Original Article

Pharmacotherapeutic Evaluation of Covid-19 Patients Suffering from Acute Kidney Injury

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Abstract

The risk of developing Acute Kidney Injury (AKI) increases manifold during severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. Therefore, the aim of this study is to conduct a comprehensive pharmacotherapeutic evaluation of AKI in COVID-19 patients. A retrospective cohort study was conducted from July to August 2021 among COVID-19 patients admitted to the Institute of Kidney Diseases, Hayatabad Medical Complex hospital in Peshawar Pakistan. The data were extracted based on demographics, diagnosis, laboratory parameters, vital signs, and the treatment used during hospitalization. The association of independent variables was explored using parametric statistics such as regression analysis, one-way ANOVA, and Kruskal-Wallis. Data of N=595 COVID-19 patients with positive PCR tests as per pre-defined criteria were collected. It was observed that fever (n=575 [96.6%]), shortness of breath (n=570 [95.8%]), dry cough (n=449 [75.5%]) and body aches (n=129 [21.7%]) were some of the most common symptoms among the patients. Most of the patients were on a multi-drug regimen during hospitalization. Overall, it was observed that most of the laboratory variables significantly declined in COVID-19 patients with Stage III AKI. Mortality among the patients with AKI was 42% [0.418 [0.269 – 0.632], p=<0.001] as compared to non-AKI patients. There was a significant reduction in mortality by 96% (1.968 [1.277 – 3.033], p-0.002) with the use of intravenous dexamethasone. The prime goal of a clinician is to avoid the use of nephrotoxic drugs during hospitalization and maintain adequate oxygen saturation in order to avoid the development of AKI in COVID-19 patients.

Keywords: COVID-19, SARS-CoV-2, Kidney disease, AKI, Renal failure

Introduction

The coronavirus class of pathogens is single-stranded RNA viruses which consist of different varieties that mainly infect humans and non-humans [1]. These viruses belong to family *coronaviridae* in order *nidovirales* and subfamily of alpha-coronavirus, beta-coronavirus, gamma coronavirus, and delta-coronavirus [2]. In late 2019, a novel coronavirus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged on the global stage and caused coronavirus disease (COVID-19) all around the globe without any discrimination [3]. Comparative analysis of clinical features of COVID-19 suggests that the infected patients show pneumonia-like symptoms. However, common symptoms after the onset of SARS-CoV-2 infection include cough, fever, and fatigue, while some other symptoms are diarrhea, dyspnea, hemoptysis, sputum production, and lymphopenia [4, 5]. Although respiratory symptoms are the main clinical manifestations of this disease renal involvement during the disease is also a serious concern as hospitalized COVID-19 patients are at increased risk of developing acute kidney injury (AKI) [6].

The risk of acute kidney injury (AKI) increases manifold during SARS-CoV-2 infection [7]. The exact mechanism of action of COVID-19 associated AKI is still unknown; however, it is believed to be associated with multi-organ shock and failure indicating acute tubular necrosis during AKI [7]. Elevated blood urea nitrogen (BUN), baseline serum creatinine, proteinuria, and hematuria are some of the manifestations of AKI during COVID-19 [8]. The symptoms of AKI sometimes become so severe during COVID-19 that

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they can't be controlled through conservative management; hence, there starts to exist an urgent need for renal replacement therapy (RRT) [9]. Continuous renal replacement therapy (CRRT) has been very successful in reducing the level of inflammatory cytokine levels [10].

Various studies have reported the development of acute kidney injury during the hospital stay of COVID-19 patients and the injury was more common among critically ill patients or patients with other comorbid conditions. In a cohort study on 99 critically ill coronavirus patients, AKI was developed in 42.9% of patients and the majority of these patients had KDIGO (Kidney Disease Improving Global Outcomes) stage III AKI [11]. A retrospective study conducted on hospitalized patients in New York city summarized that patients suffering from COVID-19 showed a higher incidence of AKI with increased requirement for mechanical ventilation, intensive care facility, and renal replacement therapy, as compared to patients without COVID-19 [12]. In clinical investigations of COVID-19, AKI is presented as an independent predisposing cause of mortality [13]. Studies have shown that critically ill AKI patients infected with coronavirus are at increased risk of mortality ranging from 8% to 23% [14, 15]. Some studies even showed an in-hospital mortality rate of 62%, 77%, and 80% among COVID-19 patients with Stage I**,** Stage II, and Stage III AKI, respectively [16].

Globally, there is very limited data on AKI in COVID-19 patients and Pakistan is lagging far behind the rest of the world in reporting these incidents [17]. Thus, an understanding of how the kidney behaves during SARS-CoV-2 infection and how this infection leads to acute kidney injury is urgently needed, especially in the Pakistani population. Investigation of such findings from Pakistan in the form of a retrospective cohort would help us better understand the variable clinical manifestations of AKI in COVID-19 patients which will ultimately help in better handling of coronavirus patients over the course of time. Keeping in view the aforementioned realities, the motivation behind this study is to conduct a comprehensive pharmacotherapeutic evaluation of AKI in COVID-19 patients. This study aims to compare the incidence, risk factors, and outcomes associated with AKI between normal and risk populations.

Materials and Methods

Study Design and Population

A retrospective cohort study was conducted from July to August 2021 among COVID-19 patients admitted at the Institute of Kidney Diseases, Hayatabad Medical Complex hospital in Peshawar Pakistan. This medical complex was given the responsibility of treatment of patients suffering from COVID-19. This medical complex was one of the single facilities in Peshawar which hosted the greatest number of COVID-19 patients daily at that time. Ethical approval for this study was taken from the *Institutional Review Board of the Hayatabad Medical Complex*. A confirmed case of COVID-19 was defined by a positive RT-PCR assay of a specimen collected via nasopharyngeal swab. The inclusion criteria for this study were; 1) all adult patients who tested positive by polymerase chain reaction (PCR) testing of a nasopharyngeal sample for SARS-CoV-2 infection, 2) only first hospitalization record was included for the patients who had multiple qualifying hospital admissions, 3) only quantitative data from Institute of Kidney Disease, Hayatabad Medical Complex hospital were included. Whereas exclusion criteria for this study were 1) data of those patients were excluded if they were transferred to hospitals out of the health system from where it was impossible to obtain data, 2) Data from those patients were excluded from whom the consent was not obtained, and finally, 3) no data outside of Institute of Kidney Disease, Hayatabad Medical Complex hospital was included.

Data Collection

The data were extracted based on demographics, diagnosis, laboratory parameters, vital signs, and the treatment used during the hospitalization. Demographics include the gender and age of the participants. Diagnosis and classification of AKI were based on Kidney Disease Improving Global Outcomes (KDIGO) guidelines [18]. Serum creatinine of more than 0.3 mg/dl or increase to more than 1.5–1.9 times from the baseline serum creatinine level was categorized as Stage I AKI; a serum creatinine of more than 2–2.9 times from the baseline value was categorized as Stage II AKI; whereas, serum creatinine of three times more than the baseline value or a level of more than 4 mg/dl was categorized as Stage III AKI. Laboratory parameters were collected from day one of the hospitalizations till the last day at the hospital. Vital signs were included along with laboratory parameters. A list of various drugs used for the management of COVID-19 and associated symptoms were also included and compared for various outcomes.

Statistical Analysis

The collected data were processed by using Statistical Package for Social Science (SPSS) software program for windows version 21.0 (SPSS Inc., Chicago, IL). The data were analyzed using appropriate descriptive analysis such as mean and standard deviation. Apart from this, the association of independent variables like gender, age, etc., with dependent variables like clinical symptoms, hospitalization, infection severity, co-morbidity, development of AKI, and mortality was explored using parametric statistics such as regression analysis, one-way ANOVA, and Kruskal-Wallis (only if the data were not normally distributed). The statistical significance level was 0.05 with a confidence interval of 95%.

Results and Discussion

Demographic Details of the Participants

Data of N=595 COVID-19 patients with positive PCR tests as per pre-defined criteria were collected from the nephrology ward of HMC hospital. The mean age of the patients was 53

years ± 13.55; whereas, the majority of the patients were of the age of 60 years or above**.** The average number of days of hospitalization of the patients was 6 days **±** 13.55; whereas, most of the patients (n=423 [71.0%]) were either discharged or declared dead within the first 10 days of hospitalization. About 65.8% of the patients included in this cohort study were male. Most of the patients were suffering from diabetes mellitus (n=282 [47.3%]) and hypertension (n=244 [41.0%]). After assessing laboratory parameters, patients were categorized based on KDIGO criteria into Stage I (n=133 [22.3%]), Stage II (n=22 [3.6%]), and Stage III (n=42 [7.1%]) AKI. Further details of the demographic characteristics of patients suffering from COVID-19 are mentioned in **Table 1**.

Table 1. Demographic characteristics of COVID-19 patients (n=595)

Variables	Groups	N	%
Age (in years) Mean **53 years ± 13.55**	11-20	12	2.0
	21-30	42	7.0
	31-40	88	14.7
	41-50	119	20.0
	51-60	157	26.3
	60 and above	177	29.7
Gender	Male	392	65.8
	Female	203	34.1
Number of days Hospitalized Mean 6 days **± 13.55** Range **03 - 30 days**	Discharged on the same day	57	9.6
	1-10 Days	423	71.0
	11-15	77	12.9
	16-20	25	4.2
	21-25	3	0.5
	26-30	10	1.6
Comorbidities	Hypertension	244	41.0
	Diabetes mellitus	282	47.3
	Asthma/ COPD	38	6.3
	Rheumatoid / Osteo arthritis	8	1.3
	Liver and Biliary complications [HEP B, C, Gallstones, Biliary constriction	31	5.2
	Other CVS disorders like PCI, CABG, CAD, etc	99	16.7
	Tuberculosis	10	1.7
	Thrombosis/ PE/DVT	3	0.5
AKI classification on admission	No AKI	398	66.8
	Stage I	133	22.3
	Stage II	22	3.6
	Stage III	42	7.1

Clinical Symptoms of the Patients

It was observed that fever (n=575 [96.6%]), shortness of breath (n=570 [95.8%]), dry cough (n=449 [75.5%]) and body aches (n=129 [21.7%]) were some of the most common symptoms among the participant as shown in **Table 2**. In terms of AKI, most of these symptoms were prevalent in patients with Stage I AKI. Whist, the shock was observed to be significantly higher among the patients suffering from AKI-Stage I. Most of the patients on the ventilator (n=12 [33.33%]) were from the AKI Stage III, of whom a majority of these patients have undergone dialysis (p=<0.001). It was observed that the chance of fatal outcomes was higher among the patients suffering from AKI (p=<0.001) as compared to non-AKI patients. Although a majority of the patients (n=305 [51.2%]) were discharged stable from the hospital yet a significant number of patients (n=188 [31.6%]) were expired.

Table 2. Clinical features and overall outcome of COVID-19 patients according to the stages of AKI

Variables	No AKI n=429	Stage I n=151	Stage II n=30	Stage III n=62	Total	P-value
Symptoms						
Fever	366	132	24	54	576	0.727
SOB	359	133	27	51	570	0.454
Dry Cough	283	98	22	46	449	0.478
Body Aches	82	22	8	17	129	0.118
Sore Throat	50	11	1	7	69	0.262
Anorexia	22	7	0	4	33	0.587
Shock	10	11	2	2	25	0.038*
Loose Motion	22	6	3	1	32	0.319

Hemoptysis	1	0	0	0	1	0.904
Fits	1	0	0	0	1	0.908
Flu	15	9	0	1	25	0.251
Mechanical Ventilator						
On ventilator	13	7	4	12	36	<0.001*
Not on ventilator	377	126	17	39	559	
Overall Outcome						
Discharged with creatinine above normal	0	26	7	12	45	<0.001*
Discharged (recovered with hemodialysis done)	0	0	0	1	1	<0.001*
Discharged stable	273	28	3	1	305	<0.001*
Discharged and on hemodialysis	0	0	0	1	1	<0.001*
Expired	84	55	15	34	188	<0.001*
Still Admitted	34	14	1	6	55	<0.001*

Medication Use in Patients

Most of the patients were on a multi-drug regimen during hospitalization. Steroidal drugs (n=544), multiple antibiotics (n=514), low molecular weight heparin (n=481), proton-pump inhibitors (n=413), paracetamol (n=350), multiple fluids (n=257), insulin (n=215), single antibiotic (n=149), and multivitamins (n=117) were the most common medication used in patients. Overall details of medication use in patients are shown in **Figure 1**. Azithromycin (n=578), ceftriaxone (n=322), cefoperazone (n=156), and meropenem (n=142) were the most commonly used antibiotics among patients. Other antibiotics used by patients are shown in **Figure 2**.

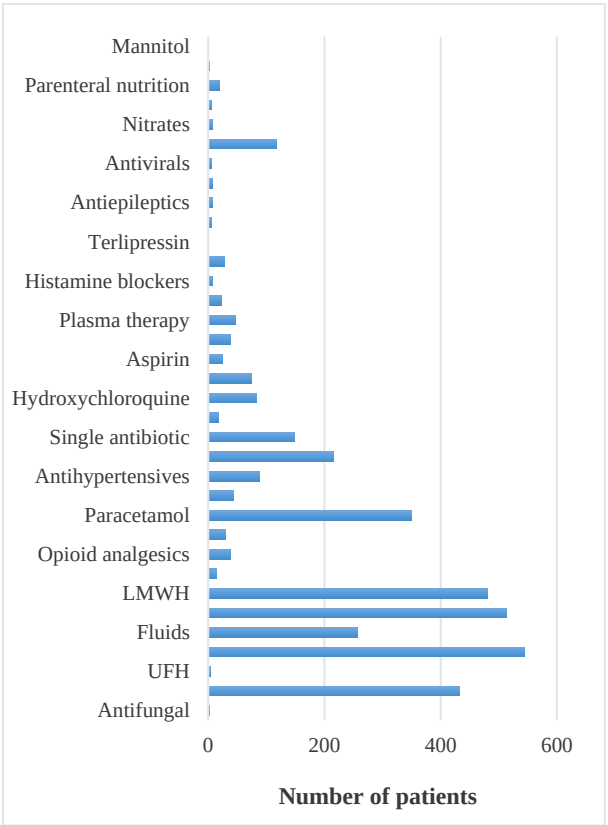

Figure 1. List of various medications used in COVID-19 patients

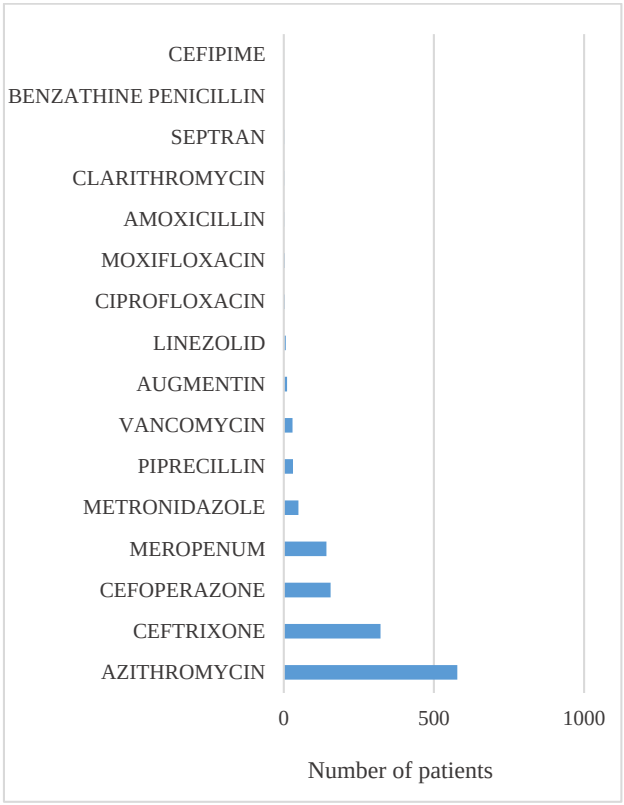

Figure 2. List of various antibiotics used in COVID-19 patients

Laboratory Variables of Patients in Association with AKI

Overall, it was observed that most of the laboratory variables significantly declined in COVID-19 patients with Stage III AKI. The creatinine value was very high both at admission and at the discharge of patients. Serum Electrolytes (SE) were in the normal range for most of the patients; however, the mean sodium concentration level gradually increased with the successive AKI stages. Complete Blood Count (CBC) values also worsened with successive worsening of AKI in patients. Liver Function Test (LFT) revealed that the values of liver markers increased over the course of hospitalization, indicating liver failure in many patients along with AKI. In addition, the oxygen saturation, pulse rate, and blood pressure

were observed to be significantly lower in the Stage III groups. Further details of the laboratory parameters of COVID-19 patients with categorization into various stages of AKI are mentioned in **Table 3**.

Table 3. Laboratory parameters of COVID-19 patients

Lab test		N	Mean	Std. Deviation	P-Value
Creatinine at admission	No AKI	231	1.19	1.765	<0.001*
	Stage I	96	1.39	0.305	
	Stage II	21	2.02	0.657	
	Stage III	44	3.19	3.012	
Creatinine at discharge	No AKI	286	0.92	0.178	<0.001*
	Stage I	74	1.28	0.353	
	Stage II	12	1.73	0.723	
	Stage III	16	4.10	3.289	
Urea	No AKI	404	42.12	32.714	<0.001*
	Stage I	141	63.32	26.292	
	Stage II	30	91.80	52.007	
	Stage III	62	125.03	94.659	
Sodium	No AKI	347	136.77	6.207	0.031*
	Stage I	141	136.43	8.400	
	Stage II	27	138.37	11.287	
	Stage III	61	139.46	9.204	
Potassium	No AKI	346	4.22	0.716	<0.001*
	Stage I	141	4.50	0.809	
	Stage II	27	4.56	1.226	
	Stage III	61	4.71	0.949	
Chloride	No AKI	346	98.36	8.320	0.024*
	Stage I	141	98.53	7.677	
	Stage II	27	102.24	10.241	
	Stage III	61	100.93	10.104	
RBC	No AKI	201	199.24	107.503	0.258
	Stage I	79	231.85	175.837	
	Stage II	17	211.94	117.363	
	Stage III	41	221.80	118.570	
Hemoglobin	No AKI	347	13.56	7.338	0.664
	Stage I	127	13.18	2.018	
	Stage II	30	12.96	1.902	
	Stage III	61	12.65	2.472	
WBC	No AKI	347	12.00	5.820	0.017*
	Stage I	127	12.86	5.453	
	Stage II	30	15.13	5.383	
	Stage III	61	27.95	1956.464	
Platelets	No AKI	347	245.60	101.251	0.565
	Stage I	127	239.14	111.329	
	Stage II	30	270.00	167.124	
	Stage III	61	241.62	126.158	
Neutrophils	No AKI	334	81.18	44.335	0.876
	Stage I	137	79.58	13.901	
	Stage II	29	83.95	11.029	
	Stage III	61	83.37	10.697	
Lymphocytes	No AKI	354	13.83	11.083	0.030*
	Stage I	127	13.95	12.801	
	Stage II	29	9.37	5.187	
	Stage III	61	8.99	9.240	

PT	No AKI	213	14.49	5.860	0.460
	Stage I	92	15.55	7.013	
	Stage II	21	16.70	5.420	
	Stage III	43	17.23	8.611	
APTT	No AKI	196	30.54	8.468	0.050
	Stage I	82	30.20	6.802	
	Stage II	19	35.89	8.743	
	Stage III	42	34.01	10.235	
INR	No AKI	213	1.29	1.205	0.864
	Stage I	93	1.27	0.598	
	Stage II	21	1.32	0.362	
	Stage III	43	1.42	0.748	
LDH	No AKI	245	617.61	374.315	<0.001*
	Stage I	79	815.28	503.551	
	Stage II	17	879.94	582.704	
	Stage III	32	868.84	322.295	
ALT	No AKI	360	60.70	66.194	0.020*
	Stage I	137	65.66	69.936	
	Stage II	28	110.25	144.444	
	Stage III	56	117.79	308.278	
ALP	No AKI	354	99.92	66.128	0.050
	Stage I	136	107.86	54.923	
	Stage II	29	117.24	56.319	
	Stage III	56	148.52	238.589	
Total bilirubin	No AKI	354	0.72	1.849	0.334
	Stage I	136	0.78	0.907	
	Stage II	29	1.07	1.353	
	Stage III	56	1.11	2.593	
CRP	No AKI	286	21.77	81.214	0.034*
	Stage I	103	14.47	11.883	
	Stage II	19	13.67	9.064	
	Stage III	39	84.91	398.888	
Ferritin	No AKI	237	1388.28	1765.571	0.842
	Stage I	79	1461.11	1626.054	
	Stage II	14	1481.79	1171.368	
	Stage III	33	1660.50	848.622	
D-DIMER	No AKI	196	10.23	64.287	0.375
	Stage I	90	32.41	179.079	
	Stage II	19	3.60	2.689	
	Stage III	36	13.10	20.053	
Oxygen Saturation	No AKI	344	83.0443	12.88103	<0.001*
	Stage I	138	79.4570	13.32053	
	Stage II	30	72.6667	17.44416	
	Stage III	62	79.2581	14.02683	
Pulse rate in BPM	No AKI	359	94.6425	16.98658	0.001*
	Stage I	138	94.7667	19.81709	
	Stage II	30	103.9000	23.88962	
	Stage III	59	109.1613	74.08064	
Systolic Blood Pressure	No AKI	361	151.5164	578.40775	0.882
	Stage I	142	122.0867	21.25806	
	Stage II	28	117.6667	20.95699	
	Stage III	62	120.8065	29.16142	
Temperature	No AKI	361	99.0925	4.97653	0.944
	Stage I	142	99.2220	1.30805	
	Stage II	30	99.4000	1.22051	
	Stage III	62	99.3435	1.43705	

Diastolic Blood Pressure	No AKI	361	77.5316	11.03306	0.163
	Stage I	138	77.9333	15.41361	
	Stage II	32	72.6667	17.20732	
	Stage III	60	75.6935	17.45213	

One-way ANOVA has applied; * p-value < 0.05 is statistically significant

Association of Mortality with Different Variables

After applying multiple linear regression analysis, it was found that the risk of mortality was 56% when the age of COVID-19 patients was 50 years or above (0.566 [0.364 – 0.873], p=0.008). Moreover, mortality among the patients with AKI was 42% [0.418 [0.269 – 0.632], p=<0.001] as compared to non-AKI patients. Additionally, mechanical ventilation significantly increased the chances of the mortality by 9% [0.095 [0.043 – 0.219], p=<0.001]. High oxygen saturation (more than 90%) could significantly [2.446 [1.550 – 3.803], p=<0.001] reduce the chances of mortality. It was further noted that the chances of mortality could also be significantly reduced with low lymphocytes level and better regulation of diastolic blood pressure.

Analysis of the drugs used in hospitalized patients revealed that the mortality was significantly higher with the use of meropenem by 62% (0.625 [0.396 – 0.982] p=0.041), intravenous hydrocortisone by 58% (0.582 [0.358 – 0.943] p=0.028), hydroxy-chloroquine by 42% (0.423 [0.245 – 0.727] p=0.002) and oral steroids by 16% (0.161 [0.092 – 0.277] p=<0.001) as compared to any other drug. However, there was a significant reduction in mortality by 96% (1.968 [1.277 – 3.033], p-0.002) with the use of intravenous dexamethasone. Further details of the predictors of mortality among COVID-19 patients are highlighted in **Table 4**.

Table 4. Predictors for mortality among COVID-19 patients

Variables	β(CI)	Std. Error	p-value
Age	0.566 [0.364 – 0.873]	0.213	0.008*
Gender	1.227 [0.791 – 1.903]	0.224	0.361
AKI	0.418 [0.269 – 0.632]	0.204	<0.001*
On Ventilator	0.095 [0.043 – 0.219]	0.408	<0.001*
Oxygen Sat	2.446 [1.550 – 3.803]	0.227	<0.001*
CPR	0.484 [0.318 – 0.734]	0.213	0.001*
Lymph	1.863 [1.237 -2.807]	0.209	0.003*
Systolic BP	1.195 [0.792- 1.805]	0.210	0.396
Diastolic BP	3.350 [1.906- 5.888]	0.288	<0.001*
LDH	0.983 [0.663 – 1.457]	0.201	0.930
Oral steroids	0.161 [0.092 – 0.277]	.277	<0.001*
Intravenous hydrocortisone	0.582 [0.358 – 0.943]	.246	0.028*
Intravenous dexamethasone	1.968 [1.277 – 3.033]	.220	0.002*
Intravenous methylprednisolone	1.118 [0.637 – 1.962]	.287	0.697
LMWH	1.340 [0.883 – 2.033]	.213	0.170
Hydroxy Chloroquine	0.423 [0.245 – 0.727]	.276	0.002*
Azithromycin	0.780 [0.451 – 1.348]	.279	0.373
Ceftriaxone	1.052 [0.723 – 1.530]	.191	0.792
Meropenem	0.625 [0.396 – 0.982]	.231	0.041*

Linear regression was applied, *p-value< 0.05 was considered statistically significant, β= standardized beta, CI= Confidence Interval

This study included an adequate sample size and provided a comprehensive baseline clinical characteristic of the patients. It gave in-depth information on patients' co-morbidities, clinical symptoms associated with COVID-19, treatment received during hospitalization, and laboratory reports based on Serum Electrolyte (SE), Complete Blood Count (CBC), Liver Function Test (LFT), Renal Function Test (RFT), etc. AKI was classified based on KDIGO guidelines using this clinical data. Various associations were explored to understand the different clinical manifestations of the COVID-19. Follow-up was ensured to record the outcomes of this disease in an infected patient.

Fever, shortness of breath, and dry cough were the most prevalent symptoms among coronavirus patients. Categorization of symptoms according to the stages of AKI revealed that these symptoms were more common in patients with no AKI than those of AKI patients, especially those who were at the third stage of AKI. The results of this study are almost similar to another study on a large population in China which reported a high prevalence of fever, cough, and other symptoms in a similar proportion [19]. Most of the patients had hypertension and diabetes mellitus in our study. This is because of the presence of a high burden of Non-communicable diseases (NCDs) along with other infectious

diseases in Pakistan [20]. According to the reports, comorbidities are significantly associated with the severity of coronavirus infection and poor outcomes [21]. Though the evidence on the association of diabetes with disease severity and subsequent mortality is very limited; however, one study with a large sample size concluded that diabetes is significantly associated with mortality and severity of COVID-19 [22]. The association between diabetes and COVID-19 was not explored in our study but the presence of a large number of diabetic patients raises concerns. Similarly, there is no clinical evidence regarding the association of hypertension with COVID-19 clinical symptoms, but some studies reported worsening of symptoms in hypertensive patients [23].

Various laboratory parameters were found highly abnormal for patients with type three AKI as compared to the patients with no AKI. The creatinine value was very high both at admission and at the discharge of patients. The mechanism associated with the increase of SARS-CoV-2 associated creatinine is the accumulation of coronavirus in the kidney which cause renal cell damage and subsequent necrosis [14]. Lymphopenia was present in almost all of the patients in this study. Various studies indicated that lymphopenia is the typical characteristic of the SARS-CoV-2 infection [24]. High IL-6 levels, coupled with increased concentration of tumor necrotic factor-alpha (TNF-alpha) in coronavirus patients induce apoptosis of lymphocytes [25]. Our study found highly abnormal liver markers which proves the fact that coronavirus also affects the liver of the host. Various studies pointed out that high-level Alanine transaminase (ALT) and Aspartate transaminase (AST) are due to the indirect effect of COVID-19 which leads to liver dysfunction [24]. A high level of Alkaline phosphatase (ALP) in the patients is reflective of an overridden immune system and serves as an early indication of multiple organ injury that needs to be ascertained [26].

Oxygen saturation of the patients was very low, especially those patients who were at the third stage of AKI. The first sign of this disease is actually the failure of the respiratory system which is often termed "silent hypoxemia" [27]. This impaired respiratory system leads to decreased oxygenation. This often leads to respiratory failure within 8-14 days. A decrease in oxygen saturation and a rise in breathing rates are indicative of impaired pulmonary diffusion. Histopathological examination of such patients often reveals diffused alveolar damage [28]. This study also found a gradual lowering of oxygen saturation in AKI patients. Moreover, after assessing the association between oxygen saturation and mortality it was found that more than 90% oxygen saturation could significantly decrease the chances of mortality in COVID-19 patients. The findings of this study are similar to another study conducted in China among COVID-19 patients. In that study, the patients were given oxygen supplementation at the cut-off value of more than 90%, and it was revealed that high oxygenation significantly reduced the chances of mortality among patients [29].

Mortality in COVID-19 patients was significantly associated with AKI ($p<0.05$) and the rate of mortality due to AKI complications was found to be 42%. The risk of mortality was found significantly higher (56%) in elderly people of age 50 years or above. It could be associated with the progressive changes in the lungs anatomy of elderly people coupled with muscular atrophy that leads to physiological changes in pulmonary functions such as reduced lungs reserve, reduced airway clearance, and reduced defense barrier related functions [30-32]. C-reactive protein levels were also very high in elderly patients than in younger or middle-aged patients [33]. Computerized tomographic studies showed that the multilobe lesions were significantly higher in elderly COVID-19 patients than in younger patients [34]. Computerized tomography is the most rapid and direct method to quickly identify the damage caused by SARS-CoV-2 to the lungs and understand the severity of the disease. Oral steroids were found to be significantly associated with mortality in COVID-19 patients in this study. The majority of patients were on oral steroids which may have been contributed to high mortality in patients. Moreover, it is a known fact that steroids cause a decline in immune functions that could provide a breeding ground for SARS-CoV-2 replications and subsequent severity of the disease [35]. Contrary to this, it was found that the risk of mortality was reduced by the use of dexamethasone in patients. A clinical trial on COVID-19 patients concluded that the use of dexamethasone combined with standard care methods significantly increased ventilator-free days and reduced mortality in patients [36].

Patients suffering from COVID-19 show various degrees of kidney damage caused by the virus. This can be evaluated based on blood urea nitrogen (BUN), creatinine levels, and other structural changes including edema or inflammation of renal parenchyma, focal fibrosis, epithelial cell necrosis with interstitial hyperemia [37, 38]. Increased release of pro-inflammatory factors in response to the viral attack is associated with the development of COVID-19-related acute kidney injury [39]. Norepinephrine and other drugs including antiviral agents, antibiotics, and NSAIDs also have the potential to cause acute kidney injury, especially in elderly patients or those having comorbid conditions like cancer, cardiovascular disease, or diabetes [37]. Diagnosis of AKI in COVID-19 patients is associated with the diagnosis of viral infection [40]. Generally, COVID-19-associated AKI is treated with CRRT along with other supportive therapies that are used against viral infection. CRRT is also of importance as it may also reduce the overload of inflammatory cytokines and if used in the early stages of AKI, could reduce the mortality rate in critically ill patients [41]. In our study, COVID-19 patients suffering from AKI showed an increased mortality rate than those without AKI and those who get discharged from the hospital, do not have complete renal recovery. It is important to timely diagnose AKI in COVID-19 patients as it may not only increase the mortality rate but can also lead to chronic kidney disease in hospital discharged patients [42].

The specific treatment for AKI is yet to be discovered but the early prognosis and early management of underlying conditions that are associated with AKI could reduce the number of AKI incidences in COVID-19 patients. These management modalities range from avoidance of various nephrotoxic drugs to the management of hypoxemic conditions. Early optimization of hemodynamics and blood volume should be considered in a high-risk group of patients to ensure effective and adequate renal perfusion pressures. However, if the patient doesn't respond to the conventional management strategies, then the next logical step is the utilization of Continuous Renal Replacement Therapy. This study will help clinicians and other decision-makers in making a sound clinical decisions based on the evidence provided by it. It will help in understanding the conclusive unfolding of this pandemic. This study also opens the room for opportunities for further studies to be conducted on this topic and explore various outcomes. It will serve as a pivot around which other studies could diversify their scope.

Conclusion

Renal involvement during the disease is of concern as hospitalized COVID-19 patients are at increased risk of developing acute kidney injury (AKI) which may lead to increased severity of disease and even death. Our study found that the clinical symptoms of the COVID-19 patients worsen with successive stages of AKI. Various factors could either increase or decrease the chances of mortality in AKI patients suffering from COVID-19. There is no specific treatment for AKI; however, the prime goal of a clinician is to avoid the use of nephrotoxic drugs during the course of hospitalization and maintain adequate oxygen saturation in order to avoid the development of AKI or to avoid the worsening of already developed AKI in COVID-19 patients. CRRT could be considered the last option in patients who are unresponsive to conservative management of AKI.

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