Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v30i19.3694

ASSOCIATION BETWEEN ALBUMIN LEVELS AND OUTCOMES IN COVID-19: A RETROSPECTIVE COHORT STUDY

Muhammad Asim Rana[1*], Afzal Bhatti[2], Muhammad Sohail Khalid[3], Ahmed Mohammed Hassan Mostafa[4], Ahmed M. Abdelbaky[5], Mohamed Ibrahim Shoaib[5], Wael Ghaly Elmasry[5], Sitara Raza[6]

[1*]Assistant Professor Amna Inayat Medical College, Consultant Physician Critical Care Medicine Bahria International Hospital, Lahore - Pakistan
[2]Professor of Medicine, Head Department of Gastroenterology and Hepatology, Bahria International Hospital Lahore - Pakistan
[3]Assistant Professor of Gastroenterology, Continental Medical College, Lahore - Pakistan
[4]Specialist Medical Intensive Care Unit, Rashid Hospital, Dubai Health, Dubai - UAE
[5]Senior Specialist Medical Intensive Care Unit, Rashid Hospital, Dubai Health, Dubai - UAE
[6]Department of Critical Care Medicine, Bahria International Hospital, Lahore - Pakistan

***Corresponding Author:** Muhammad Asim Rana
Email: drasimrana@yahoo.com

ABSTRACT:

Background: The COVID-19 pandemic presents significant challenges to healthcare systems worldwide, necessitating a comprehensive understanding of factors influencing disease prognosis. Hypoalbuminemia, characterized by low serum albumin levels, has emerged as a noteworthy feature in severe COVID-19 cases and may have prognostic value.

Methodology: This retrospective cohort study analyzed data from 109 adult COVID-19 patients to investigate the relationship between hypoalbuminemia as a predictor of disease outcomes. Relevant clinical and laboratory data were collected, and statistical analyses were conducted to explore associations.

Results: Non-survivors were significantly older and more likely to be admitted to the ICU, presenting higher rates of comorbidities, lymphopenia, and abnormalities in various blood parameters. Hypoalbuminemia correlated with older age, increased ICU admissions, elevated mortality rates, higher neutrophil-to-lymphocyte ratios, and greater inflammation markers. Dyspnea was more frequent in the hypoalbuminemia group. These findings offer insights into identifying individuals at higher risk for adverse outcomes due to hypoalbuminemia in COVID-19.

Conclusion: Our study found a significant and independent relationship between low serum albumin levels at the initial presentation and the mortality risk in COVID-19 patients. These results indicate the importance of monitoring and addressing hypoalbuminemia as a possible prognostic marker in managing COVID-19. Early detection and intervention in patients with low albumin levels can contribute to better outcomes.

Keywords: COVID-19, hypoalbuminemia, serum albumin, prognosis, mortality, ICU, lymphopenia, inflammation markers,

INTRODUCTION:

The coronavirus disease 2019 (COVID-19) pandemic has brought unprecedented challenges to global healthcare systems, with severe cases posing significant threats to patient outcomes (Al-Tawfiq and Memish, 2020). Understanding the multifaceted factors influencing disease progression and prognosis in COVID-19 is essential for effective clinical management (Bezemer and Garssen, 2021).

COVID-19 is a novel respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Lai et al., 2020). It was officially declared a pandemic by the World Health Organization due to its rapid global spread and significant impact on public health. While the spectrum of COVID-19 severity ranges from mild or asymptomatic cases to severe respiratory distress and organ failure, certain features have emerged as indicators of poor prognosis (Slutskiy and Boonchutima, 2022).

One notable characteristic that has garnered attention is hypoalbuminemia, a condition marked by abnormally low levels of serum albumin in the blood (Gremese et al., 2023). Serum albumin is a vital protein synthesized by the liver and plays a crucial role in maintaining oncotic pressure, transporting essential molecules, and modulating immune responses (Bernardi et al., 2020). In severe COVID-19 cases, a significant decrease in serum albumin levels has been consistently observed. This hypoalbuminemia is particularly intriguing due to its relationship with systemic inflammation and its potential as an independent prognostic marker (Bonilla-Palomas et al., 2014; Seebacher et al., 2013).

Hypoalbuminemia is a hallmark of various inflammatory conditions, including infections and chronic diseases. In these contexts, increased capillary permeability, cytokine release, and oxidative stress can disrupt the balance of albumin, causing it to escape from the vascular compartment into the interstitial space. This redistribution of albumin contributes to edema, impaired microcirculation, and altered immune responses. In severe COVID-19, the presence of hypoalbuminemia suggests a link between the intense systemic inflammation characteristic of the disease and this critical protein (Signorini et al., 2021; Wiedermann, 2021).

The recognition of hypoalbuminemia as a common feature in severe COVID-19 cases prompts the need to investigate its potential significance as an independent predictor of disease outcomes (Rabbani and Ahn, 2021). While age and the presence of comorbid conditions have been associated with severe COVID-19, the role of hypoalbuminemia as an independent factor remains underexplored (Garibaldi et al., 2021). Therefore, it is crucial to conduct comprehensive studies that disentangle the complex interplay between age, comorbidity, and hypoalbuminemia to assess its contribution to predicting COVID-19 outcomes.

This study investigates whether hypoalbuminemia, a marker of systemic inflammation, can be an independent prognostic factor in COVID-19, regardless of a patient's age and coexisting medical conditions. Understanding the role of hypoalbuminemia in predicting disease outcomes may offer valuable insights for risk stratification, clinical decision-making, and the development of targeted therapeutic interventions for severe COVID-19 cases.

METHODOLOGY:

This retrospective cohort study focused on adult patients who were diagnosed with COVID-19 and admitted to Bahria Town International Hospital between September 10, 2020, and December 29, 2021. To be included in the study, patients had to meet the following criteria: they had to be 18 years of age or older, have a confirmed diagnosis of COVID-19 through a positive RT-PCR test on nasopharyngeal swab specimens, fulfill the diagnostic criteria established by the World Health Organization (WHO) for COVID-19, and have complete clinical data available for analysis.

The study obtained official approval from the institutional review board of the hospital. Patient data was acquired by reviewing case notes and electronic medical records. The onset time of relevant COVID-19 symptoms to hospital presentation was noted. Underlying health conditions, including hypertension, diabetes mellitus, coronary heart disease, cerebrovascular disease, and chronic obstructive pulmonary disease, were systematically recorded. Blood samples were taken from

patients upon admission, and standardized laboratory procedures were used to conduct a comprehensive array of routine hematological and biochemical tests.
Hypoalbuminemia was defined as an albumin level below 3.5 g/dL. Statistical analysis was conducted using SPSS software version 25. Continuous variables were expressed using means accompanied by standard deviations or medians supplemented with interquartile ranges. Categorical variables were presented as percentages. Statistical tests such as the Student's t-test and the Mann-Whitney U test were used to assess differences. Categorical variable distinctions were evaluated through the χ^2 test or Fisher's exact test as deemed appropriate. Pearson correlation analysis was used to investigate the relationships between serum albumin levels and various inflammatory indicators. A significance threshold of a P-value less than 0.05 was considered statistically significant.

Results:
In the study, 109 participants were analyzed and divided into two categories based on their outcomes - survivors (101 participants) and non-survivors (8 participants). Out of the total participants, 55.0% were male. Among survivors, 56.4% were male, while among non-survivors, only 37.5% were male. However, the difference in gender distribution was not statistically significant ($p = 0.260$). The average age of all participants was 54.2 years. Survivors had an average age of 53.4 years, while non-survivors were notably older, with an average age of 64.6 years. This age difference was statistically significant ($p < 0.001$).
The median onset time for all participants was 3 days, with an interquartile range (IQR) of 2 to 5 days. Non-survivors had a slightly longer median onset time (5 days) compared to survivors (3 days), which was statistically significant ($p = 0.052$). Out of all the participants, 33.0% were admitted to the ICU. Among survivors, 28.7% required ICU admission, while this percentage was notably higher among non-survivors at 87.5%. The difference in ICU admission was highly statistically significant ($p = 0.001$).
Lymphopenia was present in 54.1% of all participants. Survivors had a lower percentage of lymphopenia (50.5%), while non-survivors had a significantly higher percentage (100%). The difference in lymphopenia was statistically significant ($p < 0.001$). Hypoalbuminemia was found in 41.3% of all participants. Survivors had a lower percentage of hypoalbuminemia (34.7%), whereas non-survivors had a notably higher percentage (87.5%). The difference in hypoalbuminemia was highly significant ($p < 0.001$).
Comorbidities were prevalent among COVID-19 participants. Hypertension was the most common comorbidity. Non-survivors had higher percentages of comorbidities compared to survivors. Presence of symptoms was similar between survivors and non-survivors. Notable differences were observed in blood parameters and biochemical markers, with non-survivors generally exhibiting abnormal values compared to survivors. However, differences in other parameters were not statistically significant between the two groups.
Table 1 provides insights into the characteristics of COVID-19 patients who either survived or did not survive. Non-survivors were older, had a higher rate of ICU admissions, and exhibited a higher prevalence of comorbidities. Lymphopenia, hypoalbuminemia, and abnormal values of various blood parameters were more common among non-survivors.

Table 1: Baseline characteristics of the study population

Variable	Total (N=109)	Survivors (N=101)	Non-Survivors (N=8)	P-value
Male (%)	60 (55.0)	57 (56.4)	3 (37.5)	0.260
Age, (y)	54.2 ± 16.0	53.4 ± 15.7	64.6 ± 14.4	**0.012**
Onset time, median (IQR)	3 (2, 5)	3 (2, 5)	6 (2.5, 8.75)	0.052
ICU (%)	36 (33.0)	29 (28.7)	7 (87.5)	**0.001**
Lymphopenia (%)	59 (54.1)	51 (50.5)	8 (100.0)	**<0.001**
Hypoalbuminemia (%)	45 (41.3)	35 (34.7)	7 (87.5)	**<0.001**

Comorbid Conditions				
Hypertension (%)	27 (24.8)	23 (22.8)	4 (50.0)	**0.019**
DM (%)	15 (13.8)	14 (13.9)	1 (12.5)	0.907
CHD (%)	7 (6.4)	6 (5.9)	1 (12.5)	0.298
CVD (%)	5 (4.6)	5 (4.9)	0 (0.0)	0.889
COPD (%)	2 (1.8)	2 (2.0)	0 (0.0)	0.969
Hematological and Biochemical Markers				
WBC, ×10^9/L	4.5 ± 2.2	4.3 ± 2.0	7.1 ± 5.9	**0.009**
Neutrophil, ×10^9/L	2.8 ± 1.4	2.7 ± 1.3	5.1 ± 4.4	**0.013**
Lymphocyte, ×10^9/L	1.3 ± 0.5	1.3 ± 0.5	0.6 ± 0.3	**<0.001**
Monocyte, ×10^9/L	0.3 ± 0.2	0.3 ± 0.2	0.4 ± 0.2	0.105
CRP, mg/L	16.5 ± 21.6	15.7 ± 20.7	37.4 ± 33.3	**0.019**
Procalcitonin, µg/L	0.2 ± 0.6	0.2 ± 0.6	0.3 ± 0.2	0.418
D-dimer, mg/L	0.7 ± 1.2	0.7 ± 1.1	0.9 ± 1.3	**<0.001**
Total bilirubin, µmol/L	10.8 ± 6.5	10.7 ± 6.6	11.0 ± 5.3	0.872
Albumin, g/L	40.6 ± 4.4	40.6 ± 4.3	40.5 ± 5.8	0.885
LDH, U/L	209.1 ± 82.4	204.6 ± 80.4	267.3 ± 112.9	**0.037**
ALT, U/L	27.5 ± 21.3	27.6 ± 21.3	26.9 ± 21.4	0.936
AST, U/L	23.9 ± 13.6	23.7 ± 13.7	26.4 ± 12.4	0.629
Creatinine, mg/dL	0.9 ± 0.7	1.0 ± 0.3	1.2 ± 0.5	0.919

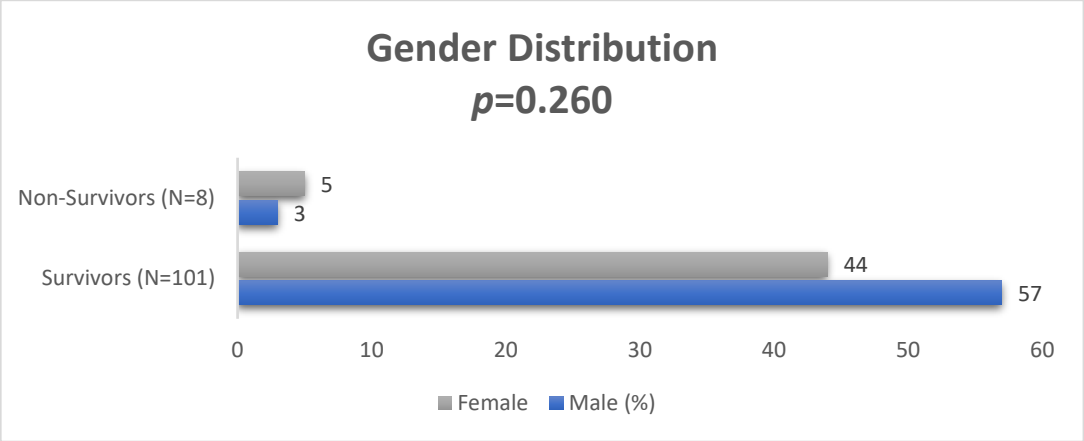

Figure 1: Distribution of gender between the Survivors and non-survivors

Table 2 compares individuals with hypoalbuminemia (low levels of albumin) and those with normal levels of albumin in a population of 109 individuals. It assesses various demographic, clinical, comorbidity, clinical symptoms, and hematological/biochemical factors to understand how these variables differ between the two groups.

Both groups have a similar gender distribution, with around 56% males in the hypoalbuminemia group and 54.7% in the normal albumin group (p-value: 0.501). The age of individuals in the hypoalbuminemia group is significantly higher (62.9 years on average) compared to the normal albumin group (48.2 years on average), indicating that older individuals are more likely to have hypoalbuminemia (p-value: <0.001). The onset time of symptoms is also significantly different, with a median onset time of 4 days in the hypoalbuminemia group and 3 days in the normal albumin group (p-value: 0.002).

A significantly higher proportion of individuals with hypoalbuminemia were admitted to the ICU (44.4%) compared to those with normal albumin (7.8%), indicating a more severe disease course in the hypoalbuminemia group (p-value: <0.001). The death rate is notably higher in the hypoalbuminemia group (13.3%) compared to the normal albumin group (0%) ($p < 0.005$).

The study found that individuals with hypoalbuminemia, a condition characterized by low levels of albumin in the blood, tend to have a higher prevalence of comorbidities such as hypertension,

diabetes, coronary heart disease, cerebrovascular disease, and chronic obstructive pulmonary disease. They also have lower lymphocyte counts and albumin levels, and higher levels of inflammatory markers, which may indicate a higher risk of adverse outcomes. These findings may help clinicians identify individuals at higher risk for adverse outcomes in cases of hypoalbuminemia.

Table 2: A comparison between the clinical and biochemical profiles of individuals with low albumin levels and those with normal albumin levels

Variable	Hypoalbuminemia (N=45)	Normal albumin (N=64)	P-value
Male (%)	25 (55.6)	35 (54.7)	0.901
Age, years	62.9 ± 13.1	48.2 ± 16.1	**0.001**
Onset time, median (IQR)	4 (2, 7)	3 (2, 5)	0.126
ICU (%)	20 (44.4)	5 (7.8)	**0.002**
Death (%)	6 (13.3)	0 (0)	**0.005**
Lymphopenia (%)	25 (55.6)	15 (23.4)	**0.003**
Comorbid conditions			
Presence of at least one comorbidity	23 (51.1)	21 (32.8)	0.097
Hypertension (%)	20 (44.4)	13 (20.3)	**0.017**
DM (%)	11 (24.4)	5 (7.8)	**0.008**
CHD (%)	8 (17.8)	2 (3.1)	**0.010**
CVD (%)	5 (11.1)	1 (1.6)	**0.027**
COPD (%)	3 (6.7)	1 (1.6)	0.174
Hematological and Biochemical markers			
WBC, ×10^9/L	5.6 ± 3.3	4.5 ± 1.7	**0.031**
Neutrophil, ×10^9/L	4.1 ± 3	2.9 ± 1.4	**0.004**
Lymphocyte, ×10^9/L	1 ± 0.5	1.3 ± 0.5	**0.007**
Monocyte, ×10^9/L	0.4 ± 0.4	0.3 ± 0.2	0.642
CRP, mg/L	43.9 ± 45.3	16.5 ± 21.7	**0.005**
Procalcitonin, µg/L	0.3 ± 1	0.1 ± 0.2	0.103
D-dimer, mg/L	3.1 ± 8.9	0.7 ± 1.2	**0.023**
Total bilirubin, µmol/L	11.3 ± 7.6	10.8 ± 6	0.618
Albumin, g/dL	3.12 ± 0.8	4.6 ± 0.4	**0.002**
LDH, U/L	315.5 ± 269.6	209.1 ± 78.4	**0.001**
ALT, U/L	27.9 ± 20.7	27.5 ± 22.1	0.948
AST, U/L	30.1 ± 24.5	23.9 ± 13.3	0.101
Creatinine, mg/dL	0.83 ± 0.26	0.71 ± .21	0.322

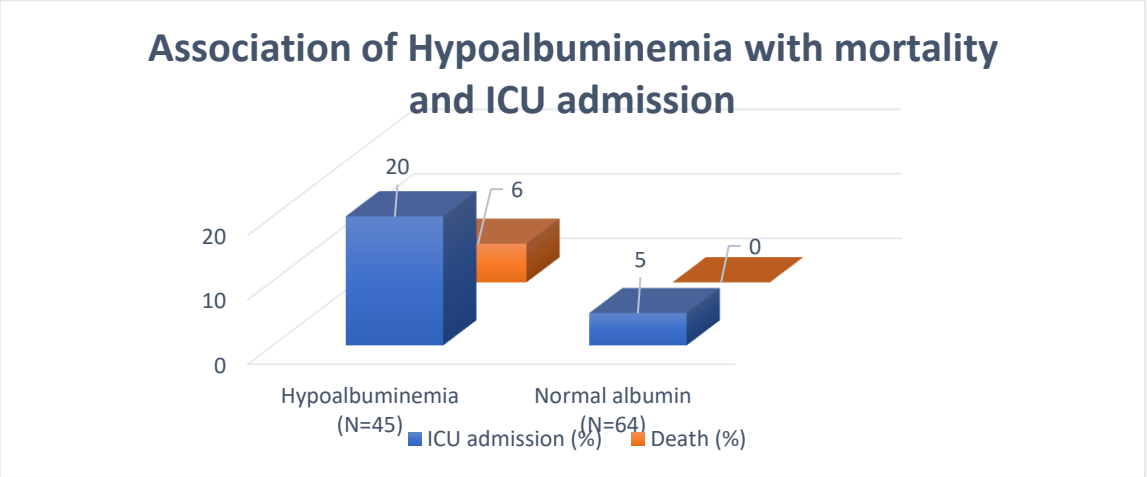

Figure 2: Association of Hypoalbuminemia with mortality and ICU admission in the study population

Table 3: Pearsons's Correlation of Albumin levels with various variable in COVID-19 Patients:

	Hypo-Albumin	TLC	Lymphocytes	Neutrophils	CRP	Procalcitonin	D. Dimer	LDH	Creatinine	Death	ICU Admission
Hypo-albumin	1										
TLC	-0.340**	1									
Lymphocytes	0.590**	-0.280*	1								
Neutrophils	-0.240*	0.100	-0.110	1							
CRP	-0.290*	-0.050	-0.240*	0.370**	1						
Procalcitonin	-0.520**	0.200	-0.360**	0.330**	0.440**	1					
D. Dimer	-0.630**	0.210	-0.520**	0.200	0.140	0.480**	1				
LDH	-0.660**	0.260*	-0.550**	0.400**	0.380**	0.460**	0.630**	1			
Creatinine	0.090	0.200	-0.050	-0.060	-0.080	-0.010	0.020	-0.110	1		
Mortaliy	0.660**	0.080	0.120	0.050	0.090	0.130	0.070	0.130	-0.070	1	
ICU Admission	0.630**	0.120	0.140	0.070	0.110	0.200	0.150	0.210	-0.040	0.220	1

Table 3 presents Pearson's correlation coefficients reflecting the relationships between Albumin levels and various other medical parameters in the context of a COVID-19 study. These correlation coefficients help quantify the strength and direction of the associations between albumin and these parameters.

First, there is a negative correlation between Albumin and Total leucocyte count (TLC). This implies that as Albumin levels decrease, TLC tends to increase. This could indicate that a reduction in albumin might be linked to compromised immune function, as evidenced by an increase in TLC.

In contrast, there's a direct correlation between Albumin and Lymphocytes. As Albumin levels decrease, Lymphocyte count tends to decrease as well. This suggests that lower Albumin levels are associated with a reduction in lymphocytes, which play a crucial role in the immune system. Similarly, a negative correlation exists between Albumin and Neutrophils. A decline in albumin is linked to an increase in Neutrophil count. This may signify that lower Albumin levels are associated with an elevated inflammatory response in the body, given the role of neutrophils in inflammation.

Albumin and various markers show a negative correlation. As Albumin levels decrease, C-reactive protein (CRP), Procalcitonin, D-Dimer, and Lactate Dehydrogenase (LDH) tend to increase. This implies that lower Albumin levels are linked to higher levels of inflammation, a higher likelihood of bacterial infection, a higher risk of clot formation, and tissue damage or cell breakdown. Additionally, there is a weakly positive correlation between Albumin and Creatinine levels, which suggests that lower Albumin levels may be linked to mild kidney dysfunction.

Finally, the last two correlations are of significant clinical importance. There's a strong positive correlation between hypoalbumin and mortality, implying that as Albumin levels decrease, the risk of mortality significantly rises. Additionally, there's a strong positive correlation between hypo-albumin and ICU Admission. Lower Albumin levels are associated with a significantly higher likelihood of requiring intensive care.

Table 3 underscores the critical role of hypo-albuminemia as a biomarker in assessing the severity and prognosis of COVID-19 patients. Lower Albumin levels are associated with increased inflammation, a higher risk of bacterial infection, a higher likelihood of thrombosis, tissue damage, and a significantly elevated risk of death or ICU admission in the studied COVID-19 population.

Discussion:

Serum Albumin plays a crucial role in various physiological functions within the body. Some of its essential functions include maintaining colloidal osmotic pressure, binding to different compounds, and acting as a plasma antioxidant (Sitar et al., 2013).

One significant aspect of albumin is its role in maintaining colloidal osmotic pressure, vital for regulating fluid balance within blood vessels and the surrounding tissues. This helps prevent

excessive leakage of fluids from blood vessels into the interstitial space, contributing to stable blood volume and pressure (Bihari et al., 2020).

Albumin also acts as a binding agent, capable of binding to various molecules in the blood. This includes hormones, fatty acids, drugs, and other substances. By binding these compounds, albumin helps transport them throughout the body, affecting their distribution and function (De Simone et al., 2021; Kragh-Hansen, 2016).

Furthermore, albumin exhibits plasma antioxidant activity. It can counteract the harmful effects of oxidative stress by scavenging free radicals and protecting cells and tissues from damage (Soriani et al., 1994).

There is a notable decrease in serum Albumin levels in various acute and chronic diseases. This decrease is often related to the magnitude of the inflammatory response generated by these diseases. This phenomenon has led to albumin being referred to as a "negative acute phase reactant." In other words, while many proteins increase in response to inflammation (positive acute phase reactants), Albumin levels tend to decrease (Ramsay and Lerman, 2015).

Several mechanisms have been proposed to explain the decrease in Albumin levels during inflammation. Firstly, releasing cytokines and chemokines can lead to capillary leakage, causing albumin to shift from the bloodstream to the interstitial space. In this new location, albumin is an antioxidant and a source of amino acids for cellular and matrix synthesis (Quinlan et al., 2005).

Secondly, inflammation is associated with an increased degradation of albumin and a reduced synthesis response. This decrease in Albumin synthesis is primarily mediated by cytokines like interleukin (IL)-6 and tumor necrosis factor (TNF)-α. These cytokines inhibit the transcription of Albumin genes, further reducing circulating Albumin levels during inflammatory states (Alcaraz-Quiles et al., 2018; Fearon et al., 1998).

Hypoalbuminemia, characterized by low serum Albumin levels, has been linked to adverse outcomes in both short-term and long-term contexts among hospitalized patients in various medical and surgical settings. Studies in patients with SARS-CoV-2 infection, the virus responsible for COVID-19, have also reinforced the significant association between serum Albumin concentration and mortality (Ramadori, 2022).

Research conducted by Violi and colleagues identified that the lowest tertile of Albumin concentration (<32 g/L) predicted a higher risk of mortality (Hazard Ratio 2.48, 95% Confidence Interval: 1.44–4.26, $p = 0.001$). This association remained significant even after adjusting for age, ICU admission, gender, heart failure, chronic obstructive pulmonary disease, and high-sensitivity C-reactive protein (hs-CRP) levels (Viana-Llamas et al., 2021).

Another study led by Huang et al. reported that hypoalbuminemia, defined as Albumin levels below 35 g/L, was a predictor of patients at high risk of progressing to severe COVID-19 infection. Other risk factors for severe disease included lymphopenia (lymphocyte count below 1000/μL) and the presence of comorbidities, such as older age, elevated lactate dehydrogenase (LDH) levels, high C-reactive protein (CRP) levels, a high coefficient of variation of red blood cell distribution width, and the presence of at least one other underlying medical condition. These factors were identified as independent predictors of mortality (Huang et al., 2020).

Gong et al. developed a nomogram, a predictive model, for early identification of at-risk individuals based on several parameters, including Albumin levels, direct bilirubin, blood urea nitrogen, and Albumin concentration. This tool can help healthcare professionals assess the risk of severe outcomes and death in COVID-19 patients (Gong et al., 2020).

Our study's key and significant finding is the existence of a strong inverse relationship between the level of albumin and the risk of death in COVID-19 patients. Through our retrospective analysis, we uncovered that individuals with a serum albumin level of less than 35 g/L at the time of presentation faced a substantially elevated risk of death due to COVID-19. This underscores the critical role of serum albumin as a prognostic marker and its potential utility in identifying patients at greater risk of severe outcomes and mortality associated with COVID-19. These findings are also reported in many studies (Bennouar et al., 2021; Vaid et al., 2020)

Our study assessed the risk of ICU (Intensive Care Unit) admission among COVID-19 patients. We found a notable correlation between low serum albumin levels and an increased risk of ICU admission. Specifically, individuals with serum albumin levels below 35 g/L had a substantially elevated risk of being admitted to the ICU.

The limitations of this study include its retrospective design, a relatively small sample size, potential selection bias, missing data, and the fact that it is a single-center study. These factors may limit the generalizability of the findings. Additionally, while the study highlights a significant association between low serum albumin levels and increased risk of death in COVID-19 patients, it cannot establish a causal relationship. Other unmeasured variables and variations in treatment approaches could also impact the outcomes. Therefore, further research in larger, multicenter, prospective studies is needed to confirm and expand upon these findings.

Conclusion:

In conclusion, our study demonstrates a substantial and independent association between low serum albumin levels at presentation and a significantly increased mortality risk in COVID-19 patients. These findings underscore the importance of monitoring and addressing hypoalbuminemia as a potential prognostic marker in COVID-19 management. Early identification and intervention in patients with low albumin levels may contribute to better outcomes. However, further research is necessary to elucidate the underlying mechanisms and validate these results in larger, more diverse patient populations.

References:

1. Al-Tawfiq, J. A., and Memish, Z. A. (2020). COVID-19 in the Eastern Mediterranean Region and Saudi Arabia: prevention and therapeutic strategies. *International Journal of Antimicrobial Agents* **55**, 105968.
2. Alcaraz-Quiles, J., Casulleras, M., Oettl, K., Titos, E., Flores-Costa, R., Duran-Güell, M., López-Vicario, C., Pavesi, M., Stauber, R. E., and Arroyo, V. (2018). Oxidized albumin triggers a cytokine storm in leukocytes through p38 Mitogen-Activated protein kinase: role in systemic inflammation in decompensated cirrhosis. *Hepatology* **68**, 1937-1952.
3. Bennouar, S., Cherif, A. B., Kessira, A., Bennouar, D.-E., and Abdi, S. (2021). Development and validation of a laboratory risk score for the early prediction of COVID-19 severity and in-hospital mortality. *Intensive and Critical Care Nursing* **64**, 103012.
4. Bernardi, M., Angeli, P., Claria, J., Moreau, R., Gines, P., Jalan, R., Caraceni, P., Fernandez, J., Gerbes, A. L., and O'Brien, A. J. (2020). Albumin in decompensated cirrhosis: new concepts and perspectives. *Gut* **69**, 1127-1138.
5. Bezemer, G. F., and Garssen, J. (2021). TLR9 and COVID-19: a multidisciplinary theory of a multifaceted therapeutic target. *Frontiers in Pharmacology* **11**, 601685.
6. Bihari, S., Bannard-Smith, J., and Bellomo, R. (2020). Albumin as a drug: its biological effects beyond volume expansion. *Critical Care and Resuscitation* **22**, 257-265.
7. Bonilla-Palomas, J. L., Gámez-López, A. L., Moreno-Conde, M., López-Ibáñez, M. C., Anguita-Sánchez, M., de la Sacristana, Á. G., García-Catalán, F., and Villar-Ráez, A. (2014). Hypoalbuminemia in acute heart failure patients: causes and its impact on hospital and long-term mortality. *Journal of cardiac failure* **20**, 350-358.
8. De Simone, G., di Masi, A., and Ascenzi, P. (2021). Serum albumin: a multifaced enzyme. *International Journal of Molecular Sciences* **22**, 10086.
9. Fearon, K., Falconer, J. S., Slater, C., McMillan, D. C., Ross, J. A., and Preston, T. (1998). Albumin synthesis rates are not decreased in hypoalbuminemic cachectic cancer patients with an ongoing acute-phase protein response. *Annals of surgery* **227**, 249.
10. Garibaldi, B. T., Fiksel, J., Muschelli, J., Robinson, M. L., Rouhizadeh, M., Perin, J., Schumock, G., Nagy, P., Gray, J. H., and Malapati, H. (2021). Patient trajectories among persons hospitalized for COVID-19: a cohort study. *Annals of internal medicine* **174**, 33-41.

11. Gong, J., Ou, J., Qiu, X., Jie, Y., Chen, Y., Yuan, L., Cao, J., Tan, M., Xu, W., and Zheng, F. (2020). Multicenter development and validation of a novel risk nomogram for early prediction of severe 2019-novel coronavirus pneumonia.
12. Gremese, E., Bruno, D., Varriano, V., Perniola, S., Petricca, L., and Ferraccioli, G. (2023). Serum Albumin Levels: A Biomarker to Be Repurposed in Different Disease Settings in Clinical Practice. *Journal of Clinical Medicine* **12**, 6017.
13. Huang, W., Li, C., Wang, Z., Wang, H., Zhou, N., Jiang, J., Ni, L., Zhang, X. A., and Wang, D.-W. (2020). Decreased serum albumin level indicates poor prognosis of COVID-19 patients: hepatic injury analysis from 2,623 hospitalized cases. *Science China Life Sciences* **63**, 1678-1687.
14. Kragh-Hansen, U. (2016). Human serum albumin: a multifunctional protein. *Albumin in medicine: pathological and clinical applications*, 1-24.
15. Lai, C.-C., Shih, T.-P., Ko, W.-C., Tang, H.-J., and Hsueh, P.-R. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *International journal of antimicrobial agents* **55**, 105924.
16. Quinlan, G. J., Martin, G. S., and Evans, T. W. (2005). Albumin: biochemical properties and therapeutic potential. *Hepatology* **41**, 1211-1219.
17. Rabbani, G., and Ahn, S. N. (2021). Roles of human serum albumin in prediction, diagnoses and treatment of COVID-19. *International Journal of Biological Macromolecules* **193**, 948-955.
18. Ramadori, G. P. (2022). SARS-CoV-2-infection (COVID-19): clinical course, viral acute respiratory distress syndrome (ARDS) and cause (s) of death. *Medical Sciences* **10**, 58.
19. Ramsay, E. S., and Lerman, M. A. (2015). How to use the erythrocyte sedimentation rate in paediatrics. *Archives of Disease in Childhood-Education and Practice* **100**, 30-36.
20. Seebacher, V., Grimm, C., Reinthaller, A., Heinze, G., Tempfer, C., Hefler, L., and Polterauer, S. (2013). The value of serum albumin as a novel independent marker for prognosis in patients with endometrial cancer. *European Journal of Obstetrics & Gynecology and Reproductive Biology* **171**, 101-106.
21. Signorini, C., Pignatti, P., and Coccini, T. (2021). How do inflammatory mediators, immune response and air pollution contribute to COVID-19 disease severity? A lesson to learn. *Life* **11**, 182.
22. Sitar, M. E., Aydin, S., and Cakatay, U. (2013). Human serum albumin and its relation with oxidative stress. *Clin Lab* **59**, 945-952.
23. Slutskiy, P., and Boonchutima, S. (2022). Credibility of the Official COVID Communication in Thailand: When People Stop Believing the Government. *American Behavioral Scientist*, 00027642221118297.
24. Soriani, M., Pietraforte, D., and Minetti, M. (1994). Antioxidant potential of anaerobic human plasma: role of serum albumin and thiols as scavengers of carbon radicals. *Archives of biochemistry and biophysics* **312**, 180-188.
25. Vaid, A., Somani, S., Russak, A. J., De Freitas, J. K., Chaudhry, F. F., Paranjpe, I., Johnson, K. W., Lee, S. J., Miotto, R., and Richter, F. (2020). Machine learning to predict mortality and critical events in a cohort of patients with COVID-19 in New York City: model development and validation. *Journal of medical Internet research* **22**, e24018.
26. Viana-Llamas, M. C., Arroyo-Espliguero, R., Silva-Obregón, J. A., Uribe-Heredia, G., Núñez-Gil, I., García-Magallón, B., Torán-Martínez, C. G., Castillo-Sandoval, A., Díaz-Caraballo, E., and Rodríguez-Guinea, I. (2021). Hypoalbuminemia on admission in COVID-19 infection: An early predictor of mortality and adverse events. A retrospective observational study. *Medicina clinica* **156**, 428-436.
27. Wang, Y., Kang, H., Liu, X., and Tong, Z. (2020). Combination of RT-qPCR testing and clinical features for diagnosis of COVID-19 facilitates management of SARS-CoV-2 outbreak. *Journal of medical virology* **92**, 538.

28. Wiedermann, C. J. (2021). Hypoalbuminemia as surrogate and culprit of infections. *International Journal of Molecular Sciences* **22**, 4496.