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Original Research Paper

Biochemistry

'HYPOALBUMINEMIA'-A NEW PROGNOSTIC FACTOR FOR COVID -19 INFECTION.

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ABSTRACT

Introduction- Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, is known to cause serious complications in humans such as multiorgan failure and ultimately death. Albumin serves as a major anti-inflammatory agent in our body and its anti-oxidative and anti-thrombotic property are the lesser discussed topics in the literature. So, present study was conducted with aim to reveal the impact of hypoalbuminemia to predict serious outcomes in COVID-19 infection.

Methodology-The retrospective case control study was conducted in the Department of Clinical Biochemistry, VIMS Pawapuri. It consisted of 100 COVID-19 patients that were divided in two groups-ICU patients(50) and Non ICU Patients(50)). Blood samples collected were analysed for biochemical parameters e.g. albumin, Aspartate aminotransferase(AST), Alanine aminotransferase (ALT), CRP, D-dimer and hematological parameters.

Result- Laboratory examination revealed significant elevation of CRP (65.5mg/L,30.5-133.7, $p<0.001$), D-dimer(770 ng/L, 636.5-770.5,$p<0.001$), Neutrophils(10.1×10^3/L,6.1-11.8,$p<0.001$) with significant male predominance in ICU group(64.6%). Serum albumin was significantly low in ICU (30gm/L,25.2-37.7,$p<0.001$). Hypoalbuminemia across the COVID-19 patients was significant with $p<0.001$ by Fischer exact test(Odds ratio=95.12, 95% CI,12.06-749.67,$P<0.001$).Pearson's correlation analysis showed significant negative relationship of albumin with CRP ($r= -0.4333, p<0.001, R^2=0.188$) and D-dimer ($r= -0.451, p<0.001, R^2=0.204$) respectively.

Conclusion- Low serum albumin in COVID-19 infection is associated with serious outcomes. Thus, serum albumin levels may present as an prognostic tool for the early identification of serious outcomes and mortality risk in COVID-19 patients.

KEYWORDS : SARS-CoV-2 - Severe Acute Respiratory Syndrome Coronavirus 2, CRP-C Reactive Protein, Hypoalbuminemia, D-dimer.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a novel viral disease. It was first discovered in December 2019 in Wuhan, China. The World Health Organization officially announced it as pandemic later on [1]. The disease primarily affects the respiratory system. More so it leads to complications causing injuries to kidney, liver and heart. It may also lead to encephalopathy, stroke, post-infection deblities, coagulopathy etc. Majority of the patients survive the infection without any complications, but a notable proportion of patients develop serious complications. Several other factors have been found to be associated with severe COVID-19, such as old age, immunocompromised state and underlying co-morbid diseases e.g.- diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease (COPD) etc.. Among laboratory variables, D-dimer, CRP, ferritin, lymphopenia and troponins are associated with poor survival [2,3].

Albumin is a protein synthesized in the liver that has many physiological functions such as providing oncotic pressure, binding and transporting substances, and maintaining acid-base equilibrium, among other functions. Significantly decreased albumin level is also seen in severe COVID -19[4,5] but the change in albumin does not parallel the severity of hepatocellular injury in COVID -19[5]. This suggests that there may be some mechanisms other than a hepatocellular injury that explains the profound hypoalbuminemia seen in COVID-19[6]. During critical illness, inflammatory mediators decrease albumin synthesis in order to prioritize synthesis of other acute phase reactants. Additionally, these mediators increase vascular permeability allowing albumin to escape to the extravascular space, which may also lead to low serum albumin levels[7].

Albumin, a negative acute-phase reactant, decreases in acute infection. Low albumin levels are associated with mortality risk in hospitalized patients[8]. Albumin has a long half-life (approx. 3 weeks) and 90% of it is in plasma [9].The level of plasma drops rapidly during acute inflammation due to transcapillary leakage into the interstitial space.

This has been hypothesized that serum albumin levels at admission may reflect the severity of systemic inflammation and thus can serve as a predictive factor for COVID-19 outcomes. This is a cheap and easy method to predict mortality in COVID-19 patients . With this background the present study has been designed to study the role of albumin in predicting mortality in patients with COVID-19.

Aim of the Study

To explore the impact of low albumin level in the prognosis of COVID -19 infection.

MATERIAL AND METHODS

The retrospective case control study was conducted in the Department of Clinical Biochemistry, VIMS Pawapuri. The study was approved by the Institutional Ethical Committee. We reviewed the charts of patients with the discharge diagnosis of COVID-19. Then included 100 such patients.

These were further divided in two groups

- ICU patients(50)
- Non ICU Patients(50)

Inclusion Criteria:-

1) Age ≥ 18 years
2) Positive RT-PCR assay from oropharyngeal swab.
3) Meet the criteria set out by WHO for COVID -19 infection[10].

Biochemical parameters e.g., albumin, Aspartate aminotrans ferase (AST), Alanine aminotransferase (ALT), CRP and D-dimer and routine hematological parameters were recorded.

Statistical Analysis

Categorial variables were expressed as percentage(%). Continuous variables were expressed in terms of mean ± SD or medians with interquartile ranges (IQRs). These were then compared between the groups using Student's t-test, Mann-whitney U test. The differences of categorial variables were then examined using Chi square test ^{2}. Albumin levels were compared using Fischer exact test($p<0.05$) and odds ratio. Pearson's Correlation 'r' was used to analyze the relationship between S. albumin and CRP (an inflammatory marker) and D-dimer. Statistical analysis was done on SPSS version 22.0.

RESULT

Mean age of the ICU patients (52.4 ±13.3)years show nonsignificant ($p=0.2$) difference with that of the non-ICU patients (55.7±14.5)years. (Table 1).

Chi square test show significant ($p=0.005$) difference with male predominance(64.6%) in ICU group. While other group comprised predominantly of females (63.5%).

Laboratory examination showed significant elevation of CRP (65.5mg/L,30.5-133.7,$p<0.001$),D-dimer (770ng/dl,636.5-770.5,$p<0.001$), Total Count (12.98 $\times 10^3$/L,9.9-15.2,$p<0.001$), Neutrophils (10.1$\times 10^3$/L,6.1-11.8, $p<0.001$). Serum albumin showed considerable ($p<0.001$) difference between the comparative groups (30,25.2-37.7 Vs 45.05,42.5-47.1). On contrary, lymphocyte count and hemoglobin showed nonsignificant differences ($p=0.9$; $p=0.5$) respectively .

Liver enzymes showed variable results. While ALT showed significant ($p<0.001$) elevation, AST values were nonsignificant ($p=0.3$).

Table 1.Parameters across ICU-Non ICU Patients(N=100)

Parameters		Non-ICU group(n=50)	ICU-Group (n=50)	P Value*
Age(years)		55.7±14.5	52.4±13.3	0.2
Gender(%)	Female	33(63.5)	19(36.5)	0.005
	Male	17(35.4)	31(64.6)	
ALT(IU/L)		21.4 (15.135.8)	39.5(32-51.7)	<0.001
AST(IU/L)		26.9 (19.631.7)	22.5(20-33.7)	0.3
Serum Albumin (g/L)		45.05 (42.5-47.1	30(25.2-37.7)	<0.001
CRP(mg/L)		2.1 (1.2-3.6)	65.5(30.5-133.7)	<0.001
D-dimer (ng/dl)		53(35.7-90.5)	770(636.5-770.5)	<0.001
Total Count(10^3/L)		6.78 (5.6-7.7)	12.98(9.9-15.2)	<0.001
Neutrophils (10^3/L)		4.1 (3.03-4.7)	10.1(6.1-11.8)	<0.001
Lymphocytes (10^3/L)		1.83 (1.5-2.4)	1.84(1.01-2.6)	0.9
Hemoglobin (g/dl)		12.06±1.6	12.4±1.80	0.5

Table 2 illustrates Fischer Exact test showing significant ($p<0.001$) comparative values of albumin across the ICU and non-ICU patients (OR=95.12,95%CI, 12.06-749.67).

Table 2. Albumin categories across ICU/Non ICU groups (N=100)

Albumin levels	Non ICU(%)	ICU(%)
<35g/L	1(3.6)	33(97.1)
≥35g/L	49(68.1)	17(25.8)
P<0.001 by Fischer exact test		
Odds ratio(95% CI)=95.12(12.06-749.67),P<0.001		

Pearson's correlation analysis (fig1,2) was performed to explore the relationship of albumin with CRP (r=-0.4333, $p<0.001$, $R^2=0.188$) and D-dimer (r= -0.451,$p<0.001$, $R^2=0.204$) respectively. A negative significant correlation of albumin with that of CRP and D-dimer was observed resp.

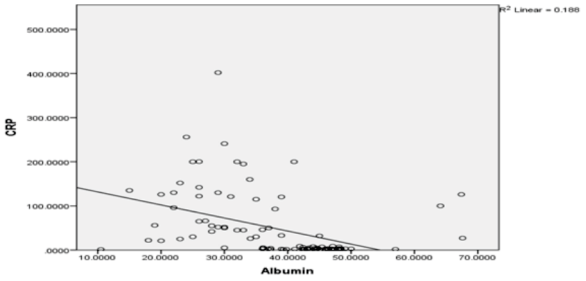

Fig 1.Scattered plot showing correlation between S. Albumin and CRP levels

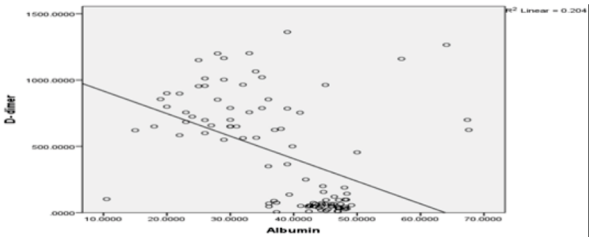

Fig 2.Scattered plot showing correlation between S.Albumin and d-Dimer levels

DISCUSSION

Hypoalbuminemia in severe COVID-19 has been repeatedly explained in various studies[6,11,12-13]. In this retrospective study we could explore that low albumin levels were associated with serious consequences in COVID-19. This was consistent with a few previous studies[14,15]. Hypoalbuminemia on admission can predict the serious outcomes in COVID-19 patients independent of lymphocyte count or comorbidities[3,16]. Total count and neutrophil count increase in severe viral infections. Neutrophils are known to release chemokines and cytokines leading to storm like condition. This produces lung injury and ARDS. Various studies have shown raised neutrophils count in COVID-19[17,18]. Our findings are consistent with the literature.

Hypoalbuminemia was seen predominantly in ICU COVID-19 patients with slightly increased ALT values. This phenomenon cannot be explained by hepatocellular dysfunction alone. On contrary, in acute liver injury ALT rise is supposed to be 5 times the normal values[19]. Thus, hypoalbuminemia as a reflection of concomitant acute liver disease can reasonably be excluded by the present and previous studies[3].

Albumin is the biggest and most abundant protein in plasma. It is also the negative acute phase reactant with low level in acute inflammation. It escapes into the interstitial space due to increased capillary permeability in inflammation[2,7].

CRP has been established as an important marker of inflammation. In the present and previous study[3], inverse correlation of CRP and albumin has been demonstrated. Systemic inflammation is common in severe COVID-19[20]. Thus, our study strongly implies that low serum albumin might

be due to Systemic inflammation as explained by the inverse correlation between the parameters.

Furthermore, albumin exhibits anticoagulant properties[21] thereby inhibiting the oxidative stress induced clotting factor and platelets activation[22]. Previous studies have addressed the association of low albumin with increased risk of arterial and venous thrombosis[21,23]. These findings were further corroborated by this study, where albumin level show inverse significant correlation with D-dimer, a recognised marker of thrombotic events and serious complications in COVID-19.

In addition to volume expansion, albumin exhibits therapeutic efficacy in inflammation and oxidative stress. So, albumin treatment could be a potential approach in COVID-19. However, further studies are required to illuminate the efficacy and safety of albumin.

Our study has to be interpreted in light of few limitations. We have produced a single-center data interpretations. However, the baseline factors in our study were consistent with the present literature available. Furthermore, being a retrospective study follow-up with patients couldn't be made.

CONCLUSION

Hypoalbuminemia in COVID-19 infection is associated with higher incidence of serious outcomes like hypercoagubility etc. Thus, serum albumin levels may present as an prognostic tool for the early identification of serious outcomes and mortality risk in COVID-19 patients.

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