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Correlation of biochemical profile at admission with severity and outcome of COVID-19

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ABSTRACT

Background

COVID-19 was detected in China in December 2019. The rapid dissemination and novelty of the disease resulted in an epidemic. This study aimed to identify biochemical parameters at admission that can be used to categorize severity and outcome of COVID −19 infection.

Materials and Methods

This cross-sectional study was conducted at Allied Hospitals of RMU from April 2020 to July 2020. It included 128 randomly selected confirmed COVID-19 patients. At admission, biochemical profile (total bilirubin, alanine aminotransferases {ALT}, aspartate aminotransferases {AST}, urea, creatinine, uric acid, sodium, potassium, and chloride were correlated with severity and outcome of COVID-19 by employing t-tests and ANOVA where required. Cut-off values to predict disease severity and outcome were calculated using ROC curve.

Results

The study comprised 46.1% non-severe, 29.7% severe, and 24.2% critical COVID-19 patients. 84.4% patients improved and 15.6% expired. Urea was increased in critical disease patients ($p < 0.000$). Higher ALT (p 0.030) and AST (p 0.004) levels were noted in severe and critical disease. Sodium (p 0.001) and chloride (p 0.026) were decreased in critical disease. Patients who expired had increased urea (p 0.000), ALT (p 0.040) and AST (p 0.002). At admission, urea >42.7 mg (sensitivity of 64.7%, specificity of 87.5%), AST >43.5 IU/L (64% sensitivity, 60% specificity), and sodium <136.9 mmol/L (sensitivity of 70.6%, specificity of 71.2%) predicted critical COVID-19 infection.

Conclusion

At admission, increased urea, AST, and ALT along with decreased sodium can help in identifying COVID-19 patients with severe illness and poor outcome.

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Abbreviation

AS: wrote the original manuscript, quality control; MK: conception of idea, reviewed final version of the article; JM: Data collection; NAC: Data analysis, manuscript editing; MMK: Review of final version of manuscript; TY: Data collection; HWB: Data analysis

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome virus (SARS-CoV-2) was detected in Wuhan, Hubei, China in December 2019, causing a cluster of pneumonia cases[1]. Rapid dissemination and novelty of the disease with a lack of specific intervention resulted in an epidemic[2]. As the disease became a global concern, it was declared a Public Health Emergency of International Concern (PHEIC) by the World Health Organization (WHO). Coronavirus is an enveloped positive-sense RNA virus that matures in epithelial cells and mainly causes respiratory infection, including severe acute respiratory syndrome (SARS), and acute exacerbation of chronic bronchitis (AECB) in humans[3]. Recent data suggests COVID-19 to be regarded as a multi-systemic disease involving the cardiovascular, respiratory, gastrointestinal, neurological, hematopoietic, and immune system [4–6].

The biochemical profile of patients plays an important component in estimating the severity and prognosis of the disease. Several studies have focused on various biochemical markers such as urea, alanine aminotransferases (ALT), aspartate aminotransferases (AST), and sodium levels in COVID-19 infections. These parameters have not only been associated with the severity of COVID-19 infection but also with the worst outcomes in terms of in-hospital mortality.

This study aims to identify at admission biochemical parameters that can discriminate between patients with mild to moderate (non-severe), severe, and critical disease in confirmed COVID-19 infection cases. This will help in prompt identification and focused management of COVID-19 patients from the day of admission.

2. Materials and methods

This cross-sectional study was conducted at the Allied Hospitals of Rawalpindi Medical University, Rawalpindi, Pakistan (RMU) from April 2020 to July 2020 after approval from Institutional Research Forum (Reference no. 46/IREF/RMU/2020). A sample size of 128 was calculated by using WHO Sample Size Calculator keeping in mind anticipated 9% disease proportion that was the approximate positivity rate of new COVID-19 infections during April 2020, 5% margin of error, and 95% confidence level. Confirmed COVID-19 patients admitted during the study period were included by simple random sampling (lottery method) after informed consent. Confirmed COVID-19 meant that patients had clinical features suggestive of COVID-19 and positive reverse transcriptase-polymerase chain reaction (RTPCR) of nasal and pharyngeal swabs.

The severity of COVID-19 was graded into non-severe (mild to moderate), severe and critical disease. Non-severe disease included patients with minor respiratory complaints, fever, respiratory rate <30 breaths/minute, mean oxygen saturation ≥ 94%, and no or <50% involvement on pulmonary imaging. Patients with severe disease in addition to fever, and respiratory tract symptoms had one of the following; 1) respiratory distress, 2) respiratory rate ≥30 breaths/minute, 3) mean oxygen saturation <94%, 4) arterial blood oxygen partial pressure/oxygen concentration ≤300 mmHg, and 5) pulmonary imaging showing >50% involvement. Patients with critical disease suffered from one of the following conditions i.e., respiratory failure, septic shock, and multi-organ failure.

On admission, following biochemical parameters of patients were obtained; 1) liver function tests [LFT's]- total bilirubin, alanine aminotransferases [ALT], aspartate aminotransferases [AST], 2) renal function tests [RFT's]- Urea, Creatinine, Uric acid, and 3) serum electrolytes- Sodium, Potassium, and Chloride. Each patient was managed according to national and international guidelines by a multidisciplinary team. Patients were followed up until recovery and discharge or death.

Biochemical parameters along with age, gender, comorbidities, severity, and outcome of the disease with reference to each patient was noted on a specifically designed proforma. Data was entered and analyzed using Statistical Package for Social Sciences (SPSS). Qualitative variables like age groups, gender, comorbid, outcome, and severity of COVID-19 were represented as frequencies and percentages. Quantitative variables i.e., age, and biochemical parameters were represented as mean±SD. Age wise patients were divided into three groups; <40 years, 41–60 years and >60 years. Chi-square test and One-Way Analysis of Variance (ANOVA) were applied for comparing the groups. Independent samples Kruskal-Wallis tests were applied for comparing quantitative variables across categories of qualitative variables. Receiver operator curves (ROC) were obtained for detecting the cut off points of significant biochemical parameters for predicting severity and outcome of

disease. Cut-off points for significant biochemical parameters were selected on the basis of sensitivity and specificity. A p-value of ≤ 0.05 was considered significant.

3. Results

During the study period, 1119 COVID-19 patients were managed at Allied Hospitals of RMU. Of the 128 included patients, 72 (56.3%) were male and 56 (43.8%) female. Mean age of patients was 50.41 ± 17.97 years. Sixty-four (50%) patients had no comorbids while the rest 64 (50%) had comorbidities. At the time of admission, fifty-nine (46.1%) patients had non severe, 38 (29.7%) had severe disease, and 31 (24.2%) had critical disease. One hundred and eight (84.4%) patients improved while 20 (15.6%) expired. All the deaths were observed in critical patients (p < 0.000).

Of the 59 patients with non-severe COVID-19 illness, 37 (62.71%) were male and 22 (37.29%) female. Their mean age was 43.05 ± 17.31 years. Eighteen (47.37%) of severe COVID-19 illness patients were male and 20 (52.63%) female. Their mean age was 49.87 ± 15 years. Out of the 31 critical patients, 17 (54.84%) were male while 14 (45.16%) were female. Mean age of these patients was 65.06 ± 13.5 years.

Based on one-way ANOVA analysis mean age significantly differed among non-severe, severe, and critically ill patients. Patients with critical illness were significantly older as compared to those with severe and non-severe disease (p < 0.000). Severity of COVID-19 illness significantly correlated with presence of comorbidities (p < 0.000). Mean age of the patients who expired (65.4 ± 12.50 years) was significantly higher compared to those who survived (47.63 ± 17.48 years), (p < 0.000). Out of 20 patients who expired, 11 (55%) were male and 9 (45%) female. Seventeen (85%) of these had comorbidities (p 0.001). Seventeen (15%) had past history of medical illness. Correlation of age, gender, and comorbidities with disease severity and outcome is given in Table 1.

Urea levels were significantly higher in patients aged greater than 60 years (p < 0.000). Creatinine and uric acid levels were significantly higher in females as compared to males (p = 0.001, p = 0.038) respectively. Females also had significantly lower levels of ALT and bilirubin as compared to males (p = 0.005, p = 0.022) respectively. Table 2 gives details in this regard.

Urea levels were significantly higher in critical disease as compared to severe and non-severe disease (p < 0.000). ALT and AST levels were significantly higher in severe and critical disease as compared to non-severe disease (p = 0.030, p = 0.004) respectively. Sodium and chloride levels were significantly lower in critical disease (p = 0.001, p = 0.026) respectively. Patients who died in hospital also had significantly higher levels of urea, ALT, and AST as compared to those who survived (p < 0.000, p = 0.040, p = 0.002). Table 3 provides details in this regard.

Sodium less than cut off point of 136.9 had sensitivity of 70.6% and specificity of 71.2% in detecting critical COVID-19 infection. A cut off point of 42.7 for urea and 43.5 for AST had sensitivity of 64.7% and 64% respectively and specificity of 87.5% and

Table 1. Relationship between severity of COVID-19 with gender, presence of comorbidities and age.

		Severity (n & %)				Outcome (n & %)		
Parameter	Groups	Non-severe	Severe	Critical	p-value	Discharged	Dead	p-value
Gender	Male	37 (51.4%)	18 (25%)	17 (23.6%)	0.326*	61 (84.7%)	11 (15.3%)	0.902
	Female	22 (39.3%)	20 (35.7%)	14 (25%)		47 (83.9%)	9 (16.1%)	
Comorbid	Yes	19 (29.7%)	19 (29.7%)	26 (40.6%)	<0.000*	47 (73.4%)	17 (26.6%)	0.001
	No	40 (62.5%)	19 (29.7%)	5 (7.8%)		61 (95.3%)	3 (4.7%)	
Age	Mean ± SD	43.05 ± 17.3	49.9 ± 15	65.06 ± 13.5	<0.000**	47.63 ± 17.48	65.4 ± 12.50	<0.000

* Chi-square test
** One-way Analysis of Variance

Table 2. Comparison of biochemical parameters between gender and age groups.

Biochemical profile (mean and SD)	Total	Gender			Age groups			
		Male	Female	p-value*	≤ 40 years	41–60 years	> 60 years	p-value**
Urea (mg/dl)	32.60 (27.15)	33.50 (25.05)	32.60 (37.45)	0.076	29.30 (14.50)	31.20 (27.33)	52.50 (42.65	**< 0.000**
Creatinine (mg/dl)	1.00 (0.50)	1.00 (0.38)	1.30 (1.15)	**0.001**	1.00 (0.35)	0.90 (0.50)	1.00 (0.30)	0.348
Uric acid (mg/dl)	5.23 (1.83)	4.96 (1.89)	5.89 (2.38)	**0.038**	5.41 (1.38)	4.97 (2.12)	5.61 (2.70)	0.623
ALT (U/L)	41.00 (40.50)	45.50 (36.75)	28.00 (41.50)	**0.005**	52.00 (46.50)	41.00 (32.00)	34.00 (45.50)	0.684
AST (U/L)	45.00 (22.00)	40.00 (17.00)	50.00 (33.00)	0.585	39.00 (18.50)	40.00 (26.00)	50.00 (20.50)	0.241
Total bilirubin (mg/dl)	0.50 (0.45)	0.60 (0.55)	0.40 (0.25)	**0.022**	0.30 (0.20)	0.50 (0.50)	0.60 (0.50)	0.358
Sodium (mmol/L)	141.00 (5.00)	140.50 (5.75)	141.00 (5.00)	0.511	144.00 (9.00)	141.00 (4.00)	139.00 (10.50)	0.437
Potassium (mmol/L)	4.40 (0.65)	4.30 (0.80)	4.5 (1.01)	0.270	4.40 (0.70)	4.40 (1.14)	4.30 (0.65)	0.084
Chloride (mmol/L)	102.00 (5.00)	102.50 (6.25)	102.00 (5.50)	0.798	103.00 (4.50)	102.00 (7.00)	101.00 (5.50)	0.614

ALT; Alanine aminotransferase, AST; Aspartate aminotransferase
* Independent-samples T test
** One-way Analysis of Variance

Table 3. Comparison of biochemical parameters with severity of COVID-19 infection and outcome.

Biochemical profile (mean and SD)	Severity			p-value	Outcome		p-value p-value
	Non-severe	Severe	Critical		Discharged	Dead	
Urea (mg/dl)	27.10 (9.80)	34.20 (54.98)	51.66 (30.05)	< 0.000	31.15 (14.00)	52.50 (29.10)	<0.000
Creatinine (mg/dl)	1.00 (0.45)	0.90 (0.25)	1.25 (0.38)	0.328	1.00 (0.43)	1.20 (0.60)	0.132
Uric acid (mg/dl)	5.20 (1.32)	4.68 (2.63)	5.61 (3.50)	0.903	5.22 (1.79)	5.33 (4.08)	0.749
ALT (U/L)	30.00 (32.50)	45.50 (48.00)	44.00 (41.00)	0.030	36.00 (34.50)	47.00 (40.00)	0.040
AST (U/L)	31.00 (25.00)	47.50 (25.00)	47.50 (30.00)	0.004	39.50 (24.50)	46.00 (48.00)	0.002
Total bilirubin (mg/dl)	0.40 (0.30)	0.65 (0.78)	0.55 (0.38)	0.057	0.45 (0.43)	0.60 (0.40)	0.495
Sodium (mmol/L)	143.00 (4.50)	140.00 (2.75)	137.00 (10.25)	0.001	140.50 (5.25)	141.00 (14.00)	0.441
Potassium (mmol/L)	4.50 (0.62)	4.30 (1.13)	4.29 (0.58)	0.101	4.45 (0.76)	4.28 (0.50)	0.458
Chloride (mmol/L)	103.00 (4.00)	102.50 (9.00)	100.00 (6.95)	0.026	102.65 (5.50)	101.40 (7.00)	0.424

ALT; Alanine aminotransferase, AST; Aspartate aminotransferase

Table 4. Area under curve (AUC), cut-off values, sensitivity and specificity of different biochemical parameters for critical patients and poor outcome (mortality).

Parameter	Area under curve	p-value	Cut-off value	Sensitivity	Specificity
Sodium	0.741	0.009	136.9	70.6%	71.2%
Urea	0.798	0.001	42.7	64.7%	87.5%
AST	0.751	0.001	43.5	64%	60%
Outcome					
Urea	0.778	< 0.000	42.7	70%	84%
AST	0.762	0.002	45.5	62.5%	59%

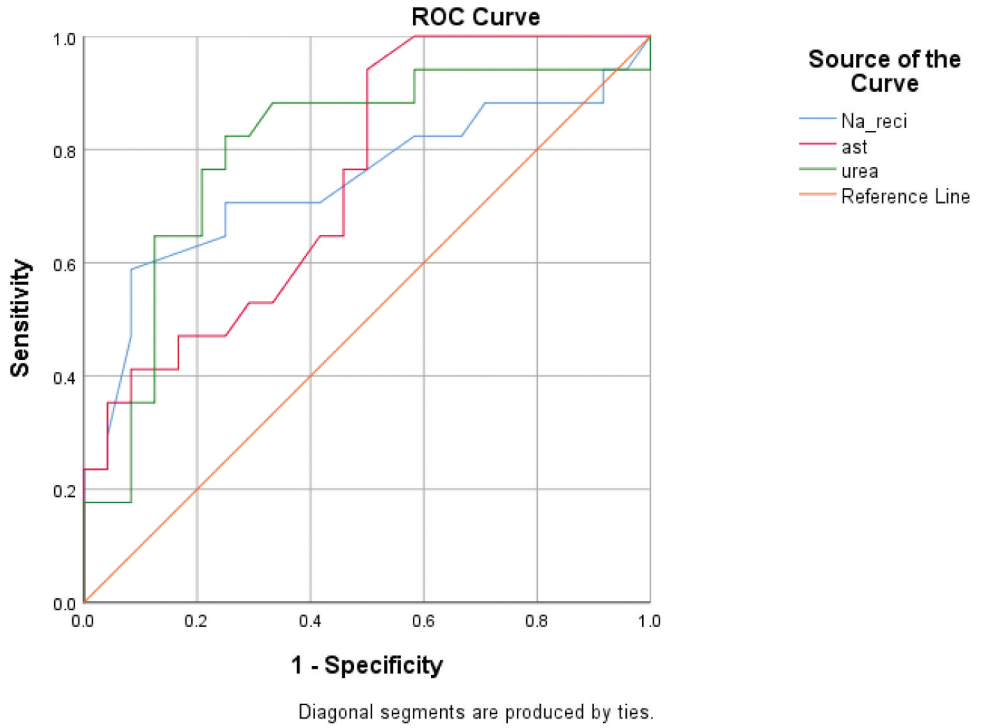

Figure 1. ROC curve showing levels of sodium AST and urea for detecting critical COVID-19 infection.

60% respectively for detecting critical COVID-19 infection. A cut off point of 42.7 for urea and 45.5 for AST had sensitivity of 70% and 62.5% respectively and specificity of 84% and 59% respectively for detecting poor outcome (mortality). Table 4, Figure 1,Figure 2 give details in this regard.

4. Discussion

The pandemic characteristics of COVID-19 infection has made it a global concern. There is limited knowledge available at present, and advances in diagnostic technologies and treatment are a need of the hour. Diagnostic tests including RT-PCR and antibody tests are very important, helping in epidemiology and early diagnosis of the disease[7]. Monitoring of clinical, hematological, and biochemical parameters is an essential component of COVID-19 patient management. Severity and outcome categorization based on biochemical parameters is important. Bilirubin, ALT, AST, creatinine kinase (CK), C reactive protein (CRP), lactic dehydrogenase (LDH),

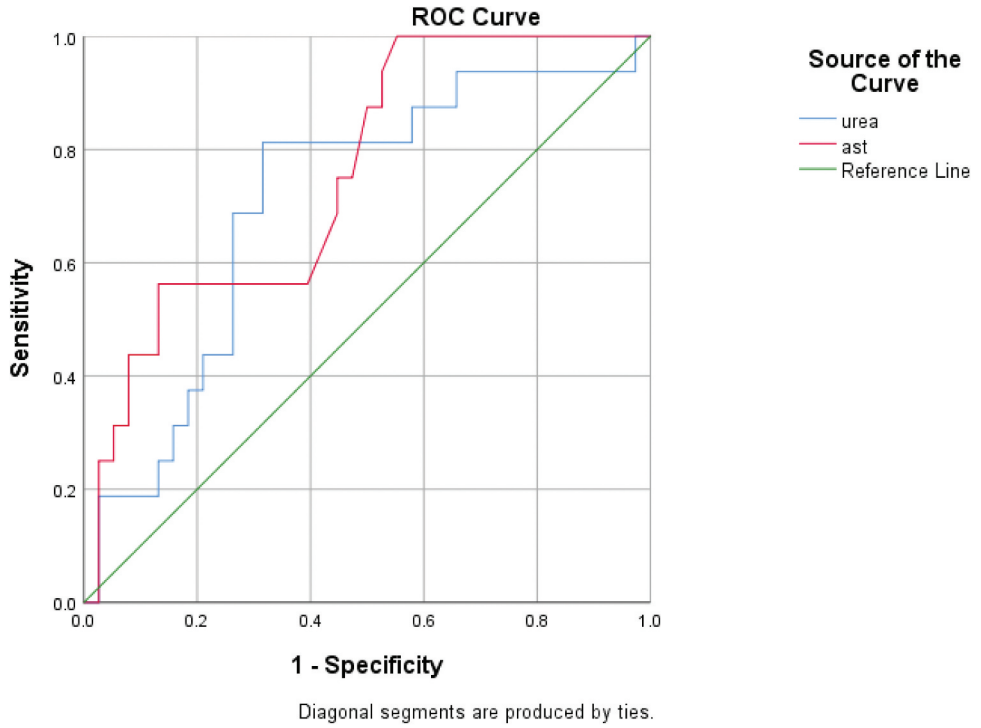

Figure 2. ROC curve showing levels of urea and AST for detecting in-hospital mortality.

cardiac troponin, ferritin, and fibrinogen have been evaluated in this regard [8–10]. In resource deficient scenarios like ours, CRP, LDH, cardiac troponin, ferritin and fibrinogen may not be available or are available at certain working hours. On the other hand simple biochemical parameters like LFTs, RFTs, serum electrolytes are available 24/7. Knowing the relationship between these parameters at admission with severity and outcome in our patients is thus important.

Identification of biochemical parameters that are available at the time of admission helps in the categorization of COVID-19 severity and outcome, which is an important utility for healthcare professionals. It can help in efficient triage of patients, personalize treatments, monitor clinical progress, and allocate proper resources at all levels of care to mitigate morbidity and mortality. This study focused on the same concept. Important findings of this study in this context include: 1) association of increased urea, ALT and AST along with decreased sodium and chloride levels with severity of COVID-19 infection, and 2) at admission, urea >42.7 mg/dl, AST >43.5 iu/L, and Sodium <136.9 mEq/L association with critical illness. We additionally noted correlation of increasing age and comorbidities with severity of COVID-19 infection, and poor outcome.

Severe COVID-19 illness leads to systemic inflammatory response and multiorgan dysfunction that can affect renal function. COVID-19 patients with cofactors like dehydration may have increased blood urea levels. COVID-19 also infects cells of renal tubule. Of these what is more important is being debated[10]. Abnormal renal profile is one of the COVID-19 infection manifestations. In a study by Wang et al., that included 138 patients, it was noted that increased urea levels correlated with severity of COVID-19 infection[11]. According to Mahmoudi et al., impaired renal function is important cause of death in COVID-19 patients[12]. In a study by Li et al., urea levels were significantly related with prognosis of disease[13]. A meta-analysis by Henry et al. showed significant relationship between urea and COVID-19 severity[14]. A study by Asghar et al. showed that COVID-19 patients managed in ICU had deranged RFTs and worse outcomes[15]. As severity increases, chances of multi-organ failure rise. Our results correspond with international and national data. At admission, a cut off value of urea >46.8 mg/dl as the predictor of severity and poor outcome of COVID-19 illness is novel however.

Hyponatremia is noted in more than quarter of pneumonia patients and is associated with severity and poor outcome[16]. Sodium abnormalities in setting of COVID-19 have been assessed. Hyponatremia in COVID-19 infection is due to Syndrome of Inappropriate Anti Diuretic Hormone (SIADH) that occurs due to the release of inflammatory markers. Berni et al. noted in a study of 29 COVID-19 patients that hyponatremia correlated with severity and outcome of COVID-19 infection along with increased levels of interleukin-6 (IL-6)[17]. Frontera et al. studied the prevalence and impact of hyponatremia (Sodium <135 mmol/l) in 4654 COVID-19 infection patients. 30% of these patients had hyponatremia[16]. Increased risk of mechanical ventilation and poor

outcome were noted in hyponatremic patients as well. Our findings are similar.

ALT and AST levels have remained subject of research in settings of COVID-19. In one study both ALT and AST were significantly associated with severity of COVID-19[18]. In another study, only AST was significantly associated with severity of illness[11]. Significant relationship between ALT and AST has been observed with the outcome of disease[13]. A meta-analysis by Henry et al. showed a significant relationship of ALT and AST with severity of COVID-19 disease[14]. AST was shown to be significantly related to the severity in a study by Asghar et al [15]. Our study showed a significant relationship between severity and outcome of COVID-19 with ALT and AST levels at admission. It can thus be inferred that as the severity of COVID-19 infection increases, the markers of liver injury increase which in turn are associated with increased risk of mortality.

In the elderly, weaker immunity and decreased tolerance and response to infections can lead to increased severity and worst prognosis. Liu et al. noted that as the age of the COVID-19 patients increases, the severity of the disease also increases [19]. In a study by Yang et al., age and comorbidities were associated with increased mortality[20]. A study by Wu et al. also showed that advanced age was associated with a higher fatality[21]. According to Li et al., as age increases the prognosis of the COVID-19 disease worsens[13]. Our results are similar. We also noted that that there is a significant relation between urea and age in COVID-19 patients. In a study by Mahmoudi et al., old patients who developed impaired kidney function had a higher urea and creatinine levels[12]. Gender had no significant relation with severity in our study. Similar results have been noted earlier[22].

An interesting question arises here that these biochemical markers may get deranged in various other illnesses if they are severe. Urea levels have already been identified as predictor of mortality in non-COVID illnesses. According to one study by Arihan et al., increased urea levels (cut off >28 mg/dl) at admission have been reported to be associated with adverse outcomes in the patients admitted to ICU with non-COVID illness[23]. According to Padhi et al., hyponatremia (Sodium levels <135) is also a predictor of prolonged ICU stay, longer duration of mechanical ventilation, and increased mortality in the ICU patients with diseases other than COVID-19[24]. According to findings of a study, abnormal LFTs except for bilirubin, at the time of admission, were significantly associated with 30-day mortality in ICU settings. However these were not independent predictors of 30-day mortality in the ICU[25].

Even though common biochemical markers noted in our study may merely be correlating with disease severity in other illnesses, this study is unique in the sense that we have worked out cut off levels of urea, AST, and sodium at the time of admission that can be used for assessing severity of COVID-19. It is an important finding in our scenario as the levels of these biochemical markers that are above the cut off values can be used to prognosticate disease severity and outcome. This can forewarn the physician and thus allow for focused management of patients at risk. Validation of these cut off values needs to be the framework of further studies. Relatively less, i.e., 128 participants included in the study is another point of discussion. We included 11.43% of the COVID-19 patients managed during the study period after randomization. The number of patients in our study seems less. It is to be noted that related studies have been conducted with a sample size that is less than 50% of our sample size [9]. Nevertheless inclusion of more patients may have reinforced our findings.

5. Conclusion

This study identifies various biochemical factors that can act as predictors of severity and outcome in COVID-19 patients. At admission, increased urea, AST, and ALT along with decreased sodium point towards disease severity. Urea >42.7 mg, AST >43.5 IU/L, and sodium <136.9 mmol/L are indicators of critical COVID-19 illness. Patients with urea >42.7 mg, and AST >45.5 IU/L can have potentially poor outcome.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Ethical Approval

Institutional Research Forum, Rawalpindi Medical University (46/IREF/RMU/2020).

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