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ORIGINAL REPORT

Iranian kidney transplant recipients with COVID-19 infection: Clinical outcomes and cytomegalovirus coinfection

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Abstract

Background: There is a high risk of COVID-19 in kidney transplant recipients (KTRs) because of chronic immunosuppression and severe cytomegalovirus (CMV) pneumonitis.

Case presentation: A case series of 10 KTRs with COVID-19 in Iran was developed. Participants consisted of two female and eight male patients, aged 46-68 years old. The data related to clinical laboratory tests, outcomes, diagnosis, and drug treatments were collected. The RT-PCR confirmed the COVID-19 infection in KTRs. The assessment of serum biochemical and blood hematological factors showed that there was a strong correlation between COVID-19 intensity and high serum Cr, BUN, and ALT levels, high CRP concentration, and lower lymphocyte and platelet counts in male KTRs. Ground-glass opacity (GGO) was the main radiologic pattern visible on both chest radiographs of computed tomography scans. The COVID-19 and CMV coinfection in KTRs resulted in large-size kidneys with severe parenchymal echogenicity and hydronephrosis. The combined use of effective antibiotic and antiviral drugs was suitable to prevent COVID-19 progression in KTRs.

Conclusions: The coincidence of COVID-19 and CMV in KTRs may potentially increase the mortality risk of patients. The levels of Cr, BUN, ALT, and CRP as well as lymphocytes count in these patients should be continuously controlled.

KEYWORDS

COVID-19, cytomegalovirus, kidney transplantation, renal disease, viral coinfection

1 | BACKGROUND

The outbreak of new coronavirus disease (COVID-19) in December 2019 first occurred in the Chinese city of Wuhan, and then shortly spread throughout the world.[1] The high prevalence rate of this viral disease is because of the remarkable vital contagiousness and the rapid transmission in the pre-symptomatic phase.[2] In January 2020, the World Health Organization (WHO) announced this viral disease as a global health emergency. However, due to the substantial destructive impact of COVID-19 on the world's people's health and social life as well as on global economic status, the WHO declared COVID-19 as a pandemic on 11 March 2020.[1,2] By the end of April 2020, 94 640 patients with COVID-19 in Iran have been identified, of which 6028 deaths have been occurred by the new coronavirus. Accordingly, this country, from the point of view of the number of deaths caused by COVID-19, ranks 10th after the USA, Brazil, Mexico, India, the UK, Italy, France, Spain, and Peru.[3]

Although individuals of all ages are susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), older people with

Abbreviations: ACE2, angiotensin converting enzyme II; ARDS, acute respiratory distress syndrome; BUN, blood urea nitrogen; CMV, cytomegalovirus; Cr, creatinine; CRP, C-reactive protein; GGO, ground-glass opacity; KTR, kidney transplant recipient; NRF, normal renal function; PMNs, polymorphonuclear neutrophils; RT-PCR, real-time reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

underlying diseases show a significant number of comorbid conditions such as diffuse alveolar damage with cellular fibromyxoid exudates and severe acute respiratory distress.[4-6] This novel coronavirus after the infection of lungs may also accumulate in kidneys and cause injuries to renal cells severely.[7] The COVID-19 infection in kidney transplant recipients (KTRs) may intensify kidney failure owing to the severe immunosuppression, comorbidity/multimorbidity, and underlying disease.[8] Furthermore, cytomegalovirus (CMV) is the most prevalent pathogen causing renal transplantation complications.[9,10] The prevalence of CMV IgG and CMV IgM antibodies in Iran were estimated to be 92% (95% CI: 90-94) and 2.6% (95% CI: 1.7-3.6), respectively. Thus, the high seroprevalence of CMV IgG reflects the endemic state of CMV infection in this country.[11] Babazadeh et al[12] reported that CMV was diagnosed among 178 out of 725 (24.6%) Iranian KTRs. They also proved that the CMV seroprevalence of KTRs within an age range of 41-60 years was fourfold more than those under 20 years old.[12] Preemptive therapy (with oral valganciclovir) is usually considered as a major strategy for CMV prevention among Iranian KTRs.[12-14]

To the best of our knowledge, there is limited information about clinical symptoms, diagnosis using laboratory tests, and available therapies for KTRs infected with SARS-CoV-2. Herein, we tried to present Iranian KTRs with COVID-19 infection in terms of clinical signs and symptoms, medical managements and pivotal role of CMV co-infection,and other risk factors on the health status of patients with COVID-19.

2 | METHODS

2.1 | Study design and participants

From 8 February 2020 to 28 March 2020, a total of 10 cases of KTRs with COVID-19 infection including eight males and two females were detected and enrolled in special ward "corona patients" of the Baqiyatallah Hospital (Tehran, Iran). While our patients were maintained on cyclosporine or tacrolimus, and mycophenolic acid or mycophenolate mofetil, mycophenolic acid or mycophenolate mofetil was discontinued after COVID-19 diagnosis. According to our preventive strategy for CMV infection, preemptive therapy was performed, KTRs monitored once weekly for 12 weeks post-transplantation until detecting CMV replication and beginning the treatment with valganciclovir (900 mg twice daily in normal renal function [NRF]) and in critically ill patients with intravenous ganciclovir (5 mg/kg twice daily in NRF). Recipients were also evaluated for CMV infection in every admission due to fever. All the patients referred to the hospital presented with fever and dry cough and were in an age range of 46-68 years. None of them had a history of sick contacts in the family. No cases were missed during this period.

2.2 | Data collection and representation

Demographic details of all the participants including gender, age, previous chronic disease (eg, diabetes and hypertension), smoking history, and epidemiological history were recorded. The body temperature, systolic blood pressure, and pulse rate were determined. The respiratory rate was counted at the bedside for 1 minute. Primary symptoms of COVID-19 infection such as fever, dry cough, nausea, chills, etc were diagnosed during the admission time. The typical chest computed tomography (CT) images were obtained for each patient. CT scans were reviewed to observe the usual characteristic signs of COVID-19, such as peripheral and/or sub-pleural ground-glass opacities ground-glass opacities (GGOs). The final diagnosis of COVID-19 was confirmed using the molecular analysis of real-time reverse transcription-polymerase chain reaction (RT-PCR). Accordingly, an RT-PCR nasopharyngeal swab test was used to diagnose patients with COVID-19. All the patients were tested for CMV infection during hospitalization according to the CMV-PCR assay of whole blood samples. In brief, a quantitative real-time PCR was used to diagnose the presence of CMV. The standard test for diagnosing CMV infection on whole blood specimens was conducted with forward primer (50GCAGCCACGGGATCGTACT-30) and the reverse primer (50GGCTTTTACCTCACACGAGCATT-30), through a dual-labeled fluorogenic probe (TaqMan® probe, Novingene Sanjesh Co., Tehran, Iran).[15] Moreover, the kidney sonography with a 2.5 MHz transducer was performed. Results obtained in this research were reported as means, whereas categorical variables were summarized as counts and percentages. No imputation was made for missing data.

3 | RESULTS

The clinical appearance and some risk factors are shown in Table 1. Only 20% of these patients were female. The median age of the total population, men and women was 59.6 ± 7.72, 60.62 ± 6.69, and 55.5 ± 13.43 years, respectively. According to the checklists filled by the patient's family, the mean duration from illness beginning to admission was 7.5 days. The kidney transplantation period among patients was different from 3 months to 11 years before the COVID-19 infection. Eight patients were recovered and discharged from the hospital, while two individuals died due to the severity of the complications. The shortest and longest recovery period belonged to cases nos. 1 (7 days) and 4 (52 days), respectively. The (frequent) hospitalization index was their high serum creatinine (Cr) levels. Fever (37.1-38.5°C) in all the patients was observed, whereas seven subjects had a dry cough. Other primary symptoms were shortness of breath, weakness/fatigue, nausea, chills, abdominal pain, vomiting, diarrhea, and anorexia. The molecular testing by RT-PCR confirmed the COVID-19 in patients. Four cases suffered from COVID-19 and CMV (412-592 IU/mL) co-infection and unfortunately, two of them died. Based on past medical history, 50% of patients co-infected with SARS-CoV-2and CMV (two out of four) had diabetes mellitus for more than 7 years. The mean values of fasting blood sugar of these patients (nos. 3 and 8) during the hospitalization stay were 145 and 164 mg/dL, respectively. It is noteworthy, all of them were on cyclosporine as an immunosuppressive regimen. Overall, diabetes

TABLE 1 A list of primary symptoms, clinical signs, and disease history of Iranian KTR cases with COVID-19

	Case no.[a]									
Parameters	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Gender	Male	Male	Male	Male	Female	Female	Male	Male	Male	Male
Age (years)	56	58	68	62	46	65	48	66	67	60
Admission date	4 March	28 March	26 March	8 February	18 March	17 March	9 March	7 March	12 March	18 March
Discharge date	11 March	21 April	-	30 March	28 March	25 March	-	31 March	31 March	15 April
ICU admission (Ventilator need)	No	Yes	Yes	No	No	No	Yes	Yes	No	No
Death date	-	-	9 April	-	-	-	28 March	-	-	-
Blood type	B+	O+	A-	A+	O-	B-	AB+	A+	A+	B+
Transplantation time (yrs-before)	2	1	3.5	0.15	0.3	1	5	11	5.5	2.5
Hospitalization index	NR	High Cr	High Cr	High Cr	NR	High Cr	NR	High Cr	High Cr	High Cr
Primary symptoms	Fever Cough	Fever, Cough, Nausea	Fever, Cough, Anorexia	Fever, SB, Cough, Vomiting, Diarrhea	Fever, Chills	Fever, SB, Cough	Fever, Cough, Nausea	Fever, Weakness, Fatigue, Abdominal pain	Fever, SB, Weakness, Fatigue	Fever, Cough
Temperature (°C)	37.8	37.2	37.5	38.1	38.5	38.0	37.2	37.3	37.1	37.4
COVID-19 (+/−)	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.
CMV (+/−)	Neg.	Neg.	Pos.	Neg.	Neg.	Pos.	Pos.	Pos.	Neg.	Neg.
Diabetes (+/−)	Neg.	Pos.	Pos.	Pos.	Pos.	Neg.	Neg.	Pos.	Neg.	Neg.
FBS/BS (mg/dL)	FBS, 96	BS, 185	FBS, 145	FBS, 106	BS, 219	FBS, 68	FBS, 150	FBS, 164	FBS, 72	FBS, 241
Hypertension (+/−)	Neg.	Neg.	Neg.	Pos.	Neg.	Neg.	Pos.	Neg.	Neg.	Neg.
Blood pressure (mm Hg)	120/80	120/80	130/70	110/65	140/90	110/70	NR	130/80	120/80	120/80
Smoking habit (+/−)	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Pos.	Pos.	Neg.	Neg.
Pulse rate (bpm)	80	90	76	78	88	75	96	80	78	80
Respiratory rate (bpm)	20	20	18	19	18	17	24	18	20	19

Abbreviations: BS, Blood sugar; Cr, Creatinine; FBS, Fasting blood sugar; NR, Not reported; SB, Shortness of breath.

[a]All the demographic and basic information were obtained during the admission time.

mellitus (in five cases) and hypertension (in two cases) were considered as underlying diseases to COVID-19. The other non-diabetic patients were treated with tacrolimus or cyclosporine. The levels of fast blood sugar among the patients ranged from 68 to 241 mg/dL. The blood pressure mainly was in a normal range. Two co-infected cases with SARS-CoV-2 and CMV had history of cigarette smoking. The pulse and respiratory rates among patients were 75-96 and 18-24 bpm, respectively. The case no. 7 coinfected with SARS-CoV-2 and CMV and a smoking history had the maximum pulse (96 bpm) and respiratory (24 bpm) rate (Table 1). Overall, four KTR patients were admitted in the ICU on a ventilator.

Table 2 exhibits the serum biochemical and blood hematological parameters of 10 KTRs with COVID-19. The blood urea nitrogen (BUN) and Cr levels ranged from 26 to 105 and 1.0 to 10.4 mg/dL, respectively. The highest BUN and Cr amounts were observed in case no. 10, while cases nos. 1 and 4 recorded the maximum triglyceride (364 mg/dL) and cholesterol (178 mg/dL), respectively. This case also revealed notable levels of liver enzymes of AST (135 U/L) and ALT (89 U/L) compared to the other patients. The normal homeostasis of sodium (Na) and potassium (K) is a an indicator of normal renal function. The Na and K levels were 118-142 and 3.5-5.7 mg/dL, respectively. Lymphocytes as primary targets of COVID-19 were

TABLE 2 Serum biochemical and blood hematological factors of samples collected from Iranian KTR cases with COVID-19

	Case no.									
Parameters[a]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Serum biochemistry										
BUN (mg/dL)	36	61	99	80	36	22	23	97	82	105
Cr (mg/dL)	3.5	5.7	7.0	6.6	2.2	1.0	2.5	3.9	3.8	10.4
Cholesterol (mg/dL)	-	71	70	178	-	2.5	-	122	101	-
TG (mg/dL)	364	271	92	128	-	87	-	200	92	-
LDL (mg/dL)	252	-	-	-	-	-	-	53	-	-
HDL (mg/dL)	-	-	-	-	-	-	-	45	-	-
Calcium (mg/dL)	9.2	7.8	-	6.8	9.2	-	-	-	9.5	-
Inorganic phosphate (mg/dL)	-	-	-	11.7	-	2.7	-	-	-	-
Potassium (mg/dL)	4.1	5.5	5.7	4.7	4.0	3.5	3.5	4.6	4.5	5.3
Sodium (mg/dL)	142	133	118	130	136	143	133	135	139	139
Magnesium (mg/dL)	-	-	-	1.7	2.2	-	1.8	-	-	-
AST (SGOT, U/L)	23	17	260	22	-	21	22	43	13	135
ALT (SGPT, U/L)	44	34	231	10	-	13	100	10	10	89
ALP (U/L)	-	-	-	-	-	-	-	-	150	427
LDH (U/L)	-	-	2750	552	-	-	-	1205	-	1182
Blood/hematology										
WBC (×1000)	7.4	9.8	4.0	6.6	5.9	11.0	9.1	4.2	10.8	19.6
Lymphocytes (×1000)	2.5	1.41	0.40	2.13	0.76	0.88	0.80	0.49	1.08	0.90
Polymorphonuclear leukocytes (×1000)	3.9	7.05	3.70	3.82	3.59	9.79	7.46	3.31	9.39	17.85
HGB (g/dL)	12.6	9.4	8.1	9.7	39.3	11.4	11.1	9.1	8.8	9.3
HCT (%)	34.2	29.2	22.9	30.7	107.5	35.3	34.9	25.8	25.1	29.3
PLT (×1000)	202	192	131	151	211	158	122	146	259	126
PCT (μg/L)	0.1	-	0.1	-	0.3	0.1	-	0.092	-	-
CPK (U/L)	-	-	-	26	49	-	-	-	-	-
ESR (mm/h)	-	-	-	55	81	22	-	45	40	-
Troponin (ng/mL)	-	-	-	0.01	0.002	-	-	-	-	-
CRP (mg/L)	30.1	28.3	52.9	45.7	12	2.6	43.1	40.2	19.5	20.4

Abbreviations: ALP, Alkaline phosphatase; ALT (SGPT), Alanine aminotransferase (Serum glutamic pyruvic transaminase); AST (SGOT), Aspartate aminotransferase (Serum glutamic oxaloacetic transaminase); BUN, Blood urea nitrogen; CPK, Creatine phosphokinase; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; HCT, Hematocrit; HGB, Hemoglobin; LDH, Lactate dehydrogenase; LDL, Low-density lipoprotein; PCT, Procalcitonin; PLT, Platelet; TG, Triglyceride; WBC, White blood cell.

[a]All the data were analyzed on the second day of hospitalization.

TABLE 3 A summary of lungs CT scan data, transplanted kidneys sonography results, and drug treatments of Iranian KTR assessed in this study

	Case no.									
Parameters	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
CT scan results of lungs	Patchy GGO in both lobes	Multifocal patchy GGO in both lobes	Multifocal patchy GGO in both lobes, Paracardiac opacity in the left lobe	Pleural effusion and GGO, especially in the peripheral segments	Multifocal patchy GGO in both lobes, mainly in the peripheral segments	Multifocal patchy GGO in both lobes, mainly in the peripheral segments	Bilateral multilobar infiltrate, Patchy GGO	Multifocal patchy GGO in both lobes, mainly in the peripheral segments	Patchy consolidation in the left lung (inferior lobe)	Patchy GGO in both lobes
Sonography results of transplanted kidney[a]	Small SCH; Normal HP	Normal HP, Normal kidney volume, No HN, stone, and tumor	Remarkable RPE; Large dimensions with a high number of cysts	Echogenic focus with dirty shadow, Gas presence in parenchymal areas and pyelocaliceal systems	No HN, stone, and tumor; RCMD	No HN, stone, and tumor; RCMD	Increased RPE; Large dimensions with many cysts	Normal kidney volume and indexes (e.g., RI)	Normal kidney volume and indexes (e.g., RI); No HN and stone	Normal RAIs; No HN, stone, and tumor
Antibiotic treatment(s)	-	-	AZ, MP, TC-400, CM-900	TC-400 ampule (t.d.s.), PT[b]	-	MP	MP (t.d.s.), V (1.0 g)	-	AZ, MP (1.0 and 500 mg/b.d.), TC-400, CX	MP, Linezolid (600 mg/d)
Antiviral treatment(s)	-	-	GCV (100 mg/d)	-	-	GCV (25 mg/b.d.)	OTV (75 mg/d), RBV (50 and 75 mg/d)	OTV (30 mg/d)	-	
Immunosuppressive drug(s)	-	MPN	MPN (15 mg/d), H, CSP (25 mg/b.d.)	MPN (30 mg/d), CSP (150 mg/b.d.), MPA (360 mg/b.d.)	MPN (5 mg/d), TAC 1.0 mg	TAC 1.0 mg	MPN (5 and 15 mg/d), CSP	-	MPN (5 mg/b.d.), CSP (50 mg/b.d.)	Fentanyl
Other medical intervention(s)	IVIG (High-dose)	PPH, IVIG, HCQ	PP, M, NX (250 mg/b.d.)	Insulin (10U, t.d.s.)	DZ, MF (500 mg/d), Clestra (2 tablets/d), FI/C (12 mg/d), HCQ	G-CSF, NX, HCQ, Nystatin	PP, NX, Clestra (2 tablets/d), FI/C (12 mg/d)	HCQ (200 mg/d)	PP, DZ (60 mg/b.d.), M (50 mg/b.d.), TSL, FS, AP (100 mg/d), CCT (25 mg/d)	IVIG, PP, EPO

Abbreviations: AP, Allopurinol; AZ, Azithromycin; CCT, Calcitriol; CM-900, Clindamycin-900 mg; CSP, Cyclosporine; CT, Computed tomography (taken on the first day of hospitalization); CX, Ceftriaxone; DZ, Diltiazem; EPO, Erythropoietin; FI/C, Formoterol inhaler/capsule; FS, Finasteride; G-CSF, Granulocyte-colony stimulating factor; GCV, Ganciclovir; GGO, Ground-glass opacity; H, Heparin; HCQ, Hydroxychloroquine; IVIG, Intravenous immunoglobulin; M, Metoprolol; MF, Metformin; MP, Meropenem; MPA, Mycophenolic acid; MPN, Methylprednisolone; NX, Naproxen; OTV, Oseltamivir; PP, Pantoprazole; PPH, Plasmapheresis; PT, Piperacillin/Tazobactam; RBV, Ribavirin; TAC, Tacrolimus; TC-400, Teicoplanin-400 mg; TSL, Tamsulosin; V, Vancomycin.

[a]Analyzed on the second and third days of hospitalization and represented as an average of results. SCH: Subcapsular hematoma, HP: hepatic parenchymal, HN: Hydronephrosis, RCMD: Renal corticomedullary differentiation, RI: resistive index, RAI: Renal arteries index, RPE: Renal parenchymal echogenicity.

[b]PT: A combination medication containing the antibiotic piperacillin (P) and the β-lactamase inhibitor tazobactam (T).

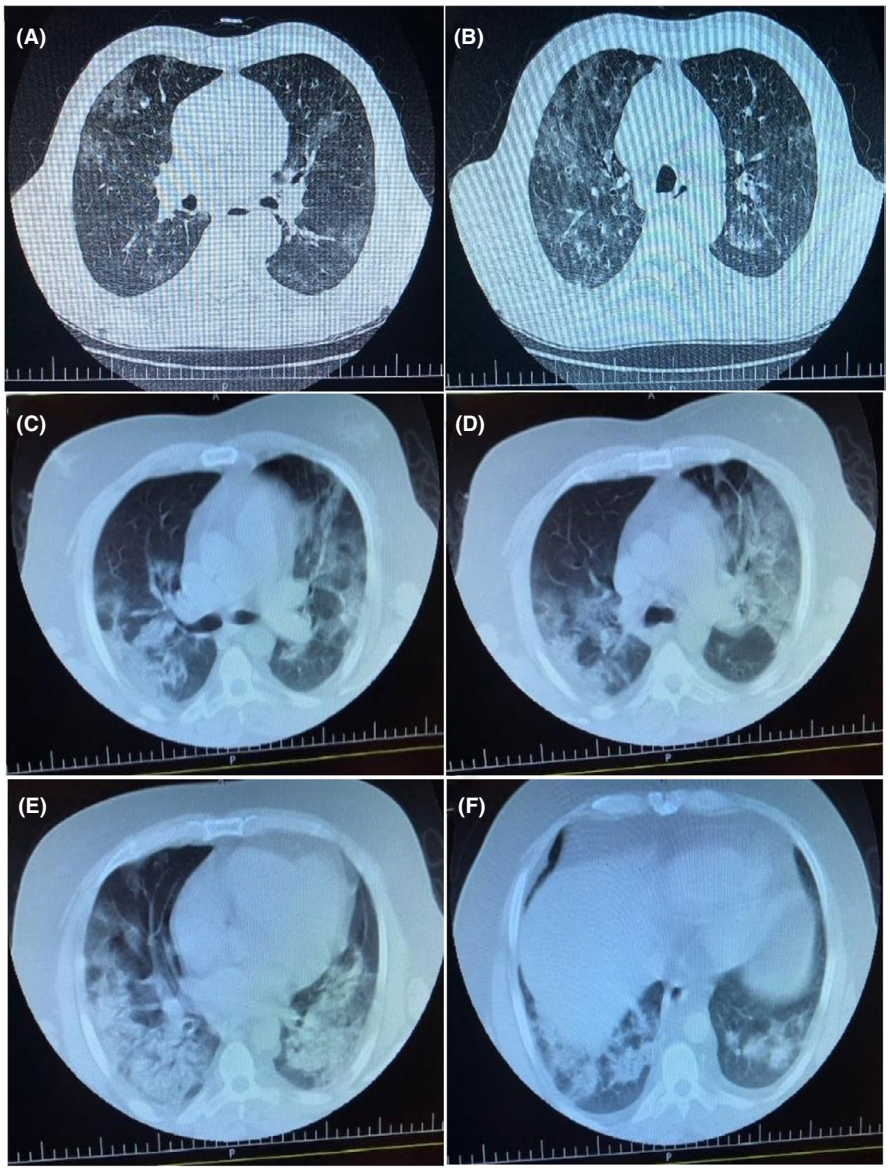

FIGURE 1 CT scan images of Iranian KTR cases with COVID-19 (A, C, E), as well as with COVID-19 and CMV (B, D, F) on the admission (A, B) and the 3rd (C, D) and 5th (E, F) days after the hospitalization

significantly reduced. Although there was no significant difference in the decreased number of lymphocytes between cases nos. 3 and 8, the lowest lymphocytes count (~400) and hemoglobin (8.1 g/dL) belonged to the dead case (no. 3), who suffered from the coinfection of SARS-CoV-2 and CMV. The platelet count among KTRs with COVID-19 ranged from 101 000 to 259 000. The higher C-reactive protein (CRP) level was associated with more severe symptoms.

Ground-glass opacity (GGO) was the most common radiologic finding in chest computed tomography (CT) scan when admitted in hospital (Table 3). Even though multifocal patchy GGO in both lungs was found, especially when KTRs are coinfected with SARS-CoV-2 and CMV (Figure 1A and B). As the COVID-19 progresses, paracardiac opacity, pleural effusion, bilateral multilobar infiltrate, crazy paving pattern, and consolidations mainly in the peripheral segments can be seen in the chest CT imaging. Figure 1 compares the radiologic findings such as GGOs and other pulmonary manifestations with blurred borders mainly distributed in the middle and lower lobes of both lungs in patients with COVID-19 alone or those with COVID-19 and CMV co-infection. Ultrasonographical study in all patients revealed unremarkable findings in allograft unless in COVID-19 and CMV co-infected patients whose expired allografts were enlarged with an increase in parenchymal echogenicity and hydronephrosis. However, there were small irregular cystic lesions in KTRs' kidneys before the COVID-19 infection. Meropenem, teicoplanin, and azithromycin were the most common administered antibiotics, respectively. Also, antiviral agents such as ganciclovir, oseltamivir, and ribavirin were used in some patients as indicated. Moreover, hydroxychloroquine and pulse corticosteroid therapy were administered for four KTRs during the hospitalization period (Table 3).

4 | DISCUSSION

According to the WHO's list, COVID-19 has become one of the biggest threats to global health security. The COVID-19 management and control in patients with kidney transplantation are very

challenging due to their chronic immunosuppression and susceptibility to a variety of viral pathogens.[16] One or more infectious processes such as atypical respiratory infections may be present in KTRs. Accordingly, there is a possibility for concurrent viral infections of CMV and SARS-CoV-2 in these patients. On the other hand, as the major receptor of SARS-CoV-2 to enter into the host cells is the angiotensin-converting enzyme II (ACE2) and expression of this receptor occurs in two vital organs of kidney and lung, renal failure similar to respiratory failure could be expected. Li et al[17] using the human tissue RNA-seq data showed that the ACE2 expression in respiratory organs (lungs) was ~100-fold less than kidneys.

In this study, KTRs about 60 years old were referred to our medical center due to fever, dry cough, and shortness of breath. RT-PCR examination was then performed to confirm COVID-19 infections. Guillen et al[18] reported a 50-year-old male KTR in Spain with COVID-19 with a 24-hour history of fever (38.2°C), cough without dyspnea, malaise, and vomiting. A recent review on KTRs with COVID-19 has shown that most cases in the world are male with a mean age of over 50 years. Patients received immunosuppressants such as tacrolimus with mycophenolate and prednisone, while 18% of them progressed to respiratory failure requiring mechanical ventilation.[19] We found similar results, although the more percentage of KTRs (40%) had a need for a ventilator. In addition, Banerjee et al[9] reported that 42.8% (three out of seven) British KTR cases with COVID-19 required non-invasive ventilation with a continuous positive airway pressure for respiratory failure. The preliminary treatment ways for most KTRs was the discontinuation of some immunosuppressive agents (ie, mycophenolic acid or mycophenolate mofetil) and beginning with a set of antibiotics and antivirals.[20] Zhu et al[21] used IVIG, steroids, and interferon α to treat a 52-year-old Chinese man with COVID-19, who received kidney transplantation 1 year ago. Guillen et al[18] and Gandolfini et al[22] applied hydroxychloroquine (HCQ) to treat KTRs with COVID-19. In our study, IVIG (patients 1 and 2) and HCQ (patients 2, 5, 6, and 8) were also administered to treat 20% and 40% KTRs. Although the use of colchicine probably could decrease the atypical inflammatory responses in KTRs,[22] Zhang et al[23] did not use HCQ to treat all five Chinese KTRs with COVID-19.

In the present study, the COVID-19 intensity with severe sign and symptoms was associated nore with high serum Cr and BUN levels and lower lymphocyte and platelet counts in male KTRs. Similar results on the increased serum Cr and BUN in KTRs with COVID-19 were reported.[24,25] Chen et al[26] earlier showed that the COVID-19 did not lead to acute kidney injury among 116 hospitalized patients from Wuhan, China, despite an increase in BUN or Cr levels after the COVID-19 infection and during the treatment. The level of creatine kinase is positively associated with the serum Cr level. According to a recent study, cytokines or mediators induced by COVID-19 can lead to a mild to moderate increase in creatine kinase.[27] The lymphopenia was also observed by COVID-19 infection in British,[9] French,[28] Thai,[29] and Indian[30] KTRs. This risk factor mainly was due to the decreased count of T-type lymphocytes (such as CD4 + T and CD8 + T cells) with the potential anti-pathogenicity effect against SARS-CoV-2.[26,31] In general, the immune response of KTRs predominantly the T-cell immune-regulatory function is highly depressed owing to immunosuppressive agents. Therefore, we recommend to reduce these agents to lower limit of maintenance as soon as possible. Under this clinical strategy, the preserved immunity might eradicate SARS-CoV-2.[32]

Although there was not an acceptable number of cases, the present study revealed that smoking and diabetes mellitus may increase KTRs' susceptibility to COVID-19 and CMV infection. Acute respiratory distress syndrome (ARDS) is one of the most important complications in smoker KTRs with a severe infection of COVID-19.[21,33] Brake et al[34] explained that the ACE2 can be upregulated on the airway epithelial cells of smokers. In a retrospective study, one-fifth of Chinese patients with COVID-19 had a history of diabetes mellitus, showing an increased risk of COVID-19 along with a poorer prognosis.[35] Thus, since ACE2 is widely expressed in different vital organs systems (eg, kidneys, lungs, heart, and brain), some patients with severe COVID-19 infection died of multiple organ failure.

The coinfection of CMV and SARS-CoV-2 in KTRs has not been yet reported. We found that this coinfection could significantly increase the disease severity and mortality rate. CMV as a prevalent infection in KTRs acts through two main cell mechanisms: (i) the transcription and upregulation of IL-2 and its receptor and the inhibitory effect of cyclosporine on the transcription of IL-2 gene, and (ii) the generation of a high number of proinflammatory cytokines as a result of the activation of cellular DNA, messenger RNA, and protein synthesis.[36] These mechanisms not only induce endothelial activation and rejection but also directly lead to an allograft injury.[37] Accordingly, the coincidence of these adverse effects with the COVID-19 infection by reducing the number of white and red blood cells can cause morbidity and mortality in KTRs. High levels of CRP in dead KTRs with CMV and COVID-19 coinfection was proved according to the disease severity. This data suggest that this biomarker might be applied to predict severe infection before their lung CT lesion appeared. Recently, Tan et al[38] also reported that CRP could be correlated with the development of this novel viral disease and represented an acceptable performance to forecast COVID-19 severity in early stages.

5 | CONCLUSIONS

This study showed that the COVID-19 changed BUN, Cr, and ALT levels, lymphocytes number, as well as CRP amount in KTRs. The GGO was the most frequent pattern induced by the process of entry of SARS-CoV-2 into the host cell in the lung CT scan. The COVID-19 and CMV coinfection especially in KTRs led to more severe symptoms and mortality. The large-size kidneys with increasing parenchymal echogenicity and hydronephrosis in these patients were found. Although it cannot be concluded that there were some associations between laboratory variables and clinical outcomes owing to the small sample size and lack of control group, implementing a case-control design with an acceptable number of participants would be

appropriate to enable the data acquisition with high reliability and repeatability. Thus, more studies are needed to obtain a more complete vision and a reliable result of KTRs infected with COVID-19 alone or in combination with CMV.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All the participants were informed with details of the study and signed the consent form after receiving spoken and written information on the study and ensuring the data confidentiality and anonymity. This case-related study was approved by the Human Ethics Committee of Baqiyatallah University of Medical Sciences (Tehran, Iran) with an ethical code of IR.BMSU.REC.1399.118.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of this research and any accompanying images.

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CONFLICTS OF INTEREST

The authors have declared no conflict of interests.

AUTHOR'S CONTRIBUTION

HM and LK designed the study. EN, ZR, and HM collected and interpreted the data and prepared the figures and tables; LK drafted the manuscript; ZR, SHS, and HM conceived the research plan and supervised and coordinated all the work. The final version of this manuscript has been read and approved by all authors and it is not under consideration for publication elsewhere.

DATA AVAILABILITY STATEMENT

All the data of this case series are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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