Original Article

TIPS Trends in Pharmaceutical Sciences 2025: 11(1): 1-16

The pattern, pharmacotherapy course, drug-drug interactions, and clinical outcome of COVID-19 in kidney transplant patients at a referral transplantation hospital in Iran: A retrospective, observational study

Tannaz Alam-Rahnama[1,2];Pharm.D, Mojtaba Shafiekhani[2,3];Ph.D, Shokooh Behdadian[1,2];Ph.D$_{student}$, Iman Karimzadeh[2*];Ph.D

[1]Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran.
[2]Department of Clinical Pharmacy, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.
[3]Shiraz Transplant Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.

Abstract

Kidney transplant recipients are at higher risk of developing coronavirus disease 2019 (COVID-19). The aim of this study was to evaluate the pattern, pharmacotherapy, drug interactions, and clinical outcome of COVID-19 in kidney transplant recipients at a referral center in Iran. This retrospective, observational study was conducted in Abu Ali Sina Organ transplantation center in Shiraz, Iran. All adult kidney transplant patients diagnosed with COVID-19 and hospitalized for at least 48 hours were included. Required data were collected by reviewing medical charts and health information system of patients at hospital. Potential drug-drug interactions were identified using Lexi-Interact online as well as the Liverpool interactions online website. A total of 108 patients were included. Fever, cough, and shortness of breath were the most common clinical symptoms. About three-fourth (74%) of patients had non-severe COVID-19. Remdesivir was the most widely used antiviral agent. mTOR inhibitors and anti-metabolites were either dose reduced or discontinued in 100% and 80.2% of cases, respectively. Age (odds ratio [OR] = 1.06, 95% [Cl] = 1.02-1.09), calcineurin inhibitor adjustment (OR = 0.26, 95% Cl = 0.09-0.75), baseline white blood cell count (OR = 1.13, 95% Cl = 1.01-1.28), baseline serum lactate dehydrogenase level (OR = 1.32, 95% Cl = 1.03-1.69), administration of tocilizumab (OR = 0.06, 95% Cl = 0.07-0.54), and the severity of COVID-19 disease (OR = 0.03, 95% Cl = 0.00-0.03) had significant association with mortality. The present investigation found that COVID-19 infection in kidney transplant patients may be severe and require hospitalization and even, critical care.

Keywords: Kidney Transplantation, COVID 19, Pharmacotherapy, Drug Interactions.

Please cite this article as: Alam-Rahnama T, Shafiekhani M, Behdadian Sh, Karimzadeh I*. The pattern, pharmacotherapy course, drug-drug interactions, and clinical outcome of COVID-19 in kidney transplant patients at a referral transplantation hospital in Iran: A retrospective, observational study. Trends in Pharmaceutical Sciences. 2025;11(1):1-16.

1. Introduction

SARS-CoV-2, the virus causing COVID-19 pandemic, was first identified in Wuhan, China, in late 2019 (1, 2). The most common symptoms of COVID-19 include headache, fever, cough, shortness of breath, fatigue, and myalgia (3). Until December 29, 2024, there were 777,126,421 confirmed cases and

Corresponding Author: Iman Karimzadeh, Department of Clinical Pharmacy, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.
Email address: karimzadehiman@yahoo.com

Received: 08/04/2024; Accepted: 01/09/2024

7,079,925 deaths related to COVID-19 have been identified worldwide. In Iran, a total of 7,627,863 cases of COVID-19 with 146,837 deaths were reported by December 29, 2024 (4).

The highest morbidity and mortality due to COVID-19 have been reported among patients with certain underlying and chronic illnesses such as kidney disease (5, 6). Besides the fact that COVID-19 can affect the kidney via different mechanisms (7), solid organ transplant patients, including kidney transplant recipients, are especially at higher risk of serious complications from COVID-19. It is mostly attributed to the use of immunosuppressive drugs, older age (> 65 years), and underlying medical conditions such as diabetes, hypertension, and ischemic heart disease (8-10).

Although national and international transplant societies have provided guidelines and recommendations for the management of COVID-19 in solid organ transplantation, there is inadequate data on different aspects of COVID-19 in kidney transplant patients. Particularly, most relevant studies from Iran are case series. This study was conducted to evaluate COVID-19 pattern, pharmacotherapy, drug-drug interactions, and clinical outcome in hospitalized kidney transplant patients at a referral transplantation hospital in Iran. These data can enrich the database of COVID-19 in kidney transplant patients and assist in updating national guidelines about COVID-19 in kidney transplantation.

2. Methods

This retrospective, observational study was conducted in Abu Ali Sina Transplantation Hospital, affiliated to Shiraz University of Medical Sciences, Shiraz, Iran. It is one of the largest centers for solid organ transplantation throughout the world. During a 15-year period, 1,200 cases of kidney transplantation had been performed in this center (11). The study protocol was approved by the ethical committee of the Shiraz University of Medical Sciences (Ethical ID: IR.SUMS.REC.1401.033).

All adult (aged ≥18 years) kidney transplant patients diagnosed with COVID-19 and hospitalized for at least 48 hours from March 2017 to November 2021 were included. COVID-19 diagnosis was based on the positive real-time polymerase chain reaction (RT-PCR) SARS-CoV-2 test on nasopharyngeal and oropharyngeal swab samples. The procedure of RT-PCR for COVID-19 used in this center was described in brief previously (12). In other words, all studied patients were definite cases of COVID-19 that acquired the disease before hospitalization. No specific criteria were taken into account for excluding patients such as type of kidney donor (deceased versus living), duration of transplantation, and severity of COVID-19.

Required data were collected by reviewing medical charts and the health information system (HIS) of patients at hospital. These included demographic (age, sex, weight, height), clinical factors related to kidney transplantation (underlying disease, donor type, duration of kidney transplantation, immunosuppressive regimen), signs as well as symptoms related to COVID-19, possible immunosuppressive medications adjustment, and anti-COVID-19 regimen, laboratory findings related to COVID-19 (e.g., white blood cell count [WBC], c-reactive protein [CRP], lactate dehydrogenase [LDH], serum ferritin), and clinical outcome. Indexes of clinical outcome were length of hospital stay, length of ICU stay (if patients need ICU admission), the need for hemodialysis or continuous kidney replacement therapy (CKRT), acute kidney injury (AKI), allograft rejection, acute respiratory distress syndrome (ARDS), and mortality. AKI definition was based on the 2012 KIDGO criteria (13). The diagnosis of rejection was based on the biopsy of the transplanted kidney tissue. The Berlin 2012 ARDS diagnostic criteria was used to identify COVID-19 ARDS (14). Glomerular filtration rate (GFR) at the time of hospital admission was calculated by the CKD-EPI 2009 formula (15). The severity and stage of COVID-19 were determined

according to the definition provided by the World Health Organization (WHO) (16).

Potential drug-drug interactions (DDIs) between either anti-viral or anti-inflammatory agents used for COVID-19 and other medications were assessed by using both Lexi-Interact online as well as Liverpool COVID-19 interactions online software. In terms of Lexi-Interact online, only type D and type X DDIs were considered to be eligible for reporting because they are more clinically relevant. Mechanisms, severity, and reliability rating of identified DDIs were also provided.

2.1. Statistical analysis

The categorical variables were reported as number (percent). Normal distribution of continuous variables was assessed by the Kolmogorov-Smirnov test. All continuous variables were expressed as means±standard deviations (SD) or standard error (SE). We applied Fisher Exact or Chi-Square tests to examine the possible association of immunosuppressive drug changes (dose reduction or cessation) with some indexes of clinical outcome including dialysis, CKRT, and rejection. Logistic regression analysis with odds ratio (OR) and 95% confidence interval (CI) was used to assess the possible association between mortality and different demographic, clinical, and laboratory features of the study population. All statistical analyses were conducted by the SPSS software version 20. P-values less than 0.05 were considered to be statistically significant.

3. Results

In this study, 108 kidney transplant recipients diagnosed with COVID-19 were included. Table 1 demonstrates the demographic, clinical, and laboratory characteristics of the study population. Most (67.7%) of the study population were male. Patients were divided into three age categories (18-39 years [young], 40-64 years [middle age], and 65 years and older [elderly]) (17), and data demonstrated that most patients belonged to the middle-age category. The most frequent underlying diseases were hypertension (35.2%) and diabetes mellitus (31.5%). Dyspnea (44.4%), fever (36.1%), and cough (34.3%) were the most common signs and symptoms at the time of COVID-19 diagnosis. HRCT findings showed that about one-third (35.61%) of the lung was involved at the time of hospital admission. About one-fourth (24%) of the patients had blood oxygen saturation less than 90 percent. Most of the participants (80.4%) were not intubated. According to WHO criteria, about three-fourths (74%) of patients had non-severe COVID-19. The portion of patients with shock state (systolic blood pressure less than 90 mm Hg) was only 3.7%. The D-dimer, serum procalcitonin as well as IL-6 level, and the percent of lymphocytes (to calculate the percent of lymphopenia) were not either available or measured at all.

The most commonly used immunosuppressive regimen included a corticosteroid + a calcineurin inhibitor (cyclosporine or tacrolimus) + an antimetabolite (azathioprine or mycophenolate) (83.33%) followed by an antimetabolite + calcineurin inhibitors (8.33%), and corticosteroids + calcineurin inhibitors (4.63%). Prednisolone, tacrolimus, and mycophenolate are the most frequently administered corticosteroid, calcineurin inhibitor, and antimetabolite agent, respectively. Details of COVID-19 treatment regimens and agents prescribed for our patients are listed in Table 2. The least commonly used antiviral drug in the studied patients was hydroxychloroquine (one patient). Interferon was not prescribed for any patient. Among anti-inflammatory drugs, dexamethasone was the most commonly used one with the mean ± SD daily dose of 9.63±5.04 mg. Overall, injectable corticosteroids including dexamethasone, methylprednisolone, or hydrocortisone were prescribed in most patients (90.7%) as a part of the COVID-19 treatment regimen. In contrast, intravenous immunoglobulin (IVIG) was not

Table 1. Baseline demographic, clinical, and laboratory characteristics of the study population (n=108)

Gender	Female (%)	35 (32.41)
	Male (%)	73 (67.59)
Age (years)	Mean ±SD	49.57±13.96
Weight (kg)	Mean ±SD	69.38±13.76
BMI (kg/m2)	Mean ±SD	24.27±4.88
Transplantation status	Kidney (%)	102 (94.44)
	SPK (%)	6 (5.56)
Underling disease	Hypertension (%)	38 (35.19)
	Diabetes mellitus (%)	34 (31.48)
Vital signs, Mean ±SD or SE	Oral Temperature (°C)	36.69±0.5
	Heart rate (per minute)	88.93±15.06
	Number of breaths (per minute)	18.96±2.73
	Systolic blood pressure (mm Hg)	126.65±24.18
	Diastolic blood pressure (mm Hg)	76.61±13.45
	O2 saturation (percent)	89.62±12.28
Time after transplant (years)	Mean ±SE	6.11±0.6
Signs and symptoms	Dyspnea (%)	48 (44.44)
	Fever (%)	39 (36.11)
	Cough (%)	37 (34.26)
	Tremor (%)	19 (17.59)
	Weakness (%)	17 (15.74)
	Diarrhea (%)	16 (14.81)
	Nausea (%)	11 (10.19)
	Body pain (%)	9 (8.33)
	Headache (%)	5 (4.63)
	Fatigue (%)	4 (3.70)
	Abdominal pain (%)	2 (1.85)
Performing HRCT	N (%)	58 (53.70)
Amount of lung involvement	Mean ±SD	35.61±21.36
Laboratory findings, Mean ±SD or SE	WBC (103/µl)	6.77±0.375
	Ferritin (ng/ml)	123.43±850.57
	Potassium (mEq/L)	4.56±1.02
	BUN (mg/dl)	39.53±25.04
	ALB (g/dl)	3.70±0.62
	LDH (U/L)	642.81±62.77
	CRP (mg/L)	56.56±6.79
	Magnesium (mg/dL)	1.91±0.36
	Serum Creatinine (mg/dL)	2.95±2.16
	FK trough level (ng/ml)	12.52±4.3
	Cycl trough level (ng/dl)	104.86±27.92
Ventilation	Room air (%)	43 (39.81)
	Nasal mask (%)	43 (39.81)
	Intubation (%)	21 (19.44)
Estimated GFR (mL/min/1.73m2)	Mean ± SD	41.341±26.4

COVID-19 severity	Non-severe (%)	80 (74.07)
	Severe (%)	6 (5.56)
	Critical (%)	22 (20.37)

*Based on WHO criteria

BMI: Body mass index, HRCT: High-resolution computed tomography, GFR: Glomerular filtration rate, SPK: Simultaneous kidney-pancreas, WBC: White blood count, BUN: Blood Urea Nitrogen, ALB: Albumin, LDH: Lactate Dehydrogenase, CRP: C-Reactive Protein, FK-level: Tacrolimus level, Cycl-level: Cyclosporine level.

given to any subject.

Table 3 provides possible modifications of immunosuppressive regimen of the participants during the COVID-19. mTOR inhibitors and anti-metabolites were undergone either dose reduction or discontinuation in 100% and 80.2% of cases, respectively. The least number of dose adjustments were performed on corticosteroids during COVID-19.

Clinical outcome indexes in transplant patients are shown in Table 4. About one-third (30.8%) of subjects needed hemodialysis at least during the course of COVID-19 in hospital. The rate of bacterial co-infection, ARDS, and biopsy-proven allograft rejection, as the major causes of mortality in our study population, were 52.8%, 18.52%, and 9.26%, respectively. The incidence of AKI in the patients during hospital stay was 47.6%. More than three-fourths (78.7%) of patients were eventually discharged from the hospital. There was no significant association between possible adjustments of immunosuppressive regimen and clinical outcomes including the need for dialysis, CKRT, and acute allograft rejection.

The results of an univariate logistic regression analysis (Table 5) demonstrated that age (OR = 1.055, 95% Cl = 1.015-1.097; P-value = 0.007), calcineurin inhibitor adjustment (OR = 0.264, 95% Cl = 0.093-0.750; P-value = 0.012), baseline white blood cell count (OR = 1.134, 95% Cl = 1.009-1.275; P-value = 0.0.35), baseline serum LDH level (OR = 1.317, 95% Cl = 1.028-1.686; P-value = 0.029), administration of tocilizumab (OR = 0.057, 95% Cl = 0.006-0.535; P-value = 0.012), bacterial co-infection (OR = 0.314, 95% Cl = 0.113-0.873; P-value = 0.026), and the severity of COVID-19 (OR = 0.003 , 95% Cl = 0.00-0.03; P-value < 0.001) had signifi-

Table 2. Anti-COVID-19 regimens and agents used in the study population (n =108).

Drug name	Dose & duration	
Favipiravir	1st Day: 1800 mg every 12 hours orally	
	Then up to 1 days: 800 mg every 12 hours orally	
Remdesivir	1st Day: 200 mg daily intravenously	
	Then up to five days: 100 mg/day intravenously	
Tocilizumab	8 mg / kg - 800 mg maximum intravenously	
Dexamethasone	6 to 8 mg/day for 7 to 10 days intravenously	
Hydroxychloroquine	1st Day: 400 mg every 12 hours orally	
	Since 2nd day, 200 mg every 12 hours orally	
Name	**Number of patients (%)**	**Average daily dose (mg/day)**
Dexamethasone	70 (64.81)	9.63±5.04
Remdesivir	64 (59.26)	
Methylprednisolone	21 (19.44)	213.09±176.38
Favipravir	11 (10.19)	
Lopinavir/Ritonavir	8 (7.41)	
Hydrocortisone	7 (6.48)	167.86±114.30
Tocilizumab	5 (4.63)	
Hydroxychloroquine	1 (0.93)	

Table 3. Immunosuppressive adjustments in the study population during the course of hospital stay.

Immunosuppressive agent	Possible change	Number
Calcineurin inhibitors, n= 104 (%)	Increase dose	7 (6.73)
	Decrease dose	22 (21.15)
	No Change	56 (53.85)
	Discontinue	19 (18.27)
Anti-metabolites, n= 105 (%)	Increase dose	---
	Decrease dose	8 (7.62)
	No Change	20 (19.05)
	Discontinue	77 (73.33)
mTOR inhibitors, n = 3 (%)	Increase dose	---
	Decrease dose	---
	No Change	---
	Discontinue	3 (100)
Corticosteroids, n = 99 (%)	Increase dose	9 (9.09)
	Decrease dose	20 (20.20)
	No Change	70 (70.71)
	Discontinue	---

cant association with mortality in the study population. In other words, having older age, higher baseline white blood cell count as well as serum LDH level, either severe or critical COVID-19, bacterial co-infection, changing calcineurin inhibitor regimen, and receiving tocilizumab significantly increased the risk of mortality in kidney transplant patients with COVID-19. According to the number of independent variables and also sample size, performing multivariate logistic regression analysis was not statistically feasible.

Concerning the potential DDIs identified by Lexi-Interact online software, among 16 type D DDIs, 5 patients, 3 patients, and 1 patient experienced 2, 1, and 3 interactions, respectively. The most frequent type D DDIs were tacrolimus + lopinavir/ritonavir (7 cases) and dexamethasone + lopinavir/ritonavir (7 cases). The predominant mechanism of identified DDIs (93.75%) was pharmacokinetics. The reliability rating of most DDIs (87.4%)

Table 4. Clinical outcome of the study population during the hospital stay

Outcome	Value
Duration of hospital stay (days), Mean ± SE	10.61±1.02
Duration of ICU stay (days), Mean ± SD	7.51±2.38
Intubation time (days), Mean ±SD	6.96±1.95
Hemodialysis (%)	33 (30.56)
CKRT (%)	6 (5.56)
Bacterial co-infection (%)	57 (52.78)
ARDS (%)	5 (4.63)
AKI (%)	51 (47.22)
Allograft rejection (%)	10 (9.26)
Discharged (%)	85 (78.70)
Death (%)	23 (21.29)

CKRT: Continuous kidney replacement therapy, ARDS: Acute respiratory distress syndrome, AKI: Acute kidney injury.

Table 5. Comparison of different demographic, clinical, and laboratory variables between survived and dead patients during hospital stay*.

Variable		Clinical outcome		Univariate logistic regression	
		Survived	Dead	P value	OR (95% CI)
Sex (%)	Female	28 (25.92)	7 (6.49)	0.82	1.12 (0.41-3.04)
	Male	57 (52.78)	16 (14.81)		1
Age, years (Mean ± SD)		47.61 ± 14.09	56.83 ± 10.94	0.01	1.06 (1.02-1.09)
Body Mass Index, kg/m2 (Mean ± SD)		23.14 ± 5.46	24.66 ± 6.05	0.14	1.08 (0.98-1.19)
Time after transplant, years (Mean ± SE)		5.99 ± 0.65	6.52 ± 1.47	0.71	1.02 (0.94-1.09)
Underlying diabetes mellitus (%)	No	60 (55.56)	14 (12.96)	0.38	1.54 (0.59-4.02)
	Yes	25 (23.15)	9 (8.33)		1
Receiving favipravir (%)	No	78 (72.2)	19 (17.59)	0.21	0.43 (0.11-1.61)
	Yes	7 (6.48)	4 (3.73)		1
Receiving remdesivir (%)	No	35 (32.41)	9 (8.33)	0.86	1.09 (0.42-2.79)
	Yes	50 (46.30)	14 (12.96)		1
Receiving lopinavir/ritonavir (%)	No	81 (75)	19 (75)	0.05	0.24 (0.05-1.02)
	Yes	4 (3.70)	4 (3.70)		1
Receiving tocilizumab (%)	No	84 (77.78)	19 (17.60)	0.01	0.06 (0.01-0.54)
	Yes	1 (0.92)	4 (3.70)		1
Receiving corticosteroids (%)	No	24 (22.22)	0 (0)	0.99	---
	Yes	61 (56.48)	23 (21.30)		
Mechanical ventilation (%)	No	84 (78.50)	2 (1.87)	0.99	---
	Yes	0 (0)	21 (19.63)		
CNI change (%)	Without	50 (48.08)	6 (5.77)	0.01	0.26 (0.09-0.75)
	With	33 (31.73)	15 (14.42)		1
Anti-metabolite change (%)	Without	19 (18.81)	1 (0.99)	0.11	0.18 (0.02-1.47)
	With	63 (62.38)	18 (17.82)		1
Baseline GFR, ml/min/1.73m2 (Mean ± SD)		46.34 ± 37.69	31.66 ± 24.25	0.08	0.98 (0.96-1.00)
Baseline WBC, 103/µl (Mean ± SD)		5.70 ± 4.50	7.80 ± 6.50	0.04	1.13 (1.01-1.28)
Baseline Ferritin, ng/ml (Mean ± SD)		1.13 ± 0.49	1.61 ± 0.99	0.36	1.49 (0.64-3.49)
Baseline LDH, U/L (Mean ± SD)		5.33 ± 2.40	6.71 ± 4.73	0.03	1.32 (1.03-1.69)
Severity of COVID-19 (%)	Non-severe	79 (73.15)	1 (0.93)	0.01>	0.03 (0.00-0.03)
	Sever or critical	6 (5.55)	22 (20.37)		1

*Percent values were reported through dividing the number of patients in each group by the total number of patients in the study.

were either good or fair (Supplementary 1). No type X potential DDIs have been identified. According to Liverpool COVID-19 interactions online software, 80 DDIs were detected. The three most frequent DDIs were dexamethasone + tacrolimus (58 cases), dexamethasone + cyclosporine (13 cases), and tocilizumab + tacrolimus (3 cases). Except for hydroxychloroquine + dexamethasone (1 case), all other identified DDIs (98.75%) were classified to be pharmacokinetics (Supplementary 2).

4. Discussion

This paper presented the clinical as well as laboratory characteristics, pharmacotherapy course, DDIs, and clinical outcome of the kidney transplant recipients infected with COVID-19 and hospitalized at a referral transplantation hospital in Iran. The main strength of this study is the relatively adequate sample size compared to other studies (that are mostly case series) and also considering the potential

DDIs between anti-COVID-19 agents with other drugs used in kidney transplant patients.

In our study, mTOR inhibitors (100%) and antimetabolites (75%) were the most commonly modified immunosuppressive medications during the course of COVID-19 in hospital. Similarly, a study at a hospital in the north of Iran reported that among 22 kidney transplant recipients with COVID-19, mycophenolate was discontinued in 21 patients and doses of cyclosporine and tacrolimus were empirically reduced by 20% to 100% in 17 patients (18). In another study in solid organ transplantation at the same center in southwest of Iran, decreasing calcineurin inhibitor dose along with discontinuing antimetabolite, discontinuation of all immunosuppressive medications, and only the cessation of mTOR inhibitors use were identified in 37%, 21%, and 1% of the subjects, respectively (12). In a single center case series study in Belgium, the protocol of immunosuppression minimization during the course of COVID-19 in hospital included stopping antimetabolite treatment along with reducing the dose of tacrolimus/cyclosporine/everolimus dose to achieve trough level targets, and continuing routine steroid dose (19). Report from a medical center in New York in the United States implicated that discontinuing antimetabolites and tacrolimus were done in 86% and 21% of kidney transplant recipients with COVID-19, respectively (20). According to Banerjee *et al.* case series on 7 kidney transplant patients with COVID-19, it has been suggested that antimetabolite should be discontinued, the prednisolone dose should be either unchanged or increased, and tacrolimus dose should be reduced during the course of hospital stay. In the case of severe COVID-19 that needs ICU admission, stopping calcineurin inhibitors completely while maintaining corticosteroid therapy can be taken into account (21). The TANGO multicenter study at 12 transplant centers (that included 144 hospitalized kidney transplant patients with COVID-19) reported that mycophenolate or everolimus was reduced or discontinued (68%), whereas calcineurin inhibitor was discontinued in 23% of the study population (22). National guideline and suggested approach to immunosuppressive regimen of kidney transplant recipients during COVID-19 have been discussed elsewhere (23, 24). Overall, the management of immunosuppressive regimen during the course of COVID-19 is quite challenging and can even be deemed as a double-edged sword. It mostly depends on the patient's age, time duration after transplantation, comorbidities, and most importantly, the severity of COVID-19.

Remdesivir and hydroxychloroquine were the most and least commonly prescribed anti-COVID-19 agents in the current study, respectively. Among anti-inflammatory agents, corticosteroids including methylprednisolone, dexamethasone, and hydrocortisone were given to most patients (90.7%) during the course of COVID-19 in hospital. IVIG and interferon alpha or beta were not given to any subjects. In a study at north of Iran, hydroxychloroquine, lopinavir/ritonavir, and the combination of hydroxychloroquine + lopinavir/ritonavir + oseltamivir were given to 100%, 86%, and 72.73% of kidney transplant patients with COVID-19, respectively. In the case of hypoxemia and a creatinine rise, IVIG was added to treatment (18). In a case series study on kidney transplant patients with COVID-19 in Tehran, Iran from February 20 to May 14, 2020, all patients received IVIG and antiviral regimen, including hydroxychloroquine and umifenovir; three patients also took lopinavir/ritonavir (25). According to Abolghasemi *et al*. descriptive, cross-sectional study in two tertiary hospitals in Tehran, 100% and 75% of the patients received hydroxychloroquine and lopinavir/ritonavir, respectively. IVIG was administered to 33% of patients with severe pneumonia and hypoxemia (26). A more recently published study on kidney transplant recipients from March 2020 to May 2021 in Iran reported that remdesivir (42%) was the most commonly

prescribed anti-COVID-19 agent followed by lopinavir/ritonavir (37%) and hydroxychloroquine (32%) (27). In sum, at the early phase of COVID-19 pandemics, guidelines suggested hydroxychloroquine and lopinavir/ritonavir as the main anti COVID-19 agents; however, newer studies based on more clinical evidence discouraged the use of these two medications especially in the setting of solid organ transplantation. This is mostly due to numerous drug interactions between lopinavir/ritonavir and other immunosuppressive agents or serious adverse effects of hydroxychloroquine, especially QT prolongation. This adverse effect that mostly occurred in combination with other medications that may be given in patients with COVID-19 such as levofloxacin, azithromycin, ondansetron, and metoclopramide (28). Remdesivir use has been raised tremendously during the later phase of COVID-19 pandemic in Iran due to its FDA approval in October 2020 and also the manufacturing and availability of several generic formulations of this agent in the pharmaceutical market in Iran. The definite role of IVIG in the management of COVID-19 in both the general and specific populations (e.g., solid organ transplantation) is unclear and current national and international guidelines recommend against its common use. In terms of interferons, its clinical evidence for the management of COVID-19 is weak. More importantly, it may increase the risk of allograft rejection (29).

The mortality rate during hospitalization in our study was 21%. The death in study participants was mostly attributed to ADRS, co-bacterial infections, and acute allograft rejection/AKI. Regardless of transplantation, the mortality rate of COVID-19 significantly differs around the world, ranging from 0.3-8.4% (3). Although most literature have suggested that kidney transplant patients with COVID-19 are at high risk of mortality, few studies have evaluated and reported this issue so far. The incidence of ADRS in hospitalized kidney transplant patients with COVID-19 ranged from 29% to 68% (30). The rate of AKI during the course of COVID-19 in hospital in kidney transplant patients was reported to be 45-52% (with the average rate of 45.7%). By considering both adult inpatients and outpatients, the rate of AKI in kidney transplant patients with COVID-19 was 44% (95% CI: 39-49%) (30). The rate of AKI in our study (47.6%) is within the above range reported in the literature. The mortality rate of COVID-19 in kidney transplant recipients in three studies from Iran varied from 27.27% to 66.67% (12, 18, 25). This rate was 14% in Belgium (19), 28% in the United States (20), 14% in the United Kingdom (21), 16% in Croatia (31), 28% or 45.8% in Spain (32, 33), and 9.8% or 10.1% in first and second waves, respectively Turkey (34). The variation of the mortality rate of COVID-19 in kidney transplant patients can be largely due to the difference in the predominant strain of COVID-19, the severity of COVID-19 disease, the status of COVID-19 vaccination, time after transplantation, and the duration of patient follow-up. Despite the high risk of developing severe forms of the COVID-19 in transplant recipients, the comparison of clinical outcomes such as mortality between non-solid organ transplants and solid-organ patients including kidney has been revealed non-conclusive and even contradictory findings (35).

According to univariate regression logistic analysis, older age, dose adjustment or discontinuation of calcineurin inhibitor, tocilizumab administration, high white blood cell count at baseline, high serum LDH level at baseline, bacterial co-infection, and severity of COVID-19 have a significant association with mortality. High white blood cell count or serum LDH level at the time of diagnosis, the necessity for changing calcineurin inhibitor regimen or administering tocilizumab all can be partially explained in the context of COVID-19 severity, leading to death in our study population. Risk factors of mortality were not examined and reported in other relevant stud-

ies from Iran. Regardless of the study population, the association between older age and mortality in COVID-19 has been demonstrated in several hallmark studies worldwide. For example, analyzing records of 17,278,392 adults with COVID-19 implicated that older age significantly related to mortality (36). Similarly, the Spanish experience on COVID-19 in both solid organ (including 423 kidneys) and hematopoietic stem cell transplant revealed that the risk of death increased with age (OR for recipients >60 years: 3.7 [95% CI: 2.5-5.5]) (33). According to the TANGO multicenter study, older age, lymphopenia, higher LDH, procalcitonin, and IL-6 levels and also lower eGFR significantly associated with mortality (22). As mentioned previously, lymphocyte count, procalcitonin, and IL-6 levels were not measured at the time of hospital admission in our study. The significant association between COVID-19 severity and mortality identified in this study was in line with reports from other large investigations (37, 38).

Apart from certain demographic and paraclinical features, dose adjustment or discontinuation of calcineurin inhibitor associated with 74% increase in the risk of mortality in our survey. This finding was not observed and reported from other relevant studies in Iran. Interestingly, at least an *in vitro* study has reported the efficacy of cyclosporine A and FK506 in inhibiting the replication of SARS-CoV-1 and other human coronaviruses (39). In addition, cyclosporine treatment was associated with decreased risk of mortality in hospitalized kidney transplant patients with COVID-19 (relative risk = 0.08, 95% CI = 0.02-0.32) (30). Another possible justification of our finding in this regard is that the modification of calcineurin inhibitor, as a part of immunosuppressive regimen, may increase the risk of allograft rejection. However, we found no significant association between calcineurin inhibitor modifications with other clinical outcome indexes including the need for dialysis, CKRT, and acute allograft rejection in our study. The pooled graft loss rate among kidney transplant COVID-19 survivors was reported to be 8% (95% CI: 5-15%) (30). Albeit, the definite role of COVID-19 *per se* in allograft rejection during the course of disease is a complex issue with not fully-understood mechanisms.

Finally, the risk of mortality in tocilizumab recipients was 94% higher than those who did not receive this agent during the course of COVID-19 in hospital. Similarly, the analysis of the Spanish registry about kidney transplant patients with COVID-19 until 13 July 2020 implicated that non-survivors were more frequently treated with tocilizumab (32). This is in contrast to Shafiekhani *et al*. study that hospital as well as ICU length of stay and mortality were significantly lower in recipients than non-recipients of tocilizumab (12). The multicenter TANGO study found that the mortality rate was comparable between recipients and non-recipients of tocilizumab (22). Finally, a systematic review and regression analysis on 31 eligible articles on kidney-transplanted patients with COVID-19 failed to show any significant association between medications used for COVID-19 (e.g., tocilizumab) and mortality (37). These conflicting findings can be justified by a number of issues. First, the methodology and type of studies were diverse and encompassed case reports, case series, retrospective, and cohort studies. Second, an increase in the risk of bacterial infection secondary to leucopenia caused by tocilizumab may have an individual role. In this regard, besides leukopenia and thrombocytopenia, concomitant bacterial or fungal systemic infections and tuberculosis are generally considered as contraindications of tocilizumab use (40). Interestingly, bacterial co-infection had an independent link with mortality in our study population. Third, the appropriate dose, frequency, and more importantly, time of tocilizumab administration (as soon as possible after ICU admission and before intubation) along with co-administering

corticosteroids are crucial factors for achieving optimal clinical effectiveness of this agent in the case of severe COVID-19. Last but not least, the follow-up period for determining mortality was different. It is noteworthy that major guidelines like National Institutes of Health (NIH) and Infectious Diseases Society of America (IDSA) either recommend or suggest adding tocilizumab to the standard of care (e.g., glucocorticoids) for certain clinical conditions. These cases comprised hospitalized adults who have progressive severe or critical COVID-19 with either rapidly increasing oxygen needs or elevated markers of systemic inflammation like CRP level ≥75 mg/L, especially within the prior 24 hours of ICU admission (41, 42).

According to Lexi-Interact online software, the most frequently identified potential DDI in participants were tacrolimus + lopinavir/ritonavir and dexamethasone + lopinavir/ritonavir. Both of these two DDIs are pharmacokinetic. In terms of the former DDI, ritonavir (present in the Kaletra® formulation) can reduce hepatic metabolism and also increase tacrolimus oral absorption by the inhibition of cytochrome P450 subtype 3A4 (CYP3A4) and p-glycoprotein pump in the gastrointestinal tract, respectively. As a result, it can significantly increase serum level and eventually, adverse reactions of tacrolimus such as renal toxicity, opportunistic infections, neurotoxicity (tremor, paresthesia, encephalopathy, delirium, coma), hyperkalemia, QT prolongation, hypertension, and cardiomyopathy. Therefore, close monitoring of serum tacrolimus level and reducing its dose or increasing the time interval of administration, if needed, is necessary. In this regard, the national guideline for the management of COVID-19 has provided a detailed protocol for target trough level and required dose adjustments of tacrolimus in the setting of co-administering lopinavir/ritonavir or atazanavir/ritonavir for the management of COVID-19 with different severity stages at various time points after kidney transplantation (43).

The DDI between dexamethasone and lopinavir/ritonavir appears to be a two-way interaction. In this regard, ritonavir (present in the Kaletra® formulation) can increase the bioavailability of dexamethasone (more than three times) by inhibiting the activity of CYP3A4, involved in dexamethasone metabolism. On the other hand, dexamethasone can increase the hepatic metabolism of lopinavir via inducing the activity of CYP3A4. This could potentially lead to a decrease in maximal concentration, minimum concentration, as well as the bioavailability of lopinavir and to some extent, also ritonavir. Therefore, it is recommended that patients receiving dexamethasone and Kaletra® concurrently should be monitored for possible side effects of corticosteroids during treatment (especially hypokalemia, prolongation of the PR and QT segment, increased risk of bradycardia, heart block and related arrhythmias such as torsade de pointes). In addition, the possible diminished antiviral activity of Kaletra® and treatment failure should be also kept in mind. However, co-administering dexamethasone and lopinavir/ritonavir for the management of COVID-19 in real clinical practice is mostly inevitable. Moreover, as mentioned before, the role of lopinavir/ritonavir in the treatment regimens of COVID-19 has been considerably waned.

4.1. Limitations

This study is conducted in one kidney transplant hospital and our results may be prone to the center bias. In particular, COVID-19 treatment regimens and immunosuppressive modifications are mostly center-based and depend on physician preference. We did not consider the control group (non-kidney transplant patients with COVID-19) to compare and determine the possible risk factors of acquiring COVID-19 in kidney transplant recipients. The follow-up period of our patients were limited to the time of hospital discharge

or their death. Importantly, the COVID-19 vaccination status of the study population was unclear. Therefore, the possible impact of COVID-19 vaccinations (e.g. frequency of administration, vaccine platform and brand name) on the severity and mortality of the disease cannot be investigated. Finally, our retrospective study methodology did not allow us to determine the real clinical relevance and consequence of identified DDIs.

5. Conclusion

The present investigation found that COVID-19 infection in kidney transplant patients may be severe and they require hospitalization and even, critical care. The mortality rate of COVID-19 in kidney transplant patients is significant. Remdesivir and dexamethasone are the frequently used antiviral and anti-inflammatory agents to treat COVID-19, respectively. Our results indicated that older age, high white blood cell, serum lactate dehydrogenase levels, CNI regimen change, the severity of COVID-19 disease, bacterial co-infection, and the administration of tocilizumab were risk factors for mortality in kidney transplantation with COVID-19. Tacrolimus + lopinavir/ritonavir, dexamethasone + lopinavir/ritonavir, dexamethasone + tacrolimus, and dexamethasone + cyclosporine were the most common potential DDIs in the study population.

Data availability

All data relevant to the study are included in the article. In addition, the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

The study was approved by the Medical Ethics Committee of Shiraz University of Medical Sciences (Ethical ID: IR.SUMS.REC.1401.033).

Acknowledgements

The authors also gratefully acknowledge the Abu –Ali Sina organ Transplantation hospital in Shiraz, Iran for providing technical facilities to carry out this investigation.

Authors contributions

Tannaz Alam-Rahnama contributed in data curation, formal analysis, investigation, methodology, software, and manuscript review/ editing. Mojtaba Shafiekhani involved in conceptualization, methodology, resources, and manuscript review & editing. Shokooh Behdadian contributed in formal analysis, manuscript drafting and manuscript review/ editing. Iman Karimzadeh contributed in conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, validation, visualization, and manuscript review/editing

Funding source

This article was prepared from the data of the PharmD thesis of Tannaz Alam-Rahnama and was financially supported by the Vice-Chancellor of Research and Technology of Shiraz University of Medical Sciences (grant number: 24948).

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Yang Y, Shang W, Rao X. Facing the COVID-19 outbreak: What should we know and what could we do? *J Med Virol.* 2020 Jun;92(6):536-537. doi: 10.1002/jmv.25720. Epub 2020 Mar 5. PMID: 32091134; PMCID: PMC7228352.

2. Khodaei F, Ahsan A, Chamanifard M, Zamiri MJ, Ommati MM. Updated information on new coronavirus disease 2019 occurrence, drugs, and prediction of a potential receptor. *J Biochem Mol Toxicol.* 2020 Dec;34(12):e22594. doi: 10.1002/jbt.22594. Epub 2020 Aug 8. PMID:

32770858; PMCID: PMC7435514.
3. Kordzadeh-Kermani E, Khalili H, Karimzadeh I. Pathogenesis, clinical manifestations and complications of coronavirus disease 2019 (COVID-19). *Future Microbiol*. 2020 Sep;15:1287-1305. doi: 10.2217/fmb-2020-0110. Epub 2020 Aug 27. PMID: 32851877; PMCID: PMC7493723.
4. WHO COVID-19 dashboard. Available from: https://data.who.int/dashboards/covid19. (Accessed on January 12, 2025).
5. Ritschl PV, Nevermann N, Wiering L, Wu HH, Moroder P, Brandl A, et al. Solid organ transplantation programs facing lack of empiric evidence in the COVID-19 pandemic: A By-proxy Society Recommendation Consensus approach. *Am J Transplant.* 2020 Jul;20(7):1826-1836. doi: 10.1111/ajt.15933. Epub 2020 May 10. PMID: 32323460; PMCID: PMC7264649.
6. Caillard S, Thaunat O. COVID-19 vaccination in kidney transplant recipients. *Nat Rev Nephrol.* 2021 Dec;17(12):785-787. doi: 10.1038/s41581-021-00491-7. PMID: 34580488; PMCID: PMC8475856.
7. Diao B, Wang C, Wang R, Feng Z, Zhang J, Yang H, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 infection. *Nat Commun*. 2021 May 4;12(1):2506. doi: 10.1038/s41467-021-22781-1. PMID: 33947851; PMCID: PMC8096808.
8. López V, Vázquez T, Alonso-Titos J, Cabello M, Alonso A, Beneyto I, et al. Recommendations on management of the SARS-CoV-2 coronavirus pandemic (Covid-19) in kidney transplant patients. *Nefrologia (Engl Ed).* 2020 May-Jun;40(3):265-271. English, Spanish. doi: 10.1016/j.nefro.2020.03.002.
9. Kolla E, Weill A, Zaidan M, De Martin E, Colin De Verdiere S, Semenzato L, et al. COVID-19 Hospitalization in Solid Organ Transplant Recipients on Immunosuppressive Therapy. *JAMA Netw Open.* 2023 Nov 1;6(11):e2342006. doi: 10.1001/jamanetworkopen.2023.42006. PMID: 37934496; PMCID: PMC10630896.
10. Abu Jawdeh BG, Vikram HR. Coronavirus Disease 2019 in Kidney Transplantation - A 2024 Update. *Adv Kidney Dis Health.* 2024 Sep;31(5):458-465. doi: 10.1053/j.akdh.2024.03.004. PMID: 39232616.
11. Malek-Hosseini S, Razmkon A, Mehdizadeh A, Salahi H, Bahador A, Raiss-Jalali GH, et al. Long-term results of renal transplantation: A single-center analysis of 1200 transplants. *Transplant Proc.* 2006 Mar;38(2):454-6. doi: 10.1016/j.transproceed.2006.01.020. PMID: 16549145.
12. Shafiekhani M, Shahabinezhad F, Niknam T, Tara SA, Haem E, Mardani P, et al. Evaluation of the therapeutic regimen in COVID-19 in transplant patients: where do immunomodulatory and antivirals stand? *Virol J.* 2021 Nov 22;18(1):228. doi: 10.1186/s12985-021-01700-2.
13. Palevsky PM, Liu KD, Brophy PD, Chawla LS, Parikh CR, Thakar CV, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. *Am J Kidney Dis*. 2013 May;61(5):649-72. doi: 10.1053/j.ajkd.2013.02.349. Epub 2013 Mar 15. PMID: 23499048.
14. Gibson PG, Qin L, Puah SH. COVID-19 acute respiratory distress syndrome (ARDS): clinical features and differences from typical pre-COVID-19 ARDS. *Med J Aust.* 2020 Jul;213(2):54-56. e1. doi: 10.5694/mja2.50674. Epub 2020 Jun 22. PMID: 32572965; PMCID: PMC7361309.
15. Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. *Am J Kidney Dis*. 2010 Apr;55(4):622-7. doi: 10.1053/j.ajkd.2010.02.337. PMID: 20338463; PMCID: PMC2846308.
16. Patel MK, Bergeri I, Bresee JS, Cowling BJ, Crowcroft NS, Fahmy K, et al. Evaluation of post-introduction COVID-19 vaccine effectiveness: Summary of interim guidance of the World Health Organization. *Vaccine*. 2021 Jul 5;39(30):4013-4024. doi: 10.1016/j.vaccine.2021.05.099.
17. Yamada G, Hayakawa K, Matsunaga N, Terada M, Suzuki S, Asai Y, et al. Predicting respiratory failure for COVID-19 patients in Japan: a simple clinical score for evaluating the need for hospitalisation. *Epidemiol Infect*. 2021 Jul 30;149:e175. doi: 10.1017/S0950268821001837. PMID: 36043382; PMCID: PMC8365048.
18. Monfared A, Dashti-Khavidaki S, Jafari R, Jafari A, Ramezanzade E, Lebadi MK, et al. Clinical characteristics and outcome of COVID-19 pneumonia in kidney transplant recipients in Razi hospital, Rasht, Iran. *Transpl Infect Dis.*

2020 Dec;22(6):e13420. doi: 10.1111/tid.13420. Epub 2020 Aug 2. PMID: 32681756; PMCID: PMC7404381.
19. Devresse A, Belkhir L, Vo B, Ghaye B, Scohy A, Kabamba B, et al. COVID-19 Infection in Kidney Transplant Recipients: A Single-Center Case Series of 22 Cases From Belgium. *Kidney Med*. 2020 Jun 15;2(4):459-466. doi: 10.1016/j.xkme.2020.06.001. PMID: 32775986; PMCID: PMC7295531.
20. Akalin E, Azzi Y, Bartash R, Seethamraju H, Parides M, Hemmige V, et al. Covid-19 and Kidney Transplantation. *N Engl J Med.* 2020 Jun 18;382(25):2475-2477. doi: 10.1056/NEJMc2011117. Epub 2020 Apr 24. PMID: 32329975; PMCID: PMC7200055.
21. Banerjee D, Popoola J, Shah S, Ster IC, Quan V, Phanish M. COVID-19 infection in kidney transplant recipients. *Kidney Int*. 2020 Jun;97(6):1076-1082. doi: 10.1016/j.kint.2020.03.018. Epub 2020 Apr 9. PMID: 32354637; PMCID: PMC7142878.
22. Cravedi P, Mothi SS, Azzi Y, Haverly M, Farouk SS, Pérez-Sáez MJ, et al. COVID-19 and kidney transplantation: Results from the TANGO International Transplant Consortium. *Am J Transplant.* 2020 Nov;20(11):3140-3148. doi: 10.1111/ajt.16185. Epub 2020 Aug 4. PMID: 32649791; PMCID: PMC7405285.
23. Ahmadian E, Zununi Vahed S, Mammadova S, Abediazar S. Immunosuppressant Management in Renal Transplant Patients with COVID-19. *Biomed Res Int.* 2021 Oct 14;2021:9318725. doi: 10.1155/2021/9318725. PMID: 34692845; PMCID: PMC8531766.
24. Samavat S, Nafar M, Firozan A, Pourrezagholi F, Ahmadpoor P, Samadian F, et al. COVID-19 Rapid Guideline in Kidney Transplant Recipients. *Iran J Kidney Dis.* 2020 May;14(3):231-234. PMID: 32361701.
25. Rahimzadeh H, Keykhaei M, Razeghi E, Zivari E, Mansouri ES. COVID-19 progression in kidney transplant recipients: a single-center case series. *CEN Case Rep*. 2021 Nov;10(4):494-499. doi: 10.1007/s13730-021-00584-z. Epub 2021 Mar 26. PMID: 33770414; PMCID: PMC7994352.
26. Abolghasemi S, Mardani M, Sali S, Honarvar N, Baziboroun M. COVID-19 and kidney transplant recipients. *Transpl Infect Dis.* 2020 Dec;22(6):e13413. doi: 10.1111/tid.13413. Epub 2020 Jul 31. PMID: 32677721; PMCID: PMC7404434.
27. Shafiekhani M, Kazemi K, Bahador A, Imanieh MH, Karimzadeh P. Pediatric liver and kidney transplantation in the era of COVID-19: a follow-up study from a tertiary referral center in Iran. *BMC Surg*. 2021 May 11;21(1):240. doi: 10.1186/s12893-021-01226-y. PMID: 33975594; PMCID: PMC8112472.
28. García-Rodríguez D, Remior P, García-Izquierdo E, Toquero J, Castro V, Fernández Lozano I. Drug-induced QT prolongation in COVID-19 pneumonia: influence on in-hospital survival. *Rev Esp Cardiol (Engl Ed)*. 2021 Jan;74(1):111-112. doi: 10.1016/j.rec.2020.09.027. Epub 2020 Oct 29. PMID: 33172794; PMCID: PMC7598758.
29. Ma BM, Hung IFN, Chan GCW, Tam AR, Chan SSK, Wong BCK, et al. Case of "relapsing" COVID-19 in a kidney transplant recipient. *Nephrology (Carlton).* 2020 Dec;25(12):933-936. doi: 10.1111/nep.13786. Epub 2020 Sep 28. PMID: 32951300; PMCID: PMC7536982.
30. Toapanta N, Torres IB, Sellarés J, Chamoun B, Serón D, Moreso F. Kidney transplantation and COVID-19 renal and patient prognosis. *Clin Kidney J.* 2021 Mar 26;14(Suppl 1):i21-i29. doi: 10.1093/ckj/sfab030. PMID: 33815780; PMCID: PMC7995521.
31. Dogas T, Brkovic T, Novak I, Radic J. COVID-19 in kidney transplant recipients; a DALMATIAN single-center experience. *Ther Apher Dial*. 2023 Feb;27(1):107-116. doi: 10.1111/1744-9987.13894. Epub 2022 Jun 19. PMID: 35684944; PMCID: PMC9347706.
32. Pascual J, Melilli E, Jiménez-Martín C, González-Monte E, Zárraga S, Gutiérrez-Dalmau A, et al. COVID-19-related Mortality During the First 60 Days After Kidney Transplantation. *Eur Urol*. 2020 Oct;78(4):641-643. doi: 10.1016/j.eururo.2020.06.036. Epub 2020 Jun 19. PMID: 32624283; PMCID: PMC7303649.
33. Coll E, Fernández-Ruiz M, Sánchez-Álvarez JE, Martínez-Fernández JR, Crespo M, Gayoso J, et al. COVID-19 in transplant recipients: The Spanish experience. *Am J Transplant.* 2021 May;21(5):1825-1837. doi: 10.1111/ajt.16369. Epub 2020 Nov 10. PMID: 33098200; PMCID: PMC9906239.
34. Demir E, Ucar ZA, Dheir H, Danis R, Yelken B, Uyar M, et al. COVID-19 in Kidney

Transplant Recipients: A Multicenter Experience from the First Two Waves of Pandemic. *BMC Nephrol.* 2022 May 12;23(1):183. doi: 10.1186/s12882-022-02784-w. PMID: 35550025; PMCID: PMC9097147.

35. Schaenman J, Byford H, Grogan T, Motwani Y, Beaird OE, Kamath M, et al. Impact of solid organ transplant status on outcomes of hospitalized patients with COVID-19 infection. *Transpl Infect Dis*. 2022 Aug;24(4):e13853. doi: 10.1111/tid.13853. Epub 2022 Jun 13. PMID: 35579437; PMCID: PMC9347588.

36. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature.* 2020 Aug;584(7821):430-436. doi: 10.1038/s41586-020-2521-4. Epub 2020 Jul 8. PMID: 32640463; PMCID: PMC7611074.

37. Navari Y, Bagheri AB, Akhavan Rezayat A, SeyedAlinaghi S, Najafi S, Barzegary A, et al. Mortality risk factors in kidney-transplanted patients with COVID-19: A systematic review and regression analysis. *Health Sci Rep*. 2021 Nov 4;4(4):e427. doi: 10.1002/hsr2.427. PMID: 34761124; PMCID: PMC8567748.

38. Villanego F, Mazuecos A, Pérez-Flores IM, Moreso F, Andrés A, Jiménez-Martín C, et al. Predictors of severe COVID-19 in kidney transplant recipients in the different epidemic waves: Analysis of the Spanish Registry. *Am J Transplant.* 2021 Jul;21(7):2573-2582. doi: 10.1111/ajt.16579. Epub 2021 Apr 12. PMID: 33756067; PMCID: PMC8250925.

39. Carbajo-Lozoya J, Müller MA, Kallies S, Thiel V, Drosten C, von Brunn A. Corrigendum to 'Replication of human coronaviruses SARS-CoV, HCoV-NL63 and HCoV-229E is inhibited by the drug FK506' Virus Research (2012) 165/1 [112-117]: *Corrigendum. Virus Res*. 2023 Jan 2;323:198952. doi: 10.1016/j.virusres.2022.198952. Epub 2022 Oct 27.

40. Fu B, Xu X, Wei H. Why tocilizumab could be an effective treatment for severe COVID-19? *J Transl Med*. 2020 Apr 14;18(1):164. doi: 10.1186/s12967-020-02339-3. PMID: 32290839; PMCID: PMC7154566.

41. National Institutes of Health. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available from: https://wayback.archive-it.org/4887/20240626155208/https://www.covid19treatmentguidelines.nih.gov/ (Accessed on October 25, 2023).

42. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/ (Accessed on February 21, 2021).

43. Flowchart of diagnosis and treatment of covid-19 disease at outpatient and inpatient levels. 7th version, June 27, 2020. Available from:. chrome-extension://kdpelmjpfafjppnhbloffcjpeomlnpah/https://treatment.sbmu.ac.ir/uploads/oldfile/7__dastoor_flochart_treatment_covid_19.pdf. (Accessed on September 18, 2024).