Original Article

ASSOCIATION OF SERUM ALBUMIN AND TOTAL PROTEIN LEVELS WITH LYMPHOPENIA IN COVID-19 INFECTION AT A TERTIARY CARE HOSPITAL IN PAKISTAN

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ABSTRACT

Objective: To evaluate metabolic parameters such as serum albumin levels and serum total protein and their correlation with hematologic index such as lymphopenia in hospitalized patients with laboratory confirmed COVID-19 infection.

Material and Methods: This retrospective study was conducted in Department of Pathology, Pakistan Institute of Medical Sciences, from April 2020 to June 2020. Total 65 patients with confirmed RT-PCR for COVID-19 infection were tested for alterations in serum albumin and total protein levels, and association between these two parameters and the presence of lymphopenia was studied. Pearson chi-square test was applied to analyze statistical significance and a p value less than 0.05 was taken as significant.

Results: Age range was from 18 to 90 years of age, with a mean age of 50.6 ± 16.3 years. The male patients were in majority as compared to females. Hypoalbuminemia (serum albumin < 3.5 g/dl) was observed in 77% patients and hypoproteinemia (serum total protein < 6.6 g/dl) was observed in 57% of these patients. Lymphopenia (absolute lymphocyte count <1000/microliter) was seen in 49.2 % patients. There was significant association between lymphopenia and low albumin levels in serum (p=0.01)

Conclusion: Hypoalbuminemia and hypoproteinemia are common findings in COVID-19. Low albumin levels are significantly associated with decreased lymphocyte count in the blood.

Key Words: Serum albumin, Serum protein, Lymphopenia, Covid-19 infection.

This article can be cited as: Khan AQ, Butt I, Ali S, Sohail S, Qamar MK, Tahir F. Association of serum albumin and total protein levels with lymphopenia in COVID-19 infection at a tertiary care hospital in Pakistan. Pak J Pathol. 2022; 33(2): 65-68.

DOI: 10.55629/pakjpathol.v33i2.672.

INTRODUCTION

The most recent threat the global healthcare system has faced for the past three year till date, is from the novel coronavirus which was identified in late 2019 in Wuhan [1]. Scientists identified this new RNA virus species, by isolating it from patients in Wuhan, using whole genome sequencing on the virus, and named it as Corona Virus in the year 2019[1]. The World Health Organization (W.H.O) later abbreviated it as COVID-19 [2].

Most patients infected with COVID-19 usually show general respiratory symptoms like cough, shortness of breath, etc. Fatality rate of such patients is reported to be 1.4-4% [1]. Death occurs due to colossal damage to the alveolar lung tissue leading to the development of respiratory failure with a substantial mortality rate [1,2,3]. The purpose of this article is to investigate the laboratory parameters that are abnormal (increased or decreased) in COVID-19 patients presented with moderate to severe. This will aid the health care workers in better management of COVID-19 positive patients in the disease process by paying special attention to these deranged parameters.

Serum albumin is a negative acute phase protein and may be decreased in chronic illness [1]. These decreased levels are probably a consequence of the hepatic damage from adverse drug interaction and systemic inflammatory response in critical COVID-19 patients [2,3]. Low levels of albumin decrease the resistance of the body against the virus leading to more progressive disease [4]. Keeping in view the importance of albumin as a predictive and prognostic marker in previous literature, albumin levels in the blood may serve as an independent parameter to predict high risk of mortality in critically ill patients of COVID-19.

Moreover, there is a direct relationship between lymphopenia and severity of COVID-19 infection. Research has shown that there is a steady and significant drop in the absolute lymphocyte count as the disease progresses from moderate to severe form [5].

The rationale of this study is to determine the frequency of deranged serum albumin and total

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Received: ***28 Feb 2022****; Revised:* ***19 May 2022****; Accepted:* ***22 Jun 2022***

protein levels in COVID-19 PCR-positive cases, and to determine any association between this alteration and lymphopenia which is another high-risk parameter as shown from previous studies.

MATERIAL AND METHODS

This was a tertiary care hospital-based retrospective cross-sectional study conducted in the Department of Pathology, Pakistan Institute of Medical Sciences (P.I.M.S), Islamabad for a period of 3 months from 1st April 2020 to 30th June 2020. Approval from Hospital Ethical Board was taken. (No. F. 1-1/2015/ERB/SZABMU/670; dated 14.10.2020). This study included 65 adult patients of both genders, ≥ 18 years of age, with a laboratory confirmed COVID-19 infection by RT-PCR on nasopharyngeal and oropharyngeal swab specimens, admitted to isolation ward of PIMS Hospital with moderate to severe symptoms of disease according to NIH guidelines; and were selected by consecutive non-probability sampling technique. These patients had not received any treatment prior to admission. Patients with known diagnosis of hepatitis, diabetes mellitus and hematological disorders were excluded from the study. Demographic profile was recorded. Blood samples (clotted and EDTA-anticoagulated) of all patients at the time of admission were collected by nursing staff wearing proper personal protective equipment. In the laboratory, serum was separated after centrifugation from 2-3 ml blood samples collected in gel vacutainers, which were used for total protein and albumin level measurement on fully automated chemistry analyzer Beckman Coulter AU680. Complete Blood Count for absolute lymphocyte count was analyzed using 2 ml EDTA-anticoagulated blood samples on Mindray BC-6200 fully automated hematology analyzer, using the principle of light scattering properties. The data was entered and analyzed using SPSS version 20. Parameters were expressed as Mean ± Standard Deviation. The reference range of serum total protein was 6.6 – 7.9 g/dl, and of serum albumin was 3.5 – 4.5 g/dl. Two groups of patients with low and normal albumin levels and two groups with low and normal total protein levels were made. Similarly, on the basis of absolute lymphocyte count, patients were segregated into those having lymphopenia and those not having lymphopenia. Pearson chi-square test was applied to find any statistical association between lymphopenia and hypoalbuminemia, as well as between lymphopenia and hypoproteinemia. A p value less than 0.05 was considered statistically significant.

RESULTS

This study included 65 adult cases infected with SARS-CoV2 confirmed on RT-PCR on respiratory specimens over a period of 3 months. This included patient ranging from 18 to 90 years of age, with a mean age of 50.6 ± 16.3 years. The male patients were in majority (81%) as compared to females (19%). Majority 45/65 (69.2%) patients had moderate disease, while the remainder had severe disease. Serum total protein and albumin were measured in all patients. Hypoalbuminemia (serum albumin < 3.5 g/dl) and hypoproteinemia (serum total protein < 6.6 g/dl) were observed as key findings in our study, as shown in the Table-I.

Table-I: Serum total protein and albumin levels in study individuals (n=65).

Parameters	Mean ± SD
Serum total protein (g/dl)	6.17 ± 1.07
Serum albumin (g/dl)	3.08 ± 0.68

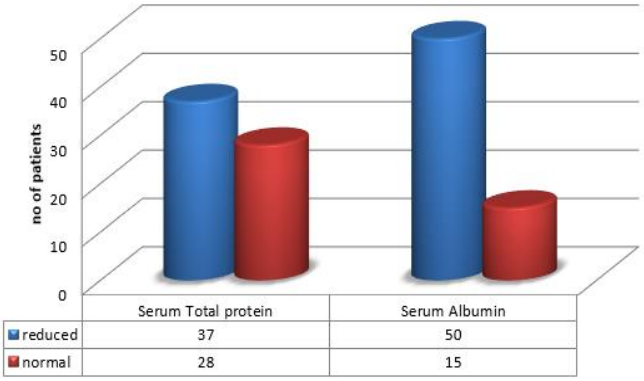

Figure-I: Estimation of serum total protein and albumin in patients (n=65).

The proportion of patients showing reduced and normal serum protein and albumin levels are shown in Figure-I. As depicted in Table-II and Table-III, decreased blood lymphocyte count was significantly associated with hypoalbuminemia but no significant relationship was found between lymphopenia and hypoproteinemia.

Table-II: Association between lymphocyte count and serum albumin.

		Lymphopenia		Total	p-value
		Present	Absent		
Serum Albumin	Normal	3	12	15	0.01
	Low	29	21	50	
Total		**32**	**33**	**65**	

Table-III: Association between lymphocyte count and serum total protein.

		Lymphopenia		Total	p value
		Present	Absent		
Serum total protein	Normal	10	18	28	0.058
	Low	22	15	37	
Total		**32**	**33**	**65**	

DISCUSSION

Albumin is a major constituent of the total protein in the human body. Low albumin levels were detected in most of the patients of COVID-19 admitted to our hospital. 76% (n=50/65) of the patients had hypoalbuminemia while 57% (n=37/65) of patients had hypoproteinemia. Decreased albumin levels, previously reported in the literature is a significant predictor of mortality in critically ill patients [6]. Albumin levels along with other laboratory parameters, can aid health care providers in predicting the severity of disease and early management of such patients [7]. In accordance with previously published data by Zhang *et al*., it was observed that hypoalbuminemia was significantly associated with prolonged hospital stay and mortality [8]. Serum albumin concentrations is a good predictor of requirement for intensive respiratory support in adult patients infected with influenza A (H1N1) at the time of admission [6]. It has been reported that hypercoagulable states, carotid atherosclerosis in AIDS patients (HIV positive patients) and inflammatory conditions are associated with low serum albumin levels [6]. Studies also show that the administration of chemically modified albumin provide immunity against the entry of the Ebola virus into cells [6]. Hypoalbuminemia could also be responsible for adverse outcomes in COVID-19 patients [6].

In another research published by Aziz *et al*, low albumin levels were found to be strongly associated with progression and severe illness in patients of COVID-19 [9]. Recently published data by the University of Illinois found significant association of hypoalbuminemia in patients with severe COVID-19 disease [10]. Hypoalbuminemia can therefore predict the onset of severe disease early on and therefore aid health care providers in timely and informed decisions regarding their patient management [10,11]. As discussed earlier, hepatocellular insult causes fall in albumin levels but interestingly, the derangements in albumin levels do not correspond to the level of liver damage in COVID-19 patients, as was shown by Zhang *et al* [11].

There is a multifactorial mechanism of hepatocyte destruction which is responsible for the abnormal albumin levels that are seen in COVID-19 patients such as direct viral injury due to ischemia. Systemic inflammatory response has been repeatedly reported in critically ill COVID -19 patients and could be a factor that is causing hypoalbuminemia in such patients [12]. Additionally, major acute phase cytokines (IL-1,IL-6 and TNF-a) that are a hallmark of the cytokine 'storm' are produced because of the virus induced damage to the lungs which in turn potentiates a further decrease in albumin levels by downregulating its production at the genetic (pre-translational) level [12]. The derangements in albumin levels result from two main pathways; firstly, by a decrease in production due to insufficient food intake and secondly by direct inhibition of albumin synthesis by inhibiting specific mRNA-synthesis which is due to the acute phase cytokines interacting with the DNA in the damaged liver tissue [12].

Certain parameters have been associated with COVID-19 mortality such as raised levels of IL-6, C-Reactive Protein (CRP), D-dimers, Lactate Dehydrogenase levels (LDH) and serum ferritin.[13,14] Similarly reduced total lymphocyte count and albumin levels has also been strongly linked to mortality in these patients [14,15]. Thus, suggesting that hypoalbuminemia may be an alarming sign of underlying cytokine storm and can be easily detected in laboratory settings and can alert the clinician for appropriate and timely intervention [16,17]. Little research has been done regarding the association of total protein levels and disease severity in COVID-19 patients [18]. Data published by Marian *et al* in July 2020 showed that the serum total protein decreased significantly with advancing disease in COVID-19 patients, as it was shown in our study, but they observed that it was not a good independent prognostic predictor in these patients [18].

LIMITATION

Clinical outcome information of these patients could not be included due to lack of clinical follow-up. Further studies in this regard that also assess these patients on follow up along with evaluation of serial assays of albumin in subsequently recovered patients can be helpful in clear understanding of the disease progression.

CONCLUSION

Our study showed that serum albumin was found to be one of the major negative acute phase proteins in COVID-19 patients who presented with significant metabolic disorders. Hypoproteinemia was a major finding in these patients. Lymphopenia was also seen in nearly half of the population included in study. A significant association was observed between hypoalbuminemia and lymphopenia in the studied population.

AUTHOR CONTRIBUTION

Armaghana Qamar Khan: Conception and Study design, Article drafting, data analysis

Iqra Butt: Manuscript writing, data analysis

Sundas Ali: Study design, data collection, article drafting, reviewing of manuscript and critical revisions
Summaya Sohail: Data collection, data analysis, manuscript writing
Mariam Khan Qamar: Analysis of results
Furqan Tahir: Manuscript writing, critical analysis of results

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