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RESEARCH ARTICLE

Safety profile of COVID-19 Medication in Chronic Kidney disease patients: renal and hepatic dysfunction associated with anti-viral and Tocilizumab use. Single Centre experience

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ABSTRACT

Introduction: It is challenging to choose appropriate therapy for COVID-19 patients with impaired renal functions due to insufficient & contradictory data about their safety in CKD patients.

Methods: Study aimed to report renal and hepatic dysfunction associated with medications, also to compare drug adverse events between CKD and Non-CKD patients & to identify safety profile of these medications in CKD patients.

Results: Favipiravir, lopinavir-ritonavir, remdesivir & Tocilizumab were used in 75.15%, 15.29% and 13.19% & 25.89% patients respectively. Incidence of renal function deterioration was 18.24%, while an increase in ALT and AST was noted in 34.24% and 23.78%. Patients with GFR <60 ml/min were 15.57% and 74-patients were on hemodialysis. In CKD population, 86.93%, 28.37%, 8.10% and 22.07% were treated with Favipiravir, lopinavir-ritonavir, remdesivir, and Tocilizumab respectively. 37.83%of patients had acute on CKD, while 35.13% and 31.98% had increase in ALT and AST. Incidence of acute renal function deterioration and increase in AST were significantly higher in CKD population. Favipiravir treated CKD patients has significant deterioration of renal functions (p=<0.05), while an elevation in ALT and AST was not significant in the two groups, where as renal & liver injury associated with other medications were not significant between two groups.

Conclusion: We observed significantly higher incidence of kidney injury and elevation in AST in CKD patients. Nevertheless, these abnormal lab parameters must be considered with other risk factors, associated with severe covid-19-infection, thus COVID medicine should not be denied to CKD patients.

Keywords: Covid-19, CKD, chronic kidney disease, Liver injury, Favipiravir, Lopinavir-Ritonavir, Remdesivir, Tocilizumab.

Introduction:

The World Health Organization (WHO) proclaimed coronavirus disease (COVID-19); a communicable viral disease caused by various strains of SARS-COV-2[1]. A world health emergency in January 2020 however notified a pandemic on 11th March 2020 due to massive global spread and higher mortality[2]. More than 700 million people got infected, and 6.9 million patients died worldwide[3]. Initially, Hypertension and Diabetes were considered as the most common comorbid and important risk factors for COVID-19[2], however, research from 2021-2022 showed that chronic kidney disease (CKD) is an independent risk factor for severe and fatal COVID-19 disease[4,5]. Immunodeficiency states associated with advanced chronic kidney disease (CKD) make them susceptible to acquiring severe COVID-19 infection, related complications, and high mortality; Bell & colleagues reported 7% 30-day mortality risk after COVID 19 diagnosis in fully vaccinated kidney failure patients[4,6]. Anti-inflammatory agents, anticoagulants, monoclonal antibodies and anti-viral therapies are known treatment options for COVID-19 infection which were used alone or in combination[7], additionally, suitability and efficacy of other classes of drugs are being assessed in clinical trials. Most of the major clinical trials exclude COVID-19-infected CKD patients, hence safety profile data on anti-COVID-19 therapies is not available[8], also vaccine effectiveness may be diminished in chronic kidney disease patients and monoclonal therapies loose its effectiveness against certain strains of COVID-19 so choosing appropriate therapy for COVID-19 patients with impaired renal functions proved challenging for healthcare professionals[9,10]. International and National health guidelines recommend anti-viral drugs like Moulnupiravir, Ritonavir, Azuvidine and Redmisivir, also other compounds are being investigated, however available data about their dosage, frequency and safety in CKD patients is insufficient, inadequate and contradictory[11]. Antiviral drugs may further deteriorate renal functions in known CKD patients or can cause other serious side effects compared to patients with intact renal functions. therefore, it is necessary to gather data about the applicability, efficacy and safety of anti-viral medications and to establish guidelines for their use in CKD patients.

Methods:

STUDY DESIGN:

This retrospective observational study was performed for a period from 28/3/2020 to 25/12/2022, for patients infected with COVID-19 infection admitted to Dubai Hospital, Dubai, United Arab Emirates. As per National guidelines for clinical management and treatment of COVID-19, patients were treated with antiviral i.e. Favipiravir (1600 mg PO twice a day on day 1, followed by 600 mg twice a day for 10-14 days), lopinavir-Ritonavir (200/50 mg 2 tab twice a day) and Remdesivir (200 mg iv day 1, followed by 100 mg iv daily for 2 days). Tocilizumab was given in case of cytokine storm, defined by high IL6 (more than 3 times of upper limit), Ferritin (> 600ug/l at admission, or > 300 ug/l double up within 24 hours of admission), LDH (>250 U/L) and D-dimer (>1 mg/L). Patients were also treated with different antibiotics and steroids on a per-need basis. Renal transplant recipients, those patients who were discharged from the emergency (not admitted), or whose length of admission was less than 2 days were excluded. We compared mortality rate & incidence of ventilation between the CKD and Non-CKD patients, also to report deterioration of renal and hepatic functions (Increase in alanine transaminase (ALT) >33 U/L & aspartate transaminase (AST) >34 U/L), presumably associated with antiviral or tocilizumab use between the CKD and Non-CKD patients.

STATISTICAL METHODS:

Mean ± standard deviation is used to describe continuous variables and for normally distributed as well as non-normally distributed data median with interquartile range (IQR) values are used. Categorical variables were expressed as frequency and percentage. For normally distributed and non-normally distributed continuous variables, Independent t-test and Mann-Whitney test were used respectively, also Pearson's $\chi 2$ test or Fischer's exact test were used to compare categorical data. A p-value of <0.05 was considered statistically significant. SPSS (Statistical Package for the Social Sciences) version 20 was used for statistical analysis.

Results:

A total of 1507 patients suffered from COVID-19 infection during the study period, 82 were excluded as they were discharged from the emergency department and could not follow their antiviral compliance. A total of 1425 patients suffering from COVID-19 infection were studied. Their mean age was 52.11±14.66 years, 52.91% (n=754) of patients were of age above 60 years. The predominant gender was male (75.50%, n=1076) and only 13.89% (n=198) were from UAE. COVID-19-infected patients suffering from chronic kidney disease were 15.57% (n=222). For COVID infection, Favipiravir, Lopinavir/Ritonavir and Remdesivir were used in 75.15% (n=1071), 15.29% (n=218) and 13.19% (n=188) respectively, also 369 (25.89%) patients received Tocilizumab. The median (IQR) duration of antiviral treatment was 6.37(4.06) days. Different types of steroids were used in 972 (64.49%) patients, Dexamethasone, hydrocortisone, methylprednisolone, and prednisolone were used in 46.18%(n=696), 16.25% (n=245), 9.09% (n=137) and 5.37% (n=88) patients respectively. The Anti-viral side effects, such as Liver dysfunction, prolonged QT interval, bradycardia, persistent vomiting, and pancytopenia were noticed in 10 (0.81%), 5 (0.40%), 4 (0.32%),3 (0.24%), 2 (0.16%) patients respectively. Post-COVID lung fibrosis was reported in 80 (5.61%) patients. The incidence of renal function deterioration was 18.24%, while the increase in ALT and AST was 34.24% and 23.78% respectively. The Median Hospital duration was 11(15) days, while the mortality rate was 9.47% (n=135), and 89.26%(n=1272) were discharged from the hospital.

CKD vs Non-CKD COVID-infected patients (table no:1):

Regarding renal functions among COVID-infected patients, 84.43% (n=1203) and 15.57%(n=222) ($p=<0.05$), patients belong to Non-CKD and CKD respectively. Among CKD patients, more than 50% were at stage IV or V {(CKD-III: 49.54%(n=110), CKD-IV:

12.16%(n=27) and CKD-V: 38.28% (n=85)} and 87.05% (n=74) of CKD-V patients were receiving maintenance hemodialysis. CKD patients were relatively older than Non-CKD patients [CKD vs Non-CKD: mean Age (STD) in years: 57.59(15.01) vs 51(14.32), p=<0.05]. Patients above 60 years of age (CKD vs Non-CKD: 52.70% vs 52.95%) and male gender (CKD vs Non-CKD: 91.89% vs 72.48%, p=<0.05) were predominant in both groups. Regarding Anti-viral, CKD and Non-CKD Patients were treated with **Favipiravir** [CKD vs Non-CKD: 86.93% (n=193) and 72.98%(n=878), p=<0.05], **Lopinavir** [CKD vs Non-CKD: 28.37% (n=63) and 12.88%(n=155), p=<0.05] and **Remdesivir** [CKD vs Non-CKD: 8.10% (n=18) and 14.13%(n=170), p=<0.05]. The median duration of anti-viral treatment in CKD and Non-CKD was 6 (5.67) and 5.79 (3.67), (p=>0.05) days respectively. Forty-nine (22.07%) patients with CKD and 320 (26.60%) patients with Non-CKD received **Tocilizumab** (p=>0.05). Steroids were given to 85.78%(n=236) CKD and 59.77%(n=737) Non-CKD patients, Dexamethasone was the most used steroid in CKD (47.44%, n=130) and Non-CKD patients (38.28%, n=472). The median (IQR) peak procalcitonin (PCT) and C-reactive (CRP) levels were significantly higher in the CKD population {CKD vs Non-CKD Procalcitonin: 1.28(11.27) vs 0.18(0.64), p=<0.05 and C-reactive protein: 122.30(199.15) vs 93.55(128.15), p=>0.05}, also need for mechanical ventilation (MV) was higher in CKD than Non-CKD COVID-19 infected patients {MV in CKD vs Non-CKD: 36.48% (n=81) vs 8.39% (n=101), p=<0.05)}, however the incidence of post COVID lung fibrosis (LF) was not statistically significant (LF in CKD vs Non-CKD: 6.75%(n=15) vs 4.82% (n=58), p=>0.05. The Incidence of acute renal function deterioration and the need for dialysis was higher in CKD patients than in Non-CKD patients: {CKD vs Non-CKD: AKI: 84(37.83%) vs 176(14.63%), p=<0.05, HD: 41(48.80%) vs 49(27.84%), p=<0.05}. The median duration of hospital admission for both groups is not statistically different {CKD vs Non-CKD: PCT: 12(15) vs 9(13), p=>0.05}. Moreover, 62.16%(n=138) CKD and 91.97%(n=1134) Non-CKD patients were discharged to home (p=<0.05), while the mortality rate was significantly higher in CKD than Non-CKD COVID-19 infected patients {CKD vs Non-CKD: 57(25.67%) vs 78(6.48%), p=<0.05}.

Table-1: Patients' Characteristics

	Total Patients (n=1425)	**CKD patients n(%) =222(15.57)**	**Non-CKD patients n(%) =1203(84.42)**	**p value**
Age in Years, Mean (SD)	52.11(14.66)	57.59(15.01)	51(14.32)	<0.05
<40 years, n(%)	292(20.49)	31(13.96)	261(21.69)	
40-60 years, n(%)	379(26.59)	74(33.33)	305(25.35)	
>60 years, n(%)	754(52.91)	117(52.70)	637(52.95)	
Gender				
Male	1076(75.50)	204(91.89)	872(72.48)	<0.05
Nationality				
UAE	198(13.89)	63(28.37)	135(11.22)	
Non-UAE	1227(86.10)	159(71.62)	1068(88.77)	
Antiviral				
Favipiravir	1071(75.15)	193(86.93)	878(72.98)	<0.05
Remdesivir	188(13.19)	18(8.10)	170(14.13)	<0.05
Lopinavir	218(15.29)	63(28.37)	155(12.88)	<0.05
Tocilizumab	369(25.89)	49(22.07)	320(26.60)	0.157
Duration of Treatment, Median (IQR)	6.37(4.06)	6(5.70)	6.15(3.99)	<0.05
Baseline Creatinine mg/dl, Median (IQR)	0.8(0.4)	2.2(3.75)	0.8(0.30)	<0.05
Renal functions				
Normal renal functions	1203(84.42)			
Chronic Kidney disease (CKD)	222(15.57)	222(15.57)		
CKD-III	110(49.54)	110(49.54)		
CKD-IV	27(12.16)	27(12.16)		
CKD-V	85(38.28)	85(38.28)		
CKD-V Conservative treatment	11(12.94)	11(12.94)		
CKD-V on Hemodialysis	74(87.05)	74(87.05)		
Steroids				
Yes	910 (63.85)	190(85.58)	720(59.85)	<0.05
No	535(35.50)	39(14.23)	496(40.22)	
Dexamethasone	696(46.18)	130(47.44)	472(38.28)	<0.05
Methylprednisolone	245(16.25)	43(15.69)	169(13.70)	<0.05
Hydrocortisone	137(9.09)	21(7.66)	93(7.54)	0.383
Prednisolone	88(5.83)	10(3.64)	68(5.51)	0.489
Lab parameters				
PCT highest, Median (IQR)	0.35(2.40)	1.28(11.27)	0.18(0.64)	<0.05
PCT lowest, Median (IQR)	0.09(0.22)	0.25(0.63)	0.07(0.13)	0.143
CRP highest, Median (IQR)	112(161)	122.3(199.15)	93.55(128.15)	0.161
CRP lowest, Median (IQR)	7(24.7)	8(27.4)	7(26.80)	0.571

	Total Patients (n=1425)	CKD patients n(%) =222(15.57)	Non-CKD patients n(%) =1203(84.42)	p value
Pulmonary sequel				
Yes	80(5.61)	19(8.55)	61(5.07)	<0.05
ARDS	7(0.49)	4(1.80)	3(0.24)	0.491
Lung Fibrosis	73(5.12)	15(6.75)	58(4.82)	0.229
Hospital Duration, Median (IQR)	11(15)	12(15)	9(13)	0.537
Outcome				
Discharged	1272(89.26)	138(62.16)	1134(91.97)	<0.05
Expired	135(9.47)	57(25.67)	78(6.48)	<0.05
DAMA	11(0.77)	5(02.25)	6(0.48)	0.771
Transferred	233(16.35)	22(09.90)	211(17.11)	<0.05
Mechanical Ventilation	182(12.77)	81(36.48)	101(8.39)	<0.05
Adverse Events				
AKI	260(18.24)	84(37.83)	176(14.63)	<0.05
Received HD	90(34.61)	41(48.80)	49(27.84)	
Liver Dysfunction				
Rise in ALT	488(34.24)	78(35.13)	410(34.08)	0.761
Rise in AST	339(23.78)	71(31.98)	268(22.27)	<0.05

Anti-COVID-19 medications and Acute Deterioration of Renal Functions (AKI and acute on chronic kidney disease (CKD)):

Favipiravir: The incidence of Acute renal function deterioration was 14.65% (n=157), and 48 (30.57%) patients needed hemodialysis in favipiravir-treated COVID-19 patients. In CKD patients as compared to Non-CKD, the incidence of renal function deterioration and need for hemodialysis was statistically higher {AKI in CKD vs Non-CKD: 28.49%(n=55) vs 11.61%(n=102) (p=<0.05) and Hemodialysis for AKI in CKD vs Non-CKD: 14.63%(n=12) vs 2.71%(n=18) (p=<0.05)}. Liver injury in the form of an increase in ALT and AST was not statistically different after favipiravir exposure in two groups of COVID-infected patients {ALT in CKD vs Non-CKD: 30.06%(n=58) vs 35.42 (n=311) (p=>0.05) and AST in CKD vs Non-CKD: 25.38%(n=49) vs 20.95 (n=184) (p=>0.05)}. Median C-reactive protein (CRP) and procalcitonin (PCT) levels at admission were significantly higher in Favipiravir treated COVID-19 patients with CKD {Median (IQR) CRP in CKD vs Non-CKD: 122.5(198.7) vs 106.3(139.9) (p=<0.05) and Median (IQR) PCT in CKD vs Non-CKD: 1.3(13.17) vs 0.21(1.07) (p=<0.05)}. In COVID-19-infected CKD patients, 42.48% (n=82) received full dose, while 57.51% (n=111) received half dose of Favipiravir, with an incidence of AKI of 26.82% (n=22) and 29.72% (n=33) respectively. Table-2 demonstrates patients characteristics, labs, Renal & hepatic dysfunction in Favipiravir recipient.

Table 2: Patients characteristics, labs, Renal & hepatic dysfunction in Favipiravir recipient:

Renal & hepatic dysfunction in Favipiravir recipient	Total Patients	CKD patients	Non-CKD patients	p value
Favipiravir	1071(75.15)	193(86.93)	878(72.98)	
Age	52.40 (14.70)	58.61(14.60)	51.19(14.42)	<0.05
Gender	756(70.58)	126(65.28)	630(71.75)	0.0745
PCT highest, Median (IQR)	0.26(0.23)	1.3(13.17)	0.21(1.07)	<0.05
PCT lowest, Median (IQR)	0.09(0.065)	0.26(0.64)	0.08(0.013)	0.557
CRP highest, Median (IQR)	108.4(129.9)	122.5(198.7)	106.3(139.9)	<0.05
CRP lowest, Median (IQR)	7(26.6)	10.2(28.95)	7(25.22)	0.249
Rise in ALT n (%)	369(34.45)	58(30.05)	311(35.42)	0.155
Rise in AST n (%)	233(21.75)	49(25.38)	184(20.95)	0.176
Hyperuricemia	121(11.29)	23(11.91)	98(11.16)	0.229
Acute deterioration of renal functions n (%)	157(14.65)	55(28.49)	102(11.61)	<0.05
Received HD n (%)	48(30.57)	23(11.91)	25(2.84)	
Full dose	745(69.56)	82(42.48)	663(75.51)	
Acute deterioration of renal functions	92(12.34)	22(26.82)	70(10.55)	
Received HD	30(32.60)	12(14.63)	18(2.71)	
Half dose	326(30.43)	111(57.51)	215(24.48)	
Acute deterioration of renal functions	65(19.93)	33(29.72)	32(14.88)	

Renal & hepatic dysfunction in Favipiravir recipient	Total Patients	CKD patients	Non-CKD patients	p value
Received HD	18(27.69)	11(09.90)	7(3.25)	

Lopinavir-Ritonavir: The incidence of Acute renal function deterioration in lopinavir-treated patients was 28.89% (n=63), and 26 (30.57%) patients required hemodialysis. The CKD patients suffer significantly more renal function deterioration than Non-CKD {CKD vs Non-CKD: 38.09% (n=24) and 25.16 (n=39) (p=<0.05)}. ALT and AST elevation is observed in 29.35%(n=64) and 27.06% (n=59) of lopinavir-treated patients respectively, however, both enzyme elevation is not different statistically in both group of patients {ALT in CKD vs Non-CKD: 25.39 (n=16) vs 30.69 (n=48) (p=>0.05) and AST in CKD vs Non-CKD: 26.98 (n=17) vs 27.09 (n=42) (p=>0.05)}. Median C-reactive protein (CRP) and procalcitonin (PCT) levels at admission were significantly not different in lopinavir-treated COVID-19 patients with CKD {Median (IQR) CRP in CKD vs Non-CKD: 121(167.8) vs 128.1(238.2) (p=>0.05) and Median (IQR) PCT in CKD vs Non-CKD: 1.9 (14.81) vs 0.54 (14.40) (p=>0.05)}, see table-3.

Table 3: Patients characteristics, labs, Renal & hepatic dysfunction in Lopinavir-Ritonavir recipient:

Renal & hepatic dysfunction in Lopinavir-Ritonavir recipient	Total Patients	CKD patients	Non-CKD patients	p value
lopinavir	218(15.29)	63(28.37)	155(12.88)	
Age	51.42(14.38)	55.06(16.12)	48.66(13.40)	<0.05
Male Gender	174(79.81)	42(66.66)	132(85.16)	<0.05
PCT highest, Median (IQR)	0.19(12.92)	1.9(14.81)	0.54(14.4)	0.349
PCT lowest, Median (IQR)	0.14(0.33)	0.34(0.81)	0.11(0.21)	0.385
CRP highest, Median (IQR)	122.65(207.67)	121(167.8)	128.1(238.2)	0.104
CRP lowest, Median (IQR)	8.7(21.1)	6.9(17.8)	8.7(22.6)	0.056
Rise in ALT	64(29.35)	16(25.39)	48(30.96)	0.412
Rise in AST	59(27.06)	17(26.98)	42(27.09)	0.986
Acute deterioration of renal functions	63(28.89)	24(38.09)	39(25.16)	<0.05
Received HD	26(41.26)	15(23.80)	11(7.09)	<0.05

Remdesivir: Out of 188 remdesivir-treated COVID-19-infected patients, forty (21.27%) had acute renal function deterioration and sixteen (40%) required hemodialysis. Also, the rise in the liver enzyme is observed in 29.25% (n=55) and 25% (n=47) patients for ALT and AST respectively. The incidence of acute renal function deterioration {CKD vs Non-CKD: 27.77% (n=5) and 20.58% (n=35) (p=>0.05)} and the elevation of ALT and AST {ALT in CKD vs Non-CKD: 22.22% (n=4) vs 30% (n=51) (p=>0.05) and AST in CKD vs Non-CKD: 27.77 (n=5) vs 24.70 (n=42) (p=>0.05)} is statistically not different between CKD and Non-CKD patients. Median C-reactive protein (CRP) and procalcitonin (PCT) levels at admission were significantly not different in remdesivir-treated COVID-19 patients between two groups {Median (IQR) CRP in CKD vs Non-CKD: 149.30(204.82) vs 156(185.27) (p=>0.05) and Median (IQR) PCT in CKD vs Non-CKD: 4.1(225.4) vs 0.58 (3.22) (p=>0.05)}, table-4.

Table 4: Patients characteristics, labs, Renal & hepatic dysfunction in Remdesivir recipient:

Renal & hepatic dysfunction in Remdesivir recipient	Total Patients	CKD patients	Non-CKD patients	p value
Remdesivir	188(13.19)	18(9.57)	170(90.42)	
Age	52.41(13.80)	56.28(12.85)	52.10(13.86)	0.261
Male Gender	124(65.95)	11(61.11)	113(66.47)	0.648
PCT highest, Median (IQR)	0.62(4.76)	4.15(225.4)	0.58(3.22)	0.157
PCT lowest, Median (IQR)	0.07(0.23)	0.25(0.35)	0.07(0.20)	0.299
CRP highest, Median (IQR)	156(182.7)	149.30(204.82)	156(185.27)	0.903
CRP lowest, Median (IQR)	5(16.32)	5.40(9.27)	4.85(16.5)	0.958
Rise in ALT	55(29.25)	4(22.22)	51(30)	0.490
Rise in AST	47(25)	5(27.77)	42(24.70)	0.982
Acute deterioration of renal functions	40(21.27)	5(27.77)	35(20.58)	0.585
Received HD	16(40)	3(16.66)	13(7.64)	0.725

Tocilizumab: Tocilizumab was used in COVID-19-infected patients with other antiviral medicines: Favipiravir (61.24%, n=226), Lopinavir (n=33) and Remdesivir (29.81%, n=110). A total of eighty-four (21.59%) patients had acute renal function deterioration and twenty-nine (34.52%) required hemodialysis, also abnormal increase in ALT and AST was observed in 14.63% (n=54) and 13%(n=48) patients respectively. Acute renal function deterioration was observed in 30.61%(n=15) and 21.56% (n=69) in CKD and Non-CKD patients treated with tocilizumab respectively. Tocilizumab and lopinavir combination is associated with a higher incidence of acute renal dysfunction in CKD than in Non-CKD patients{CKD vs Non-CKD: 33.33%(n=5) vs 8.71% (n=6) (p=<0.05)}, while tocilizumab combination either with favipiravir {CKD vs Non-CKD: 53.33% (n=8) vs 65.21% (n=45) (p=>0.05)} or remdesivir {CKD vs Non-CKD: 13.34% (n=2) vs 26.08% (n=18) (p=>0.05)} is not associated with a statistically different incidence of acute renal dysfunction in CKD and Non-CKD patients. Similarly, the abnormal liver enzyme elevation is not statistically different in the two groups {ALT in CKD vs Non-CKD: 12.24% (n=6) vs 15% (n=48) (p=<0.05) and AST in CKD vs Non-CKD: 8.16% (n=4) vs 13.75 (n=44) (p=>0.05)}. Median C-reactive protein (CRP) and procalcitonin (PCT) levels at the admission were significantly not different in tocilizumab-treated COVID-19 patients between two groups {Median (IQR) CRP in CKD vs Non-CKD: 121.35(151.65) vs 164.85(195.14) (p=>0.05) and Median (IQR) PCT in CKD vs Non-CKD: 2.14(4.32) vs 0.54 (2.93) (p=>0.05)}, table-5.

Table 5: Patients characteristics, labs, Renal & hepatic dysfunction in Tocilizumab recipient:

Renal & hepatic dysfunction in Tocilizumab recipient	Total Patients	CKD patients	Non-CKD patients	p value
Tocilizumab	369(25.89)	49(22.07)	320(26.60)	
Age	53.66(14.49)	60.66(13.12)	52.61(14.41)	<0.5
Male Gender	257(69.64)	37(75.51)	220(68.75)	0.337
PCT highest, Median (IQR)	0.64(3.19)	2.14(4.32)	0.54(2.93)	0.386
PCT lowest, Median (IQR)	0.06(0.19)	0.23(0.74)	0.05(0.01)	<0.5
CRP highest, Median (IQR)	159.2(188.1)	121.35(151.65)	164.85(195.14)	0.210
CRP lowest, Median (IQR)	1.1(7.9)	3.8(8.1)	3.55(7.50)	0.855
Favipiravir	226(61.24)	32(65.30)	194(60.62)	0.531
Lopinavir	33(8.94)	10(20.40)	23(7.18)	<0.5
Remdesivir	110(29.81)	7(14.28)	103(32.18)	<0.5
Acute deterioration of renal functions	84(21.59)	15(30.61)	69(21.56)	0.159
Favipiravir	53(63.09)	8(53.33)	45(65.21)	0.673
Lopinavir	11(13.09)	5(33.33)	6(8.71)	<0.5
Remdesivir	20(23.80)	2(13.34)	18(26.08)	0.656
Received HD	29(34.52)	7(14.28)	22(6.87)	0.072
Rise in ALT	54(14.63)	6 (12.24)	48(15)	0.611
Rise in AST	48(13)	4(8.16)	44(13.75)	0.278

Discussion:

In this retrospective study, Favipiravir was the most commonly used antiviral agent in COVID-19-infected patients, followed by lopinavir and remdesivir. Kidney and liver injury were commonly observed in the study population, however, cannot attributed solely to the antiviral medications, as other factors like inflammation, antibiotics, superimposed sepsis, and other medications including steroids can also potentially cause organ damage. The incidence of Acute renal function deterioration in our study population was 18.24% (n=260), Mousavi et al reported an overall AKI incidence in 13.6% COVID infected patients with normal kidney functions and 17.3% in patients treated with antiviral (remdesivir and Lopinavir)[12].

Favipiravir:

Favipiravir is a broad-spectrum anti-viral, that belongs to purine nucleic acid analogue. T-705-RTP (Favipiravir ibofuranosyl -5-triphosphate) prodrug of favipiravir is generated by phosphorylation and ribolysation[11]. T-705-RTP is integrated into viral RNA by competing with purine nucleotide therapy leading to suppressed RdRp & hinder viral RNA replication[13]. Ebola, influenza and norovirus are treated with Favipiravir, also it is considered a treatment alternative for COVID-19 infection[14]. Aldehyde oxidase and Xanthine oxidase enzymes metabolize favipiravir into inactive metabolite T-705M1[15], which is excreted by the kidney (90%) and 82 to 92.4% of the total is M1. In mild to moderate renal impairment, the M1 level is elevated up to 2.5 times. Favipiravir accumulates in patients with renal impairment and M1 is a potential molecule causing toxicity, however, there is no sufficient evidence available to prove the hazardous effect of favipiravir in CKD or dialysis patients[16,17]. According to United Arab Emirate's National guidelines published on 3rd April 2020, version-2, for clinical management and Treatment of COVID-19, Favipiravir was recommended as a first-line agent for COVID-19-associated upper respiratory tract infection, pneumonia, severe pneumonia, or critically ill patients[18]. In our study population, Favipiravir was used in more than 75% (n=1071) of COVID-19 infected patients from April 2020 to December 2022, and 86.93% (n=193) CKD patients were also treated with this antiviral agent. Due to a lack of safety data on renal impairment patients, CKD patients were prescribed Full dose and Half dose of favipiravir in 42.48% and 57.11% of CKD patients respectively, including 46 maintenance dialysis patients. The incidence of Acute on CKD in patients treated with favipiravir was 28.49%, and 11.91% required hemodialysis, while in Non-CKD patients AKI was observed in 11.61%, and 2.84% required hemodialysis ($p<0.05$). Ozsurekci Y et al, used Favipiravir safely in pediatric renal impairment patients[19], additionally, blood concentrations of Favipiravir were not different between dialysis and non-dialysis patients[20]. An increase in liver enzymes[21] and uric acid level[22] are the most common favipiravir-associated laboratory changes, nevertheless, liver function abnormalities are commonly associated with severe COVID-19 infections[23], thus, it is challenging to distinguish between COVID-19-related liver injury and drug-induced liver injury[24]. We found a rise in ALT in 35.13% and 34.08% of CKD patients and Non-CKD patients treated with Favipiravir respectively, while an abnormal increase in AST was observed in 25.38% and 20.95% in CKD patients and Non-CKD patients. Bayram et al reported a rise in ALT and AST in 27% and 25% of COVID-19 Patients with normal functions treated with Favipiravir respectively[25], also Gök S et al reported a 35.5% and 21.5% rise in ALT and AST in CKD patients[14]. Studies evaluating drug-induced hepatotoxicity with histopathology findings found 90% acute hepatocellular injury associated with favipiravir[26], however cholestatic DILI (Drug-Induced Liver Injury) is observed in multiple cases, with a single case of acutely decompensated cirrhosis with cholestatic jaundice due to favipiravir[27]. Similarly, an increase in ALT and AST were observed in COVID-19 infection, 21.3 and 22.2 % according to Guan WJ et al, also severe disease is associated with higher levels of hepatic enzyme elevation[28]. On the other hand, Pilkington et al appreciated a well-characterized safety profile of favipiravir in 4299 patients despite all hematological and biochemical abnormalities[29]. Favipiravir is used with other medications, also CKD patients in favipiravir treated group had significantly high C-reactive protein levels; therefore, the sole responsibility of side effects cannot be attributed to favipiravir[30]. Moreover, and in terms of safety, there was no difference in terms of adverse events in comparison to placebo. Also, Efficacy trials showed that Favipiravir failed to show any positive impact on ICU admission, the need for oxygen therapy and the timing of viral clearance in COVID-19 infected patients, though there was a slight benefit observed in the context of clinical improvement[31]. Favipiravir was removed from national guidelines version IV in January 2022 [32].

Lopinavir:

Lopinavir and Ritonavir belongs to the protease inhibitor group of antivirals used against HIV and Chronic Hepatitis B and C. Lopinavir is dispensed with low dose ritonavir for clinical use as later inhibits cytochrome CYP3A4 mediated lopinavir metabolism[33]. It is excreted significantly via the urinary route in humans. Lopinavir is associated with tubular injury and causes kidney injury on prolonged exposure, so should be taken for a short period and may be avoided in CKD patients [34,35]. In our study population, 218 patients were treated with lopinavir, and 28.37% were suffering from CKD. Twenty patients had acute on CKD and fifteen patients required hemodialysis. There was advice not to use lopinavir in CKD patients, however, it was used because COVID-19 infection carries a high mortality, and no other agents were available. Thirty-nine Non-CKD patients develop AKI and eleven require hemodialysis. The association of lopinavir with AKI is proven in many studies[35,36]. FDA in their disproportionate analysis in 2020-2021, reported lopinavir-associated liver injury in 403 (37%) COVID-19 patients out of 845 patients, while liver injury associated with other medication was 16.4%[37]. In our study population, and among the 218 patients were treated with lopinavir, an increase in ALT and AST was observed in 29.35 and 27.06% of patients respectively, also there was no significant difference seen in transaminitis in CKD and Non-CKD patients. Lopinavir is metabolized by cytochrome p450 which may induce hepatotoxicity[38]. RECOVERY trial and Coa et al proved that lopinavir does not improve survival in severe COVID infection in hospitalized patients[39,40]. Subsequently, WHO and IDSA

recommend not to use this agent in COVID-19 hospitalized patients[41,42].

Remdesivir:

Due to broad spectrum anti-viral effectiveness against RNA virus, the FDA (Federal Drug Association) issued a permit (emergency use authorization: EUA) for its use in COVID-19-infected patients in May 2020. The mechanism of action is to inhibit RNA-dependent polymerase (RdRP), which is quite crucial for SARS-COV2 replication[43]. We use it at a dose of 200 mg IV on day 1, followed by 100 mg daily for 3 days and can go up to 10 days in severe infection[44]. Remdesivir is metabolized in the liver, and 10% of the parent compound and 40% of the by-product GS-441524 get excreted in urine[45,46], so a dose of more than 200mg may cause hepatotoxicity or nephrotoxicity[47]. The Infectious Disease Society of America (IDSA) recommends its use in mild to moderate COVID-19 infection, as it not only speeds up the recovery process but also reduces complication rates[48]. ERA-EDTA Council observed that a normal dose of remdesivir in CKD patients does not yield optimal results, as COVID-19-infected CKD patients carry higher viral load than Non-CKD patients[5]. Mitochondrial injury in kidney epithelial cells is generally attributed to Antiviral, however, remdesivir seemed to have less mitochondrial injury potential[47], also sulfobutylether-b-cyclodextrin is used as a vehicle for drug in remdesivir preparation, which is known to be tubulotoxic and can cause nephrotoxicity[49]. Despite the nephrotoxic potential of remdesivir, Petit et al[50] and Thakre et al[51] found it safe in chronic kidney disease patients. We observed an acute renal function deterioration in 27.77% (n=5) CKD patients and 20.57% Non-CKD patients. Also, a rise in ALT and AST were observed in 22.22% and 27.77% CKD patients respectively, however, remdesivir was not stopped for any patient and the difference was not statistically significant as compared to Non-CKD patients. Thakre et al used remdesivir in 16 hemodialysis patients and 30 AKI patients, and mild liver enzyme derangement was observed in 30% of patients, however renal function or liver enzyme derangement cannot be attributed solely to remdesivir use, nor should mildly increase in transaminases be regarded as contraindications to remdesivir use[51].

Tocilizumab:

Tocilizumab is a recombinant humanized monoclonal antibody that binds to both membrane bound as well as soluble forms of IL6 receptor. It is known for its use in rheumatological disorders and chimeric antigen receptor T (CAR T) cell therapies[52]. The efficacy of Tocilizumab was investigated in COVID-19-associated critically ill patients in a Randomized Embedded Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP), which showed 90 days improved survival than the control group (HR: 1.61, 95%CI: 1.25-2.08)[53]. An increase in cholesterol, ALT, AST, and injection site reaction are common side effects, also reactivation of latent tuberculosis is a common threat after Tocilizumab administration[54]. Tocilizumab is a cytochrome P450 enzyme inducer and has significant interaction with apixaban and rivaroxaban, therefore, it is recommended to avoid apixaban and rivaroxaban and to adjust the dose of warfarin in conjunction with this therapy[54]. In our study population, we found that 21.56% of patients developed AKI and 30.61% of CKD patients had deterioration of renal functions while receiving tocilizumab. Aljuhani et al reported an incidence of 72.2% AKI in tocilizumab patients, though they reported a better survival rate than the control group[55]. We used tocilizumab in 13 maintenance hemodialysis patients, and only one patient died. There are reports demonstrating safely using tocilizumab in CKD and dialysis patients[56,57]. We did not report any local or systemic side effects associated with tocilizumab. In our population, there is an increase in ALT and AST in 14.63 and 13% of patients, while in CKD patients the rise in ALT and AST was 12.24% and 8.16%, and there was no significant difference in comparison to the Non-CKD population. Gatti et al reported 91 DILI reports out of 2443 COVID-19-infected patients who received tocilizumab while analyzing the FDA adverse event reporting system (FARES) [58]. IL6 is important for liver regeneration, Tocilizumab inhibits IL6 and causes liver injury that can be serious enough to require a liver transplant[59]. COVID-19 infection can potentially cause liver injury with a number of mechanisms. COVID-19 virus enters the hepatocyte expressing a low level of ACE2[58], since ACE2 levels generate energy, and protect from inflammation and oxidative stress, so by dysregulating the ACE2 virus will cause impaired energy metabolism and inflammation[60,61]. COVID-19 virus can cause a cytokine storm by inducing immune cells to release cytokines and chemokines[62], which can disrupt liver microtexture[63]. Cai et al reported about half of COVID-19 infected patients had liver enzyme elevation at the time of admission, most (>90%) had mild elevation, while 25% had liver enzyme more than 3 UNL, suggesting liver injury is due to viral infection per se rather than other factors are involved[64]. Moderate steatosis and mild lobular and portal damage were observed in post-mortem liver biopsies in COVID-19 patients [63]. There are scattered reports of tocilizumab-associated liver injuries however those were not backed by liver biopsies[66,67].

Limitations:

A retrospective kind of study conducted in a single center can be considered a limitation. The side effects like Diarrhea, chest pain, nausea, and vomiting cannot be evaluated as it was a retrospective study. We observed renal and hepatic parameters after anti-viral and tocilizumab medications, however, it does not indicate that these derangements are due to these medications, as they can be linked to the severity of the disease or other medications used during the treatment course, also renal and hepatic parameters of affected patients were not followed on regular basis after given anti-viral and tocilizumab.

Author Contribution:

F.A: conceived the idea of research, proposal writing, and data collection. ***K.G***: conceived the idea of research, data analysis and manuscript writing. ***A.B***: conceived the idea of research and data collection. **A.E.H**: data collection. ***A.S***: data collection. ***D.K***: data collection. ***H.R.A***: data collection. ***H.A***: data collection ***H.M.A***: data collection. ***M.A.A***: data collection. ***M.H.J***: data collection.

N.N: data collection. ***R.A.A***: data collection. ***T.H.I***: data collection. ***T.A***: data collection. ***N.M.A***: data collection & ***A.A***: conceived the idea of research, supervision of the study, and creative input.

Conclusion:

COVID-19-infected patients of either CKD or Non-CKD group were prone to kidney and liver injury, and it can be due to virus, cytokine storm, associated sepsis, hemodynamic instability, and medicines including antiviral, monoclonal antibodies and antibiotics. We observed that CKD patients had a significantly higher incidence of deterioration of renal function and abnormal rise in AST. Faviriravir treated CKD patients suffered from a higher incidence of deterioration of renal function than Non-CKD population, however, these abnormal lab parameters must be considered with other risk factors as mentioned earlier. Therefore, we believe COVID medicine shouldn't be denied to CKD patients solely based on low GFR but ought to be evaluated on individual case basis. Furthermore, the effects of these medicines on renal & hepatic functions should be assessed in organized & more focused studies.

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