European Journal of Clinical Medicine
www.ej-clinicmed.org

Outcome of Acute Kidney Injury in COVID-19 Patients – A Prospective Cohort at a Single Centre in Pakistan

F. Saeed, A. Alam, S. Memon, J. Chughtai, S. Ahmed, S. Tariq, B. Salman, and S. Imtiaz

ABSTRACT

Introduction: **There is continuous experience that AKI is very common in COVID-19 patients and that SARS-CoV-2 specifically invades the kidneys with poor outcome. In-hospital AKI is associated with multiple risk factors including DM, CCF, drugs etc. Also, there is difference in the mortality rate all over the world for various reasons. To date no data has been found from Pakistan on outcome of AKI with COVID-19 infection. Therefore, this study was conducted to help determine the outcome and associated risk factors in this part of the world.**

Material and Method: **This is a prospective cohort of COVID-19 adult patients with AKI admitted in Indus Hospital COVID ICU from March 2020 to September 2020. History, clinical examination, laboratory investigations, and ultrasound imaging of the kidneys was acquired from the Health Management Information System (HMIS) record of the patients. The data was analyzed in SPSS version 21. Association between outcomes of AKI with different variables was assessed by applying Chi square test. P value of less than 0.05 was considered significant.**

Results: **There were total 208 patients with AKI in our study, in which 146 (70.2%) were male while 62(29.8%) were female. The mean age was 60.3± 12.7 years and the most prevalent comorbid was HTN 147(70.7%) in our patients, while the most common cause of AKI was sepsis 188(90.4%) and on the same way, oliguria was the most common symptoms of AKI 76(36.5%). Death was the most frequent outcome of our patients 147(70.7%) as compared to recovery 47(22.6%). There was male predominance in patients, who died with AKI as compared to female 112(76.2%) and 35(23.8%) respectively. Also, treatment didn't show any benefit on worst outcome. Similarly, 124(59.6%) patients needed ventilatory support in which 118(95.2%) died while only 5 (4%) recovered (p <0.001)**

Conclusion: **Renal involvement in SARS-COV-2 infection is more common than initially thought and has been associated with increased morbidity and mortality. We have found significant association of AKI in covid-19 with outcome variables.**

Keywords: COVID-19, Acute kidney Injury, Sepsis.

Published Online: June 25, 2021

ISSN: 2736-5476

DOI:10.24018/ejclinicmed.2021.2.3.61

F. Saeed*
FCPS (Neph), Nephrology Department, The Indus Hospital, Karachi, Pakistan.
(e-mail: faiza.saeed@tih.org.pk)
A. Alam
FCPS (Neph), Associate Professor, Nephrology Department, The Indus Hospital, Karachi, Pakistan.
(e-mail: ashar.alam@tih.org.pk)
S. Memon
FCPS (Neph), Nephrology Department, The Indus Hospital, Karachi, Pakistan.
(e-mail: shoukat.memon@tih.org.pk)
J. Chughtai
FCPS, Registrar Nephrology Department, The Indus Hospital, Karachi, Pakistan.
(e-mail: javeria.chughtai@tih.org.pk)
S. Ahmed
Resident Nephrology Department, The Indus Hospital, Karachi, Pakistan.
(e-mail: shahzad.ahmed03@tih.org.pk_
S. Tariq
Resident Nephrology Department, The Indus Hospital, Karachi, Pakistan.
(e-mail: sobia.tariq@tih.org.pk)
B. Salman
Epidemiologist and Biostatician, The Kidney Centre, Karachi, Pakistan.
(e-mail: binasalman75@hotmail.com)
S. Imtiaz
MBBS, MRCP, FRCP, FCPS (Neph), Senior Consultant, Professor and Head of The Nephrology Dept. Chairperson Indus Nephrology Network. The Indus Hospital, Karachi, Pakistan.
(e-mail: salman.imtiaz@tih.org.pk)

Corresponding Author

I. Introduction

Critically ill patients frequently come across with acute kidney injury (AKI), especially those with serious infections, and has been associated with substantial morbidity and mortality [1]. A certain portion of COVID-19 patients required admission in high dependency and intensive care area due to respiratory compromise or other issues. The AKI is well-known to occur in patients being admitted in such special care areas, as around 19%, in the earlier days of epidemic [2]. Although, at the time of emergence of disease few of the studies reported a very low incidence of AKI [3]. However, there is continuous experience that AKI is very common in COVID-19 patients and that SARS-CoV-2 specifically invades the kidneys with poor outcome. In different studies, estimated incidence of AKI and the need for renal replacement therapy (RRT) among hospitalized COVID-19 patients varies and reportedly ranging from 0.5% to as high as 40% [4], [7]. Two of the largest studies epitomized this wide variation, for example from China Guan et al reported an AKI incidence of only 0.5% in an analysis of 1099 hospitalized patients, while a recent analysis from New York reported an AKI incidence of 26.9% among 5700 hospitalized COVID-19 patients [4], [7]. There is gross

European Journal of Clinical Medicine
www.ej-clinicmed.org

variation in the incidence of COVID-19 infection globally, it is highest in American region (now more than 20million confirmed cases) while it is lowest in Western Pacific region (around 800000 confirmed cases) [8].

Risk stratification is essential to modify monitoring and initiate prevention and/or early treatment strategies for patients who will benefit the most from intervention. Data from China and the USA propose that male sex, older age, Black race, diabetes mellitus, chronic kidney disease (CKD), hypertension, cardiovascular disease(CVD), congestive heart failure(CHF), higher body mass index, use of angiotensin-converting enzyme inhibitors and non-steroidal anti-inflammatories, acute respiratory distress syndrome, and admission elevated ferritin, creatinine kinase, brain natriuretic peptide, and troponin 1 were identified as the risk factors for in-hospital AKI [9]-[12]. Also, those with AKI are more likely to need vasopressors as well as mechanical ventilation [11], [12].

There is difference in the mortality rate all over the world for various reasons which we will discuss later. A retrospective cohort study from a tertiary teaching hospital in Wuhan, China, strikingly showed that 72% of patients with COVID-19 with AKI died during hospitalization, and AKI was an independent risk factor of in hospital mortality [13]. In a Systematic review and Meta-analysis, 30 studies including 21,591 patients from hospitals in Asia, Europe and US were analyzed among which 20 Cohorts had, Kidney related information. Prevalence of AKI was found to be 17%. The median age was 56years (range, 43-72 years) with 55% male patients. Among these 77% patient either required ICU admission or were reported to have severe infection, and mortality rate was reported to be 52% [14].

To date no data has been found from Pakistan on outcome of AKI with Covid-19 infection. Therefore, this study was conducted to help determine the outcome and its associated risk factors in our part of the world.

II. Material and Method

This is a prospective cohort of COVID-19 patients with AKI admitted in Indus Hospital COVID ICU from March 2020 to September 2020. We included all patients of more than 16 years of age and the diagnosis was made by RT-PCR by nasopharyngeal swab. Patients with a history of maintenance dialysis, chronic kidney disease, or renal transplantation were excluded. Permission from the institutional ethical review committee was taken prior to conduction of study. History, clinical examination, laboratory investigations, and ultrasound imaging of the kidneys was acquired from the Health Management Information System (HMIS) record of the patients. Data was collected on a structured proforma which included variables like age, gender, residence, socioeconomic status, profession, comorbid conditions, drug history, clinical presentation, hemodynamic status and lab parameters and cause of AKI on admission. Outcome variables were recovery from AKI, developing chronic kidney disease and death. All the patients who got discharged with deranged creatinine were followed as a routine in the clinic for three months from the time of admission to label them as CKD. Therefore, serum creatinine for these patients were rechecked at discharge, then at 2nd and 3rd months at nephrology clinic of Indus hospital. All the patients received standard treatment of COVID according to hospital protocol along with hemodialysis and CRRT when needed.

III. Statistical Analysis

The data was entered and analyzed in SPSS version 21. Cleaning and coding of data was done prior to analysis. Mean ± STD and median with IQR were computed for continuous data while for categorical variables frequency with percentages were measured. We made categories of some continuous variables like age and laboratory parameters for the purpose of analysis. Association between outcomes of AKI with different variables was assessed by applying Chi square test. P value of less than 0.05 was considered significant.

IV. Results

There were total 208 patients with AKI in our study, in which 146 (70.2%) were male while 62(29.8%) were female. The mean age was 60.3± 12.7 years with minimum of 17 year and maximum of 90 years. The most prevalent comorbid was HTN 147(70.7%) in our patients, while the most common cause of AKI was sepsis 188(90.4%) and in the same way, oliguria was the most common symptoms of AKI 76(36.5%) (Table I).

TABLE I: Demographic and Clinical Parameters of COVID Patients with AKI

Variables	N=208 (%)/ Mean±Std
Gender	
Male/Female	146(70.2)/62(29.8)
Age (years)	60.3 ± 12.7
Cause of AKI	
Sepsis	188(90.4)
Volume depletion	10(4.9)
Cardiogenic shock	10(4.8)
Sign and symptoms	
Diastolic Blood pressure	72.7±16.5
Systolic Blood pressure	126.8±26
Respiratory rate	25.2± 6.9
Oliguria	76(36.5)
Anemia	60(28.8)
Confusion	63(30.3)
Dehydration	30(14.4)
Drowsiness	58(27.9)
Pedal edema	39(18.8)
Edema	35(16.8)
Vomiting	25(12)
Anorexia	19(9.1)
Nausea	13(6.3)
Hematuria	13(6.3)
Periorbital swelling	9(4.3)
Seizures	2(1)
Coma	1(0.5)
Fever	12(5.8)

All lab parameters with their mean ± std, median with IQR and minimum and maximum are shown in (Table II).

Death was the most frequent outcome of our patients 147(70.7%) as compared to recovery 47(22.6%).We analyzed the association of outcome with patient's parameters and found that the majority of patients, who died were in the age group of 51 -65 years 72(49%) as compared to other age groups, but within each age groups the death and recovery

were almost the same, therefore, p value is not significant (p=0.467). Gender was significantly associated with outcome of COVID-19 (p=0.012), there was male predominance in patients, who died with AKI as compared to female 112(76.2%) and 35(23.8%) respectively. Comorbid conditions like DM, HTN and IHD did not have any significant association with outcome of COVID-19, neither the outcome had any association with complication of the disease like thromboembolism. The reason might be a very low number of patients who suffered these events.

TABLE II: LAB PARAMETERS OF COVID PATIENTS

Variables	Mean± std & Median, IQR	Minimum	Maximum
Hb (gm/dl)	1.6 ± 2.7 & 11.8,3.6	3.5	18.5
TLC ($\times 10^9$/L)	17.4 9.5 & 15.7, 11.2	1.9	79
Lymphocyte count (%)	8.7 8 & 6, 6.5	1	49
Platelet ($\times 10^9$/L)	251.8 135.9 238, 749	18	767
Albumin (g/dl)	3 0.6 3.1, 0.8	1.4	4.3
Urea (mg/dl)	135 78.5 121, 108	15	426
Creatinine(mg/dl)	4.2 3.7 3.1, 2.9	0.3	26
Sodium (meq/l)	139.8 9.9 140,12	101	167
Potassium (meq/l)	4.8 1.2 4.6, 1.4	2	8.9
Chloride (meq/l)	105.13 8.63 105, 11	72	125
Bicarb (meq/l)	17 6.3 17, 8	5	41
Calcium (mg/dl)	7.8 1.1 8, 1.3	4.8	14.8
LDH (U/L)	940.9 1994 656, 454	190	22289
Ferritin (ng/ml)	1887.4 2928.1 1589.5, 988.8	47.2	33511
CRP (mg/L)	165.5 122.3 149.5, 178.8	1	562
Procalcitonin (ng/ml)	17.3 49.4 2.2, 12.5	0.04	612

Hb Hemoglobin, TLC Total leucocyte count, LDH Lactate dehydrogenase, CRP C reactive protein.

The patients who developed AKI in hospital succumbed to death 94(63.9%) as compared to the patients who came with AKI 53 (36.1%). Similarly, hospital acquired AKI had less recovery 18(38.3%) than AKI on arrival 29(61.7%) (p<0.001) (Table III).

To detect any association between severity markers and outcome of disease we categorized our laboratory parameters by their cutoff values. Our majority of patients had higher levels of LDH 197(94.7%), in which 143(72.6%) died, 43 (21.8%) recovered while only 11 (5.6%) developed CKD (P=0.01). Similarly, the patients with higher level of CRP, Ferritin, D-Dimer and Procalcitonin encountered death more than recovery, although the association is statistically insignificant.

In our patient with AKI, treatment did not show any benefit on worst outcome, for example Methylprednisolone was given to 159(76.4%) patients in which 121 (76.1%) died while only 32(20 .1%) recovered (p=0.001). Similarly, Remdesivir and Tocilizumab were given to 42(20.2%) and 60(28.8%) patients, respectively in which 38(90.5%) patients died who received Remdesivir (p=0.005) while 54(90%) died who were treated with Tocilizumab (p<0.001). Likewise, the hemodialysis modality also did not contribute to patients' survival, as we dialyzed 66(31.7%) patients in which 50(75.8%) died, 7(10.6%) recovered while 9(13.6%) patients developed CKD (p=0.001). In the same way 124(59.6%) patients needed ventilatory support in which 118(95.2%) died while only 5 (4%) recovered (p <0.001) (Table IV).

TABLE III: ASSOCIATION OF DEMOGRAPHIC AND CLINICAL PARAMETERS WITH OUTCOME OF AKI

Variables		Outcome of AKI n=208 (Column %)				
		Recovered 47(22.6)	CKD 14(6.7)	Death 147(70.7)	Total	p-value
Age	≤ 50 years	9(19.1)	5(35.7)	25(17)	39(18.8)	0.46
	51 - 64 years	25(53.2)	5(35.7)	72(49)	102(49)	
	≥ 65 years	13(27.7)	4(28.6)	50(34)	67(32.2)	
Gender	Male	27(57.4)	7(50)	112(76.2)	146(70.2)	0.012
	Female	20(42.6)	7(50)	35(23.8)	62(29.8)	
Type of AKI	Hospital acquired	18(38.3)	3(21.4)	94(63.9)	115(55.3)	<0.001
	AKI at arrival	29(61.7)	11(78.6)	53(36.1)	93(44.7)	
Comorbid conditions						
DM	Yes	26(55.3)	7(50)	78(53.1)	111(53.4)	0.932
	No	21(44.7)	7(50)	69(46.9)	97(46.6)	
HTN	Yes	33(70.2)	10(71.4)	104(70.7)	147(70.7)	0.995
	No	14(29.8)	4(28.6)	43(29.3)	61(29.3)	
IHD	Yes	12(25.5)	4(28.6)	34(23.1)	50(24)	0.869
	No	35(74.5)	10(71.4)	113(76.9)	158(76)	
Complications of covid 19						
ACS	Yes	1(2.1)	2(14.3)	8(5.4)	11(5.3)	0.2
	No	46(97.9)	12(85.7)	139(94.6)	197(94.7)	
CCF	Yes	4(8.5)	4(28.6)	11(7.5)	19(9.1)	0.054
	No	46(97.9)	12(85.7)	139(94.6)	189(90.9)	
PVD	Yes	2(4.3)	0(0)	6(4.1)	8(3.8)	0.999
	No	45(95.7)	14(100)	141(95.9)	200(96.2)	
CVA	Yes	2(4.3)	1(7.1)	13(8.8)	16(7.7)	0.672
	No	45(95.7)	13(92.9)	134(91.2)	192(92.3)	

AKI Acute kidney injury, DM Diabetes mellitus, HTN Hypertension, IHD Ischemic heart disease, ACS Acute coronary syndrome, CCF Congestive cardiac failure, PVD peripheral vascular disease, CVA cerebrovascular event.

European Journal of Clinical Medicine
www.ej-clinicmed.org

TABLE IV: ASSOCIATION OF SEVERITY MARKER OF DISEASE AND MANAGEMENT WITH OUTCOME OF COVID-19 PATIENTS WITH AKI

Variables		Outcome of AKI n=208 (Column %)				
		Recovered 47(22.6)	CKD 14(6.7)	Death 147(70.7)	Total	p-value
Disease Severity marker						
Lactate dehydrogenase	≤ 240 U/L	4(36.4)	3(27.3)	4(36.4)	11(5.3)	0.01
	> 240 U/L	43(21.8)	11(5.6)	143(72.6)	197(94.7)	
Ferritin	< 500	2(20)	2(20)	6(60)	10(4.8)	0.242
	≥ 500	45(22.7)	12(6.1)	141(71.2)	198(95.2)	
Procalcitonin	0.01 - 0.49	14(28)	4(8)	32(64)	50(24)	0.49
	> 0.49	33(20.9)	10(6.3)	115(72.8)	158(76)	
C reactive protein	≤10	4(30.8)	1(7.7)	8(61.5)	13(6.3)	0.528
	> 10	43(22.1)	13(6.7)	139(71.3)	195(93.8)	
D Dimer	≤ 0.5	5(33.3)	1(6.7)	9(60)	15(7.2)	0.522
	>0.5	42(21.8)	13(6.7)	138(71.5)	193(92.8)	
Management						
Remdesivir	Yes	4(95)	0(0)	38(90.5)	42(20.2)	0.005
	No	15(30.6)	8(16.3)	26(53.1)	49(23.6)	
Methylprednisolone	Yes	32(20.1)	6(3.8)	121(76.1)	159(76.4)	0.001
	No	15(30.6)	8(16.3)	26(53.1)	49(23.6)	
Tocilizumab	Yes	6(10)	0(0)	54(90)	60(28.8)	<0.001
	No	41(27.7)	14(9.5)	93(62.8)	148(71.2)	
HCQ	Yes	5(14.7)	2(5.9)	27(79.4)	34(16.3)	0.449
	No	42(24.1)	12(6.9)	120(69)	174(83.7)	
Ventilatory support	Yes	5(4)	1(0.8)	118(95.2)	124(59.6)	<0.001
	No	42(50)	13(15.5)	29(34.5)	84(40.4)	
Hemodialysis	Yes	7(10.6)	9(13.6)	50(75.8)	66(31.7)	0.001
	No	40(28.2)	5(3.5)	97(68.3)	142(68.3)	

LDH Lactate dehydrogenase, PCT Procalcitonin CRP C reactive protein, MPS Methylprednisolone, HCQ, Hydroxychloroquine, Ven.S Ventilatory support, HD Hemodialysis.

V. DISCUSSION

To our knowledge this the first publication from Pakistan on AKI and COVID-19. Pakistan was predicted to become one of the vulnerable countries for the spread of corona virus disease due to poverty, poor health literacy, imbalance and weak healthcare infrastructure, religious travelling and prayer assembly five time a day [15]. But this prediction took a nosedive when infection plummeted to very low level. There were many assumptions and supposition like relatively younger population of Pakistan like only 4% of the population is over 65 compared with USA and Italy 16% and 23% respectively. The average age in Pakistan is 22, more than a decade younger than Brazil, and 25 years younger than Italy according to United Nations data [16]. There is hypothesis for theses improved outcome, like differences in social behavior, genetic evolution, hygiene behavior and BCG vaccination [17].

We found that the demography of our patients regarding age is different as reported in other part of the world. Majority of patients in our cohort who suffered and died from COVID-19 were from middle age group (51years to 65 years) as compared to older age population of more than 65 years [18]. The reason of this discrepancy might be due to relatively low population of elderly people (majority reached to that age when they do not have the comorbid) in our country. Gender distribution of the disease is similar to other part of the world, but surprisingly, it is different from the neighboring countries of similar population in respect of demography and socioeconomic status. The male predominance in fatality was not observed in India, Nepal, Vietnam, and Slovenia where fatality rate is higher in female [19].

There has been large variations observed in the prevalence of comorbidities in patients with COVID-19 and AKI for example, we found out that hypertension was present in 70.7% of our population which is higher as compared to other studies [20], [21] on the other hand diabetes was present in 53.4% of our patients which is somewhat consistent with studies from the US as 41% to 47% but not from China which reported 14% diabetics [21]. But we did not identify hypertension and diabetes as risk factor for mortality in COVID-19 patients with AKI, in contrast to a study from the US [22]. On the contrary, the cardiac and thromboembolic complications like CCF, ACS, PVD and CVA were sparse and did not show any association with the three outcomes of the disease in contrast to the study by Kolhe and Fluck [23].

Majority of our patients developed AKI after hospitalization. The development of AKI in hospital and in community has an impact on the outcome as shown in meta-analysis that community acquired AKI has better prognosis with lesser stay in the ICU [24]. Similarly, patients who developed AKI in hospital after COVID-19 showed grave prognosis [10]. We also found the same trend of mortality in our patients as death was highly associated with hospital acquired AKI.

We found the inflammatory markers, which determine the severity of COVID infection were very high in all of our patients. The reason might be due to presence of AKI in all of our patients, which itself a bad prognostic marker and determinant of the severity of underlying infection. Lactate dehydrogenase (LDH) is a reliable predictor associated with COVID19 severity and mortality in patients with different medical conditions [25]. Although all markers were high, but we found LDH is significantly associated with the death of COVID patients.

Effect of treatment on COVID patients with severe disease is frustrating. Methylprednisolone was given to 159(76.4%) patients in which 121 (76.1%) died while only 32(20.1%) recovered. Similar observation was made by other, in a retrospective analysis of COVID patients with severe disease Zu and Li also concluded that it does not improve prognosis in this population [26]. Similar observation was made with Inj Remdesivir there was significantly high mortality (38/42) in those who received Remdesivir in patients with AKI.

Remdesivir was found superior to placebo in low-risk patients in large placebo trial [27]. But in another randomized, double-blind, placebo-controlled, multicenter trial at ten hospitals in Hubei, China. Remdesivir use was not associated with a difference in time to clinical improvement, rather adverse events were reported in 102 (66%) of 155 Remdesivir recipients versus 50 (64%) of 78 placebo recipients. Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early [28]. Similarly, Tocilizumab was given to 60 patients out of which 54 died in this group of patients in our cohort of COVID with AKI. Although not in patients with AKI this disenchanted result was observed by others, for example in a randomized, double-blind, placebo-controlled trial involving patients with confirmed severe COVID-19 infection, tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients. While patients who received tocilizumab had fewer serious infections than patients who received placebo [29]. Although it showed some improvement in retrospective trials [30]. Patients who required renal replacement therapy in the form of hemodialysis or hemofiltration also showed worst outcome in our population as observed by other [10].

There have been certain limitations in our study as relatively low number of patients can transfigure a lack of statistical power. In addition, the monocenter design may have limited external validity of our findings. We could not have the urinalysis as a baseline to find out if COVID-19 affects kidneys earlier than the biochemical changes. Further studies, assessing levels of proteinuria and hematuria, pathological findings and translational research are needed to further explore different mechanisms that may participate to AKI during severe SARS-CoV-2 infection.

VI. Conclusion

Renal involvement in SARS-COV-2 infection is more common than initially thought and has been associated with increased morbidity and mortality. We have found significant association of AKI in COVID-19 with outcome variables as 70.7% patients died, while among those who survived 22.6% experience recovery of AKI before discharge. Treatment including medications, hemodialysis and ventilatory support do not change the outcome. Further studies are needed on kidney involvement in COVID-19 so that effective strategies for prevention and early management of AKI can be established.

Acknowledgment

We acknowledged Dr Jahanzaib Khan (Senior Medical Officer- Dialysis) for helping us in collecting and arranging Data.

References

[1] Peerapornratana S, Manrique-Caballero CL, Gomez H, Kellum JA. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. Kidney international. 2019 Nov 1;96(5):1083-99.

[2] Arentz M, Yim E, Klaff L. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state [published online March 19, 2020]. JAMA. doi.;10.

[3] Wang L, Li X, Chen H, Yan S, Li D, Li Y, Gong Z. Coronavirus disease 19 infection does not result in acute kidney injury: an analysis of 116 hospitalized patients from Wuhan, China. American journal of nephrology. 2020;51(5):343-8.

[4] Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, Greninger AL, Pipavath S, Wurfel MM, Evans L, Kritek PA. Covid-19 in critically ill patients in the Seattle region—case series. New England Journal of Medicine. 2020 May 21;382(21):2012-22.

[5] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DS, Du B. Clinical characteristics of coronavirus disease 2019 in China. New England journal of medicine. 2020 Apr 30;382(18):1708-20.

[6] Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. Jama [Internet]. 2020; 1–8.

[7] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. Jama. 2020 Apr 22.

[8] covid19.who.int/coronavirus/world dashboard noted on 1-11-2020.

[9] Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, Ma Z, Huang Y, Liu W, Yao Y, Zeng R. Renal involvement and early prognosis in patients with COVID-19 pneumonia. Journal of the American Society of Nephrology. 2020 Jun 1;31(6):1157-65.

[10] Zahid U, Ramachandran P, Spitalewitz S, Alasadi L, Chakraborti A, Azhar M, Mikhalina G, Sherazi A, Narh JT, Khattar P, Bedi P. Acute kidney injury in COVID-19 patients: An inner city hospital experience and policy implications. American Journal of Nephrology. 2020;51(10):786-96.

[11] Hirsch, J. S. et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int. 98, 209–218 (2020)

[12] Mohamed MM, Lukitsch I, Torres-Ortiz AE, Walker JB, Varghese V, Hernandez-Arroyo CF, Alqudsi M, LeDoux JR, Velez JC. Acute kidney injury associated with coronavirus disease 2019 in urban New Orleans [published online ahead of print May 13, 2020]. Kidney360 doi.;10.

[13] Cheng Y, Luo R, Wang X, Wang K, Zhang N, Zhang M, Wang Z, Dong L, Li J, Zeng R, Yao Y. The incidence, risk factors, and prognosis of acute kidney injury in adult patients with coronavirus disease 2019. Clinical Journal of the American Society of Nephrology. 2020 Oct 7;15(10):1394-402.

[14] Robbins-Juarez SY, Qian L, King KL, Stevens JS, Husain SA, Radhakrishnan J, Mohan S. Outcomes for Patients With COVID-19 and acute kidney injury: a systematic review and meta-analysis. Kidney International Reports. 2020 Aug 1;5(8):1149-60.

[15] Atif M, Malik I. Why is Pakistan vulnerable to COVID-19 associated morbidity and mortality? A scoping review. The International journal of health planning and management. 2020 Sep;35(5):1041-54.

[16] Saeed Shah. Why Youthful, Conservative Pakistan Is a Coronavirus Bright. Spot.www.wsj.com . august 1, 2020.

[17] Yamamoto N, Bauer G. Apparent difference in fatalities between Central Europe and East Asia due to SARS-COV-2 and COVID-19: Four hypotheses for possible explanation. Medical hypotheses. 2020 Nov 1;144:110160.

[18] Yanez ND, Weiss NS, Romand JA, Treggiari MM. COVID-19 mortality risk for older men and women. BMC Public Health. 2020 Dec;20(1):1-7.

[19] The Sex, Gender, and COVID-19 Project. The COVID-10 sex-disaggregated data tracker. https://globalhealth5050.org/covid19/ (accessed December 6, 2020).

[20] Shibata S, Arima H, Asayama K, Hoshide S, Ichihara A, Ishimitsu T, Kario K, Kishi T, Mogi M, Nishiyama A, Ohishi M. Hypertension and related diseases in the era of COVID-19: a report from the Japanese Society of Hypertension Task Force on COVID-19. Hypertension Research. 2020 Oct;43(10):1028-46.

[21] Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, Li J, Yao Y, Ge S, Xu G. Kidney impairment is associated with in-hospital death of COVID-19 patients. MedRxiv. 2020 Jan 1.

[22] Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. Acute kidney injury in patients hospitalized with Covid-19. Kidney Int. 2020. Epub 2020 May 18. https://doi.org/10.1016/j.kint.2020.05.006 PMID: 32416116.

[23] Kolhe NV, Fluck RJ, Selby NM, Taal MW. Acute kidney injury associated with COVID-19: A retrospective cohort study. PLoS medicine. 2020 Oct 30;17(10):e1003406.

[24] Huang L, Xue C, Kuai J, Ruan M, Yang B, Chen X, Zhang Y, Qian Y, Wu J, Zhao X, Mei C. Clinical Characteristics and Outcomes of Community-Acquired versus Hospital-Acquired Acute Kidney Injury: A Meta-Analysis. Kidney and Blood Pressure Research. 2019;44(5):879-96.

[25] Chen Z, Zhang F, Hu W, Chen Q, Li C, Wu L, Zhang Z, Li B, Ye Q, Mei J, Yue J. Laboratory markers associated with COVID-19 progression in patients with or without comorbidity: A retrospective study. Journal of clinical laboratory analysis. 2020 Oct 28:e23644.

[26] Zhu HM, Li Y, Li BY, Yang S, Peng D, Yang X, Sun XL, Zhang M. Effect of methylprednisolone in severe and critical COVID-19: Analysis of 102 cases. World Journal of Clinical Cases. 2020 Dec 6;8(23):5952.

[27] Madsen LW. Remdesivir for the Treatment of Covid-19-Final Report. The New England Journal of Medicine. 2020 Oct 8;338(19):1813-26.

[28] Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, Fu S, Gao L, Cheng Z, Lu Q, Hu Y. Remdesivir in adults with severe COVID-19: a randomized, double-blind, placebo-controlled, multicentre trial. The Lancet. 2020 Apr 29.

[29] Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, Horick NK, Healy BC, Shah R, Bensaci AM, Woolley AE. Efficacy of tocilizumab in patients hospitalized with Covid-19. New England Journal of Medicine. 2020 Dec 10;383(24):2333-44.

[30] Kewan T, Covut F, Al–Jaghbeer MJ, Rose L, Gopalakrishna KV, Akbik B. Tocilizumab for treatment of patients with severe COVID–19: A retrospective cohort study. EClinicalMedicine. 2020 Jul 1;24:100418.

[31] King CS, Sahjwani D, Brown AW, Feroz S, Cameron P, Osborn E, Desai M, Djurkovic S, Kasarabada A, Hinerman R, Lantry J. Outcomes of mechanically ventilated patients with COVID-19 associated respiratory failure. Plos one. 2020 Nov 23;15(11):e0242651.