more cases of breathlessness, more younger population, rapid spread and more requirement of oxygen.

To address this question, we performed a retrospective study to compare the outcome in patients with or without hypoalbuminemia and to explore the impact of albumin in the prognosis of COVID-19.

Aims and Objectives:

The aim of this study is to analyze the value of hypoalbuminemia on

admission as a predictor of mortality and adverse events in COVID 19 patient.

Primary Objective: To evaluate the impact of low serum albumin level in admit COVID 19 patients.

Other Objective: To enhance find out percentage of patients in which the early detection of low serum albumin level and to formulate policies for prevention of disease, to study the severity and fatality to at least some extent.

Material and Methods:
Present study was single-center, Retrospective Cross-sectional study, conducted in department of general medicine, at ACPM Medical College and Hospital, Dhule, India. Case records of patients of Covid 19 hospitalized in covid ward from April 2021 to June 2021 were studied. Study approval was obtained from institutional ethical committee. In present study 100 case-records satisfying study criteria were considered for this study.

Inclusion criteria:
1. Adult patients age > 18 years.

2. All the patients who meet the diagnostic criteria of the National Institute of Health (NIH) India for COVID-19 infection which are as follows:

3. Clinical manifestations that include fever and pulmonary symptoms (cough, shortness of breath, chest pain, and tightness).

4. Radiological findings of consolidation, ground-glass opacities (GGOs) either on chest X-ray or high-resolution computed tomography (HRCT).

5. Real-time fluorescent reverse transcription-polymerase chain reaction (RT-PCR) of respiratory samples (nasal/oropharyngeal swab or tracheal secretions) positive for SARS-CoV-2.

Exclusion criteria:
1. Patients with negative detection of novel coronavirus nucleic acid.

2. Patients in whom monitoring of blood oxygen saturation (SpO2 or PaO2) was not feasible due to any reason.

3. Patients on immunosuppressive drugs (including long-term steroids).

4. Patients with incomplete chest computed tomography (CT) examination due to any reason.

Methodology:
All case papers of Covid 19 patients who got hospitalised and satisfying inclusion and exclusion criteria of study during April 2021 to June 2021 were studied thoroughly with due permission from medical record sections.

Patient's parameters such as demographic data (gender and age), comorbidities (Diabetes mellitus, Hypertension, Coronary Artery Disease), clinical manifestations of Covid 19 (fever, chest pain, cough, shortness of breath) investigations like complete blood count, differential cell count, neutrophil to lymphocyte ratio, Renal function tests, Liver function tests, Serum electrolytes, C-reactive proteins, D-dimer, HRCT Severity index were recorded. Laboratory reference range of Sr albumin is 3.4-5.4g/dL with lower detection limit of less then 3.4g/L.

Statistical Analysis: Data was collected and compiled using Microsoft Excel, analyzed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Z-test was used to compare two groups. ANOVA was applied to check significance difference between three groups. P value less than 0.5 was considered as statistically significant.

Results:
In present study 100 case-records satisfying study criteria were considered for this study.

Table 1- Demographic characteristics of patients

Characteristics		No. of patients	Percentage
Age groups (in years)	≤30 years	06	6.0%
	31-40	09	9.0%
	41-50	18	18.0%
	51-60	29	29.0%
	61-70	22	22.0%
	>70	16	16.0%
	Mean age (mean±SD)	62.37 ± 14.02 years	
Gender	Male	63	63.0%
	Female	37	37.0%
Area of living	Urban	42	42.0%
	Rural	58	58.0%

Majority cases were male 63(63.0 %) and female 37(37.0%). Majority of patients i.e. 29(29.0%) were from age-group of 51-60 years followed by age-group of 61-70 years (22.0 %). The mean age of present study patients were 62.37 ± 14.02 year. Maximum i.e. 58(58.0%) of patients were from rural area.

Table 2: Chief Complains & Comorbidities in patients

		No. of patients	Percen tage
Chief Complains	Fever	85	85.0
	Dry Cough	83	83.0
	Anorexia	16	16.0
	Fatigue	23	23.0
	Dyspnoea	79	79.0
	Diarrhoea	11	11.0
	Other	09	9.0
Co-morbidities	Present	73	73.0
	Absent	27	27.0
Present Co-morbidities [n=73]	Hypertension	49	49.0
	Diabetic Mellitus	58	58.0
	IHD	17	17.0
	Asthma	17	17.0
	COPD	03	3.0
	Chronic Kidney Disease	07	7.0
	Hypothyroidism	08	8.0
	Other	09	9.0

In present study, (79.0%) patients were having dyspnoea, (85.0%) patients were having fever and (83.0%) were having dry cough. (23.0%) of patients were reported fatigue and anorexia respectively. Majority of patients (73.0%) were having co-morbidities and (27.0%) were not having co-morbidities. Maximum (58.0%) patients were having diabetic mellitus and (49.0%) patients were having and hypertension. (17.0%) of patients reported asthma and IHD, (7.0%) of patients were having Chronic Kidney Disease.

Table 3: Respiratory Support, COVID severity and Outcome of patients

		No. of patients	Percentage
Respiratory Support	Supplemental Oxygen	57	57.0.0%
	HFO2	19	19.0%
	Non Invasive Ventilator	14	14.0%
	Mechanical Ventilation	13	13.0%
COVID severity	Mild	14	14.0%
	Moderate	52	52.00%
	Severe	34	34.0%
Clinical outcome	Discharged	84	84.0%
	Death	16	16.0%

In present study, 69% of patients required respiratory support during COVID-19, (57.0%) of patients required Supplemental Oxygen and (19.0%) of covid-19 patients were on HFO2. (13.0%) were on

Mechanical Ventilation and (14.0%) were required Non Invasive Ventilator.

Clinically & radiologically majority cases had moderate COVID (52%) as compared to severe COVID (32.0 %) & mild COVID (14.0 %). Mortality rate was reported 16.0%

Table 4: Comparison of mean Serum Albumin in disease severity [ANOVA].

		Serum Albumin Mean±SD	p value
Respiratory Support	Supplemental Oxygen	3.93 ± 1.23	P<0.0001 S
	HFO2	2.05 ± 0.98	
	Non Invasive / Mechanical Ventilation	1.49 ± 0.84	
Disease severity	Mild	4.93 ± 1.59	P=0.001 S
	Moderate	3.01 ± 1.03	
	Severe	2.09 ± 0.94	
Clinical outcome	Discharged	3.87±1.78	P<0.0001 S
	Death	1.89±0.95	

The mean Serum Albumin level was significantly lower in Non-Invasive / Mechanical Ventilation COVID cases 1.49 ± 0.84 g/dl as compared to HFO2, 2.05 ± 0.98 g/dl & Mild 3.93 ± 1.23 g/dl COVID disease severity. There was statistical significant difference in mean Serum Albumin in type of requirement of respiratory Support of COVID-19 (p<0.0001).

The mean Serum Albumin level was significantly lower in Severe COVID cases 2.09 ± 0.94 g/dl as compared to Moderate 3.01 ± 1.03 g/dl & Mild 4.93 ± 1.59 g/dl COVID disease severity. There was statistical significant difference in mean Serum Albumin in Disease Severity of COVID-19 (p=0.001).

The mean Serum Albumin level of died patients was 1.89±0.95 g/dl, which was comparatively lower as compared to live (discharged) patients 3.87±1.78 g/dl. There was statistical significant difference in mean Serum Albumin level in clinical outcome of COVID-19 patients (p<0.001).

Discussion:

In India, second wave of Covid 19 started in middle of March 2021 and was supposed to be caused by several mutants of SARS-COV2 virus and its presentation was slightly different from the first wave with newer symptoms involving gastrointestinal system, with more cases of sudden onset breathlessness, with predominant involvement of younger age group, with less comorbidities, more oxygen requirement and ICU admissions.[12]

Low serum albumin is thought to be threatening biochemical analysis in COVID-19 infections that may be considered due to the production of more cytokines in blood vascular system13. The release of cytokines causes permeation in the walls of blood vessels, that helps the diffusion of serum albumin between the extracellular spaces.14 Hypoalbuminemia is due to the liver dysfunctions, may also cause by the adverse effects of drugs and liver inflammation in sever patients of COVID-19. However, different studies have indicated that hypoalbuminemia may assess critical conditions of COVID-19 patients[15].

Nayab Gull et al found that Low Albumin is a common finding in COVID-19 along with raised transaminases. Low Albumin is associated with disease severity and poor outcomes in terms of prolonged admissions and worse respiratory failure due to alveolar endothelial damage in COVID-19.

The mean Serum Albumin level was significantly lower in Non-Invasive / Mechanical Ventilation COVID cases 1.49 ± 0.84 g/dl as compared to HFO2, 2.05 ± 0.98 g/dl & Mild 3.93 ± 1.23 g/dl COVID disease severity. There was statistical significant difference in mean Serum Albumin in type of requirement of respiratory Support of COVID-19 (p<0.0001). In present study the mean Serum Albumin level was significantly lower in Severe COVID cases 2.09 ± 0.94 g/dl as compared to Moderate 3.01 ± 1.03 g/dl & Mild 4.93 ± 1.59 g/dl COVID disease severity. There was statistical significant difference in mean Serum Albumin in Disease Severity of COVID-19 (p=0.001). So Serum Albumin level can be independent and early predictor for Severity of COVID-19 and requirement of respiratory Support.

In present study the mean Serum Albumin level of died patients was 1.89±0.95 g/dl, which was comparatively lower as compared to live (discharged) patients 3.87±1.78 g/dl. There was statistical significant difference in mean Serum Albumin level in clinical outcome of COVID-19 patients (p<0.001), as the findings of our study are consistent with Kheir et al. concluded in their study that higher albumin level on admission was associated with favorable outcomes in hospitalized COVID-19 patients.16 The low albumin has been associated with adverse outcomes in various other disease conditions.17 The hypoalbuminemia was seen predominantly in severe COVID-19 cases compared with mild cases18. Where as, Akirov et al. reported that low serum is not only associated with higher mortality, but normalization of serum albumin decreased the rehospitalization and mortality Hypoalbuminemia status has been associated with critically ill patients and mortality across numerous clinical settings19.

Conclusion:

From this study it can be concluded that low albumin is associated with disease severity and poor outcomes in terms of worse respiratory failure due to alveolar endothelial damage in COVID-19. A low albumin level can potentially help to identify patients at high risk of developing life-threatening conditions and death. The early recognition of severe disease assists clinicians in making informed decision for their patients and management treatment of patients. So, hypoalbuminemia was an independent and early predictor of in-hospital mortality in COVID-19.

Conflict of Interest: None to declare
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