International Journal of Science Academic Research
Vol. 03, Issue 05, pp.3803-3808, May, 2022
Available online at http://www.scienceijsar.com

ISSN: 2582-6425

Research Article

CORRELATION BETWEEN LIVER AND KIDNEY FUNCTIONS WITH C-REACTIVE PROTEIN IN COVID-19 PATIENTS: AN OBSERVATIONAL STUDY

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Received 19th March 2022; **Accepted** 05th April 2022; **Published online** 30th May 2022

Abstract

Coronavirus disease outbreak was caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Numerous studies have shown impact of this virus spread on liver and kidney. In the present study we aimed to evaluate the correlation of C-reactive protein with liver and kidney biochemical marker levels. Laboratory results were obtained from 40 patients with confirmed RT-PCR positive for SARS-CoV-2, who were admitted in the hospital from 14 May, 2021 to 30 June, 2021. Liver function tests, kidney function tests and C-reactive protein were included to explain the relationship among them in COVID-19 patients. The liver and/or kidney biochemical parameters being analyzed were unevenly distributed among patients with parameters either increased other decreased in comparison to normal reference range. Interestingly, we observed significant positive correlation between C-reactive protein (CRP) levels and SGOT (Aspartate Aminotransferase), alkaline phosphatase, urea and creatinine. Furthermore, other markers such as total protein and albumin were found to be negatively correlated with CRP levels in the serum of COVID-19 patients. The study demonstrated aberrant levels of various parameters for liver and / or kidney function and showed association with CRP. Therefore, measurement of these parameters might assist in monitoring the detrimental effects of SARS-CoV-2 infection on multiple organs.

Keywords: *:* SARS-CoV-2, COVID-19, SGOT, SGPT, CRP.

INTRODUCTION

The outbreak of coronavirus disease-19 (COVID-19) poses a great challenge to public health worldwide. The causative pathogen for COVID-19 has been identified as severe acute respiratory syndrome coronavirus 2 (SARS COV-2), a newly emerging virus originating from *Coronaviridae* family (genus Betacoronavirus, subgenus Sarbecovirus) [1]. It was presumably derived from a bat SARS-like coronavirus and transmitted to human after the mutations in the spike (S) and nucleocapsid (N) protein [2]. This virus is primarily transmitted through respiratory droplets, direct human to human contact, or touching the contaminated surface [3], [4].
Patients with COVID-19 have a wide range of symptoms ranging from mild to severe illness. They mainly present with clinical symptoms of dry cough, dyspnea, muscle or body aches, sore throat and fever, which in some cases lead to a critical condition necessitating the need of Intensive care [5]. Although lung is the main target of SARS-CoV-2, multiple extra pulmonary organ dysfunctions have also been reported. Previously, studies have shown abnormal liver function parameters in patients with COVID-19 [6]. The possible damaging effect of coronavirus on liver cells could be direct or indirect. In deceased SARS patients, SARS-CoV protein was expressed on liver cells itself. Also, liver injury may result from elevated inflammatory responses which culminate to immune-pathological reactions [7]. In addition, patients diagnosed with COVID-19 have displayed kidney damage through acute kidney injury, proteinuria, hematuria or increased levels of Creatinine or blood urea [8].

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Moreover, kidney disease may occur in patients due to the presence of ACE2 receptors that supports viral entry. In a study, autopsy reports have suggested necrosis and immunological reactions such as lymphocyte infiltration in kidney tubules [9]. Therefore, indicating role of various immunological and inflammatory markers in SARS-CoV-2 positive patients. C-reactive protein (CRP) is one such acute phase protein that serves as an early marker of inflammation and infection [10]. It has been found to be an important marker that is significantly elevated in mild to severe COVID-19 patients [11]. In a recent study, CRP levels were predicted as early diagnostic marker for pneumonia and markedly increased CRP levels in pneumonia in the same study were shown to be associated with severity [12]. Several studies have indicated CRP as prognostic marker in COVID-19 [13]. However, in the present study we determined the levels of CRP and other biochemical liver and kidney function parameters in the serum sample of COVID-19 patients. This study aims to correlate the serum biochemical markers of liver and kidney function with CRP levels. This analysis will also assist in predicting the favorable outcome of patients while receiving treatment at the hospital.

METHODOLOGY

Study design and Patient criteria

The study was conducted as single-centered, retrospective and observational study. This included all patients who were diagnosed as COVID-19 positive through Real-time Polymerase Chain Reaction (RT-PCR). The COVID-19 positive patients were grouped as mild to moderate while receiving treatment at National Institute of TB and Respiratory

Disease from 14 May 2021 to 30 June, 2021. For inclusion in the analysis, patients must be ≥18 years of age. The patients who presented with mild to moderate disease and were receiving oxygen supplement therapy were included. Those patients who were RT-PCR negative for COVID-19 (post COVID-19) were excluded from the present study. Patients requiring or supported on ventilator were not included in analysis.

Biochemical function abnormalities

Liver and kidney functions parameters

The biochemical markers were assessed in VITROS® 4600 automatic analyzer using Dry Chemistry technique. Liver test abnormalities were defined as elevations of the following enzymes in serum: SGOT > 40 U/L, SGPT > 40 U/L, alkaline phosphatase > 129 U/L, total bilirubin (T Bil) > 1.10mg/dl and direct bilirubin (D Bil) > 0.30mg/dl. The other markers examined were total protein (Normal reference range; 6.3-8.7 g/dl) and albumin (Normal reference range; 3.5-5.2 g/dl). Urea > 50 mg/dl and Creatinine > 1.2 mg/dl were considered as abnormal kidney function parameters. As COVID-19 is a new emerging infectious disease, these parameters should be carefully monitored for patients to assist in better specific management of the disease and to predict favorable outcome.

C-Reactive Protein: An Inflammatory Marker

The CRP levels were determined in the serum sample of COVID-19 positive diagnosed patients using VITROS® 4600 automatic analyzer based on turbidimetric-inhibition immunoassay. The CRP values above 5mg/L were considered as elevated levels.

Statistical Analysis

All the statistical analysis was performed using R software (version 4.1.0). For normally distributed data, Pearson correlation analysis was used to obtain correlation coefficient among biochemical liver or kidney parameters and CRP. A p-value of <0.05 was considered statistically significant (two-tailed).

RESULTS

Characteristics of the studied cases

A total of forty cases were included in the study. The mean age was 51.57 with a range of 19 to 89. The patients with RT-PCR SARS-CoV-2 positive were only recruited for the study. The population of COVID-19 patients included approximately 30% female and 70% male. Thus, indicating the more probability of diseased conditions in male. The demographic and laboratory features of study participants have been depicted in table 1.

Quantification of Laboratory parameters in COVID-19 patients

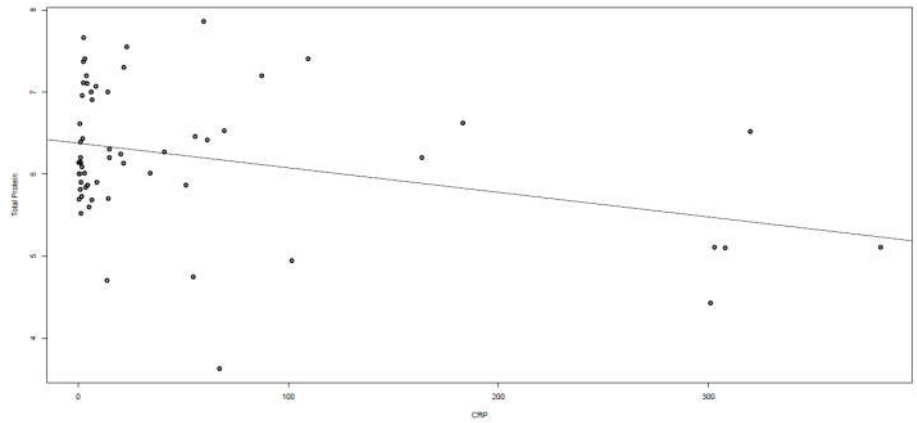
In the current study, we observed aberrant levels of liver and kidney function parameters in serum of COVID-19 patients. From the forty patients recruited in our study, 62.5% of patients had raised liver enzymes. The percentage of males with elevated levels for both SGOT and SGPT was 80%. The levels of alkaline phosphatase were also found to be high in few COVID-19 patients. Other parameters such as total and direct bilirubin were also increased, and nearly half of patients had raised direct bilirubin. In contrast, total protein and albumin levels were decreased in COVID-19 patients. The decrease in these parameters was more commonly present in males, 65% males had decreased total protein levels and 69% males had decreased albumin levels. The mean ± S.D of these parameters is tabulated in table 2. Renal injury can be a consequence of SARS-CoV-2 infection in COVID-19 patients. Therefore, in the present study the levels of blood urea and creatinine were also measured. The mean values for blood urea and creatinine were 47.51 ± 26.15 and 0.64 ± 0.34 respectively. Moreover, 92% of patients with raised urea levels were males. Creatinine levels were not considerably increased in our study. Altogether, these results corroborated with previous findings of multiple organ dysfunction in COVID-19 patients [14].

Levels of C-reactive protein in COVID-19 patients

COVID-19 is characterized by aberrant host immune response sustained with cytokine storm and massive inflammation. CRP is considered as a sensitive early biomarker of inflammation, infection and tissue injury. The levels of CRP are increased rapidly in acute inflammatory responses and have also been suggested as an efficient biomarker for disease severity in COVID-19. We next sought to determine the levels of CRP in serum of COVID-19 patients. Interestingly, we observed drastically elevated levels of CRP even in mild to moderate patients recruited in the study. Out of all patients screened for CRP levels at the time of admission, 71% had raised CRP levels. Moreover, 90% of patients with high levels of CRP were males. As evident in table 1, the average level of CRP was 51.72 ± 91.51 (Normal reference range <5mg/L). Thus, these observations, verified the fundamental role of CRP during immune response development (inflammation) in COVID-19 patients. Besides, as CRP and other routine biochemical markers are aberrantly expressed in COVID-19 patients, it was of interest to study the correlation between CRP and other parameters. This correlation analysis with CRP might assist in predicting the disease progression in patients by using routine parameters also.

Correlation of CRP with various biochemical laboratory parameters

The levels of these routine functional parameters were analyzed to demonstrate the correlation between CRP and its levels. The Pearson coefficient correlation analysis was employed for this purpose. Among the twelve parameters being analyzed, the significant correlation was obtained only for six parameters. The Pearson's coefficient (r) for each of the parameter has been mentioned in table 1. In the liver panel of biochemical markers, we found negative correlation for total protein (r= -0.33, p=0.0126) and albumin (r= -0.46, p=0.0003). Next, bilirubin (total and direct), SGPT and electrolytes did not significantly correlate with CRP. As evident in figure 1, SGOT (r= 0.31, p=0.0193) and alkaline phosphatase (r= 0.35, p=0.0064) had positive correlation with CRP. Blood urea and creatinine levels were used for correlation analysis of renal biochemical markers. Remarkably significant positive correlation was derived for blood urea (r= 0.34, p=0.0085) and creatinine (r= 0.40, p=0.0021). The Pearson correlation plots for renal markers are represented in figure 2.



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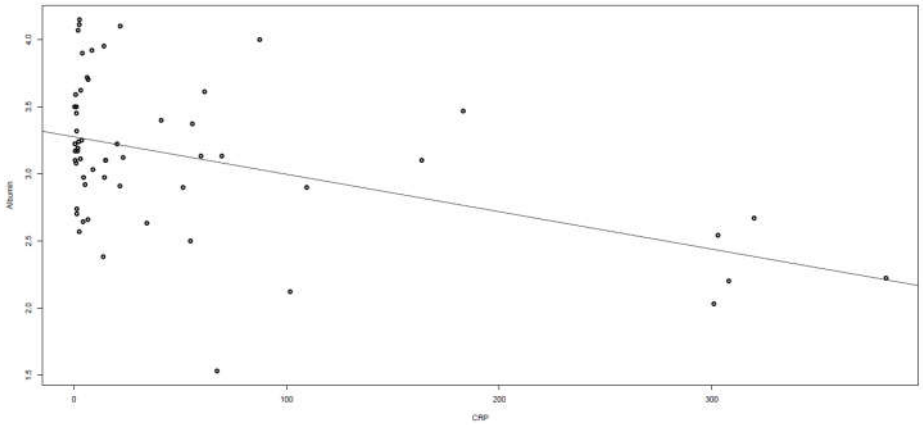

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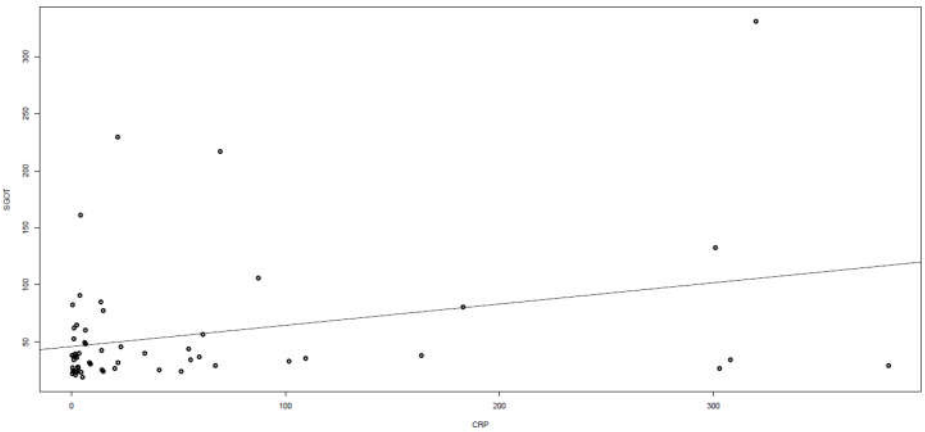

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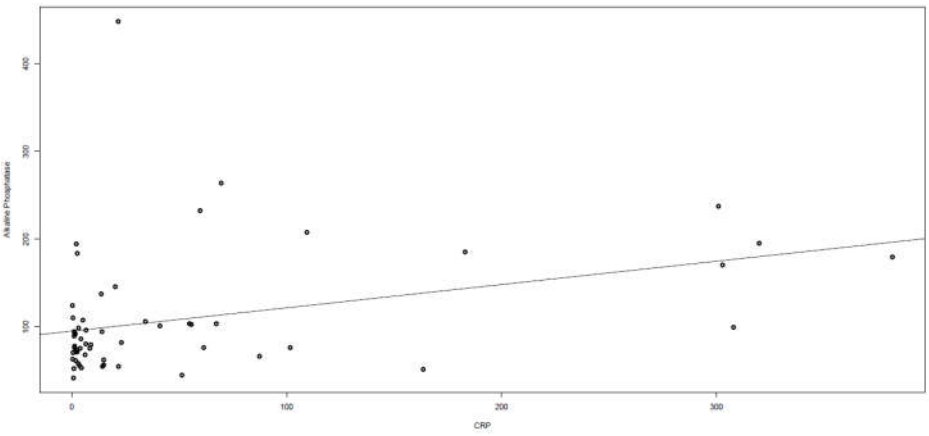
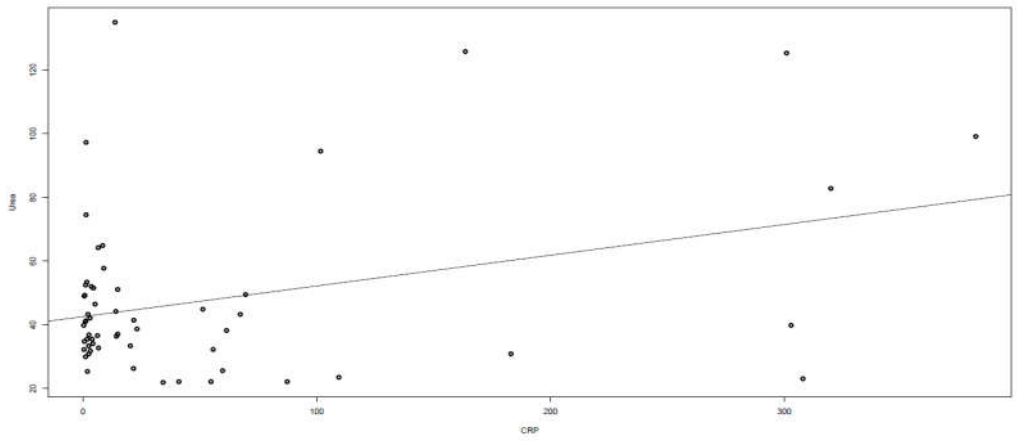


(D)

Figure 1: Correlation analysis of liver function parameters. Pearson's coefficient (r) was calculated to correlate different liver function parameters with inflammation biomarker (CRP). Levels of (a) Total protein (r = -0.33) and (b) Albumin (r = -0.46) were found to decline with increase in CRP in COVID-19 patient serum samples. The positive correlation was attained for (c) SGOT (r = 0.31) and (d) Alkaline phosphatase (r = 0.35). Results were analyzed using student's t-test (two-tailed) and p-value < 0.05 was considered statistically significant



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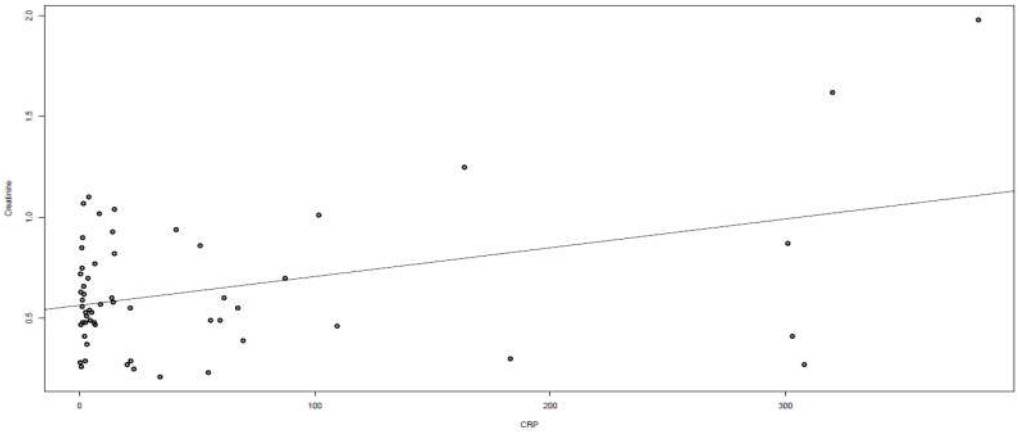

(B)

Figure 2: Correlation analysis of kidney function parameters. The renal biomarkers were evaluated to assess correlation with CRP using Pearson coefficient. (a) Blood urea (r = 0.34) and (b) Creatinine (r = 0.40) were positively correlated with CRP. Results were analyzed using student's t-test (two-tailed) and p-value < 0.05 was considered statistically significant

Table 1. Baseline characteristics and laboratory findings of COVID-19 patients

Demographic features		
Sex	Mean Age ± SD	Percentage
Male	56.27 ± 15.57	70
Female	48.24 ± 18.84	30
Total	51.57 ± 16.55	

Clinical Biochemical Parameters			
S.No	Biochemical Function Parameter	Mean ± SD	95% Confidence Interval
1	Total Protein (g/dl)	6.22 ± 0.85	6.0 – 6.4
2	Albumin (g/dl)	3.13 ± 0.56	3.0 – 3.3
3	Total Bilirubin (mg/dl)	0.79 ± 0.34	0.71 – 0.89
4	Direct Bilirubin (mg/dl)	0.43 ± 0.40	0.33 – 0.54
5	SGOT (U/l)	55.63 ± 56.48	40.8 – 70.5
6	SGPT (U/l)	78.81 ± 69.96	60.42 – 97.21
7	Alkaline Phosphatase (U/l)	108.72 ± 69.7	90.4 – 127.1
8	Urea (mg/dl)	47.51 ± 26.15	40.6 – 54.4
9	Creatinine (mg/dl)	0.64 ± 0.34	0.55 – 0.73
10	Na^+ (mmol/l)	135.32 ± 7.27	133.41 – 137.23
11	K^+ (mmol/l)	4.24 ± 0.63	4.08 – 4.41
12	Cl^- (mmol/l)	96.60 ± 7.77	94.56 – 98.65
13	CRP	51.72 ± 91.51	27.3 – 76.2

Table 2.Pearson's Coefficient Correlation test

S.No	CRP with	Pearson Coefficient (r)	P value
1	Total Protein	-0.33	0.0126*
2	Albumin	-0.46	0.0003*
3	Total Bilirubin	0.16	0.2419
4	Direct Bilirubin	-0.008	0.9469
5	SGOT	0.31	0.0193*
6	SGPT	0.004	0.9746
7	Alkaline Phosphatase	0.35	0.0064*
8	Urea	0.34	0.0085*
9	Creatinine	0.40	0.0021*
10	Na^+	0.0005	0.9965
11	K^+	0.10	0.4586
12	Cl^-	-0.05	0.6809

Note: p value less than 0.05 are considered statistically significant and have been marked by '*'.

This correlation analysis of these parameters indicates the critical role of various routine parameters in COVID-19 patients. Therefore, functional parameters such as total protein, albumin, SGOT, alkaline phosphatase, urea and creatinine should be considered in future for prediction of disease progression.

DISCUSSION

COVID-19 is a highly contagious disease characterized by respiratory illness and diverse systemic clinical presentations [15]. These abnormalities are reflected by remarkable differences in levels of the routine biochemical parameters based on disease severity. While COVID-19 is well known for causing respiratory symptoms, it can also impact

extrapulmonary organs. Majorly, array of parameters increased during infection includes inflammatory, coagulation biomarkers, tissue specific injury and derangement of CBC [16] [17] [18] [19]. The tissue injury in COVID-19 patients might include hepatocellular and/or renal injury. In the present study, we investigated the effect of COVID-19 infection on liver and kidney biochemical functions. We observed noticeably increased SGOT, SGPT and direct bilirubin levels in COVID-19 patients. There are studies reporting similar findings of raised liver enzyme levels in COVID-19 patients [20]. In addition, a recent study showed that bilirubin levels were significantly increased in mild and severe COVID-19 patients [21]. Conversely, we obtained notable decline in total protein and albumin in those patients. Decrease in the levels of protein and albumin could be attributed to poor nutritional intake and the release of various cytokines, majorly including acute-phase cytokines. These cytokines play crucial role in downregulating the synthesis of albumin in liver after onset of COVID-19 [22]. Elevated levels of blood urea were also obtained in the present study. The ACE2 receptor known to play critical role in binding with SARS-CoV-2 virus is widely present in kidney. Thus, direct interaction might be responsible for elevated renal markers in COVID-19 patients [9]. As creatinine levels were not raised effectively in the present set of patients, these results indicate only pre-renal injury in COVID-19 patients. Further extensive study with large number of samples is required for analyzing the effect of SARS-CoV-2 on kidney function.

Serious COVID-19 complications have been associated with remarkable inflammation which is characterized by the release of several inflammatory markers such as cytokines, interferons and interleukins [23]. The synthesis of acute-phase proteins is increased under influence of these inflammatory markers. C-reactive protein is one such acute phase protein synthesized by liver which is a highly sensitive biomarker for inflammation, tissue damage and infection. Elevated levels of CRP are responsible for complement system activation and pathogen removal through phagocytosis [24]. There are several studies reporting significantly elevated levels of CRP in COVID-19 patients [25] [26] [27]. The patients recruited in the present study, demonstrated similar rise in CRP levels. Also, CRP levels were observed to gradually increase among patients with mild to moderate severity conditions. Hence, these results are consistent with previous report establishing the role of CRP in disease severity and progression [28]. The significant increase in levels of CRP along with liver and kidney function markers suggested immune-mediated damage to these organs as a result of severe inflammation following COVID-19 infection. The liver and kidney function test are routine investigation at the time of patient admission to the hospital. Therefore, it was of interest to correlate their levels with CRP in serum of COVID-19 patients in order to utilize it for prediction of patient health with respect to disease progression. A significant positive correlation was observed between the inflammatory marker, CRP with liver enzymes including SGOT and alkaline phosphatase. Similar results were obtained in a study which showed positive correlation with SGOT, SGPT, ALP and GGT [29]. A very weekly positive correlation of CRP with SGPT was also obtained in our study, but this observation was not statistically significant. The total protein and albumin were observed to be negatively correlated with CRP in the present study. Although these results are contrary to a previous report which indicated positive correlation among them [29], the decrease in total protein and albumin is consistent with reduced serum concentration in COVID-19 patients [29] [30]. Furthermore, kidney function markers (Blood urea and creatinine) were also analyzed for correlation with CRP and to our interest we observed significant positive correlation. These results corroborated previous findings which stated positive correlation of CRP with blood urea and creatinine [8] [29]. Association between various function parameters highlighted the multiple organ involvement in COVID-19 outbreak. Patients admitted in the hospital were routinely examined for liver, kidney function test and CRP levels. Patients demonstrated reduction in levels of enzymes such as SGOT, SGPT and alkaline phosphatase at the time of discharge which were found to be raised at initial presentation. Also, total protein and albumin were observed to increase after treatment at hospital. Levels of blood urea in serum of COVID-19 patients were found to be declined as compared to levels obtained at the time of admission. Considering the hospital data, more than 90% of patients were discharged after being cured from the disease. Consequently, these results indicate the utility of routine liver and kidney biochemical markers along with CRP for monitoring the disease progression in patients admitted for the treatment of COVID-19 infection.

Conclusion

In conclusion, patients admitted to the hospital with SARS-CoV-2 infection had an abnormal liver and kidney profile. These patients demonstrated enhanced immune response mediated by inflammatory markers. The routine liver and kidney biochemical markers were found to be associated with raised levels of CRP (inflammatory marker). These findings may help to elucidate the role of specific liver and kidney function parameters in COVID-19 disease progression. Thus, this study helps in predicting and improving disease outcomes in patients which will subsequently assist in early diagnosis and prognosis at the primary level hospital and therefore, reduce COVID-19 associated morbidity and mortality.

Acknowledgments

The authors wish to thank Department of Biochemistry of National Institute of Tuberculosis and Respiratory Diseases. We highly appreciate the technical staff of Biochemistry department for their tremendous hard work during COVID-19 pandemic.

Conflict of Interest: The authors declare that there is no conflict of interest.

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