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Case Series of the Month

Clinical Course, Imaging Features, and Outcomes of COVID-19 in Kidney Transplant Recipients

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Abstract

Coronavirus disease 2019 (COVID-19) is a novel and highly contagious disease caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Older adults and patients with comorbidities and immunosuppressive conditions may experience severe signs and symptoms that can lead to death. This case series assesses the clinical course, imaging features, and outcomes for 12 patients with COVID-19 and a history of kidney transplantation. Patients were evaluated for symptoms, laboratory data, imaging findings, and outcomes from February 2020 to April 2020. Fever, cough, and dyspnea were the most common clinical symptoms, noted in 75% (nine/12), 75% (nine/12), and 41.7% (five/12) of the patients, respectively. Most of the patients had a normal white blood cell count, while 33.3% (four/12) had leukopenia and 8.3% (one/12) had leukocytosis. A combination of consolidation and ground glass opacity was the most predominant (75%) pattern of lung involvement on computed tomography (CT). Eight patients died of severe COVID-19 pneumonia and acute respiratory distress syndrome and four were discharged. All recovered cases had a unilateral peripheral pattern of involvement limited to only one zone on initial chest CT. It seems that CT imaging has an important role in predicting COVID-19 outcomes for solid organ transplant recipients. Future studies with long-term follow up and more cases are needed to elucidate COVID-19 diagnosis, outcome, and management strategies for these patients.

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1. Case series

1.1. Background

On December 31, 2019, a novel corona virus was extracted from the respiratory secretions of several patients presenting with lower respiratory tract infection of unknown origin in Wuhan, China [1]. While the mortality rate of coronavirus disease 2019 (COVID-19) is believed to be approximately 5% [2], older adults and those with an underlying chronic disease are specifically at high risk of presenting with severe symptoms, having poorer prognosis, and even developing fatal conditions [3]. Use of immunosuppressive medications such as steroids may also be linked to severe manifestation

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of the disease, as in patients with previous respiratory viral infections such as H1N1 [4].

Solid organ transplant recipients are on long-term immunosuppressive regimens and are at particular risk of contracting severe respiratory tract infection and possibly with atypical presentation [5]. There are currently limited data on the clinical course, imaging features, and outcomes for COVID-19 in renal transplant recipients. Although some studies noted no other outstanding severe disease among immunosuppressed patients with COVID-19 [6], other studies revealed that immunocompromised patients may have an impaired immune response and high levels of viral load [7].

Here we report clinical and imaging findings for COVID-19 and outcomes in a group of patients with a functioning renal transplant under an immunosuppressive regimen.

1.2. Cases

The study cases consisted of 12 patients with a functioning renal transplant who were admitted to our tertiary hospital with a confirmed diagnosis of COVID-19 between February 25, 2020 and April 12, 2020.

All subjects met the following inclusion criteria: (1) symptoms suggestive of COVID-19 pneumonia (ie, fever, cough, dyspnea, sore throat, myalgia, headache, nausea, or abdominal pain); (2) positive SARS-CoV-2 nasopharyngeal sample (polymerase chain reaction–based test); (3) chest computed tomography (CT) scan suggestive of COVID-19; and (4) lymphocytopenia (absolute lymphocyte count <1000) or dyspnea or O_2 saturation $<93\%$ or respiratory rate >30/min.

Nine patients were male (75%) and three were female (25%). The mean age ($\pm$ standard deviation) of the patients was 47.66 ± 1.35 (range 29–66) yr. The most common symptoms were fever, cough, and dyspnea, noted in 75% (nine/12), 75% (nine/12), and 41.7% (five/12), respectively. On admission, all patients were on standard triple immunosuppressive therapy (steroid, calcineurin inhibitor/sirolimus, mycophenolate mofetil/azathioprine). The medical history of the patients was reviewed for any chronic conditions other than chronic renal failure. Table 1 shows detailed clinical characteristics of the cases. Leukopenia was observed in 33.3% (four/12) and leukocytosis in 8.3% (one/12). C-reactive protein was elevated in 83.3% (10/12) and creatine phosphokinase in 55% (five/nine). On admission, mean blood urea nitrogen was 82.9 ± 55.2 mg/dl and creatinine was 2.30 ± 1.09 mg/dl. Graft function on admission in terms of estimated glomerular filtration rate based on the Modification of Diet in Renal Disease equation was 39.9 ± 24.5 cm^3/min. Table 2 lists detailed laboratory findings.

On admission, the oral steroid was changed to intravenous steroid administration. The immunosuppressive dose was reduced according to the protocol in our center under consultation with multidisciplinary team comprising a nephrologist, urologist, and infectious disease specialist. Hydroxychloroquine 400 mg stat, Kaletra (lopinavir/ritonavir) 400/100 mg twice daily, and suitable intravenous antibiotics were initiated for all patients. Intravenous immunoglobulin 1–2 g/kg in segregated doses over 5 d was administered in the case of hypoxemia and a creatinine rise with clinical suspicion of kidney transplant rejection.

As a part of our national COVID-19 guidelines, all patients underwent noncontrast chest CT imaging using a low-dose protocol. Two expert radiologists with 9 and 18 yr of experience interpreted the images independently. In the case of disagreement between the readings, the two radiologists reassessed the images in order to reach consensus. The laterality of the disease (unilateral vs bilateral), the distribution (peripheral vs central, anterior vs posterior), and the predominant zonal involvement (upper, middle, lower, or diffuse) were recorded. The predominant pattern of involvement in each lobe was assessed and categorized as ground-glass opacity (GGO) or consolidation. When there was a combination of GGO and consolidation, the allocation was divided between them accordingly. The percentage of lobar involvement was scored using the following system: 0, no involvement; 1, $<25\%$; 2, 26–50%; 3, 51–75%; and 4, $>75\%$ involvement [8]. The scores for each lobe were summed to calculate the total lung score (maximum score 20). The final score was multiplied by five to estimate the percentage lung involvement. The presence of other imaging features was also

Table 1 – Demographic and clinical features and outcomes for the 12 patients.

Pt	Gender	Age (yr)	Age of KTx (yr)	CMBs	Fever	Cough	HA	Myalgia	Dyspnea	GIS	SO_2 (%)	Outcome
1	Female	29	8	None	+	+	–	–	–	–	88	Discharged
2	Male	32	12	HTN	+	+	–	+	+	+	85	Discharged
3	Male	58	14	None	–	–	–	–	–	–	88	Death
4	Male	38	15	None	–	+	–	+	+	–	84	Death
5	Male	54	18	Asthma + SA	+	+	–	–	–	–	90	Death
6	Male	46	3	None	+	+	–	–	+	–	85	Discharged
7	Male	66	4	None	+	–	–	–	–	–	85	Death
8	Male	32	17	None	+	+	–	–	+	–	84	Death
9	Male	64	6	None	+	+	–	–	+	–	90	Death
10	Male	64	3	None	+	+	–	–	–	–	84	Death
11	Female	49	17	HTN	–	+	+	–	–	–	90	Discharged
12	Female	40	16	None	+	–	–	–	–	–	88	Death

KTx = kidney transplantation; CMBs = comorbidities; HTN = hypertension; SA = stable angina; HA = headache; GIS = gastrointestinal symptoms (abdominal pain/diarrhea); SO_2 = oxygen saturation on room air.

Table 2 – Baseline laboratory findings.

	Patient												Summary
	1	2	3	4	5	6	7	8	9	10	11	12	(mean ± SD)
White blood cell count	2000	5500	3800	5600	12 200	8700	7200	8800	4200	3100	7500	2500	5925 ± 3050
Neutrophil count	1040	4345	2470	4984	11 590	6264	5976	7920	3318	2697	6000	2050	4887.83 ± 2934.14
Lymphocyte count	840	1100	1140	560	610	2001	1152	704	798	279	1200	375	896.58 ± 464.81
Eosinophils (%)	3	0	2	0	0	2	0	0	1	2	2	1	–
Hemoglobin (g/dl)	9.1	11.7	15.4	11	9.9	12.4	9.1	11.7	13.6	11.1	15.2	8.5	11.55 ± 2.28
Platelets ($\times 10^3$)	131	485	123	148	263	465	160	171	107	54	161	98	197 ± 139
C-reactive protein (mg/l)	17	30	5	61	40	66	24	49	3	31	23	30	31.58 ± 19.76
Lactate dehydrogenase (U/l)	305	384	412	110	506	80	326	641	592	931	898	928	509.41 ± 297.36
Creatinine (mg/dl)	2.99	0.92	1.53	2.55	2.96	1.77	2.50	4.60	1.23	1.50	1.51	3.60	2.3 ± 1.09
Blood urea nitrogen (mg/dl)	85	23	33	119	156	60	145	150	30	39	18	137	82.91 ± 55.16
Aspartate transaminase (U/l)	19	17	25	24	19	26	12	28	37	167	31	12	34.75 ± 42.3
Alanine transaminase (U/l)	6	11	17	8	19	42	14	14	19	96	43	8	24.75 ± 25.52
Alkaline phosphatase (U/l)	92	118	203	205	128	106	90	102	148	204	237	134	147.25 ± 51.52
Albumin (g/l)	3.1	4	3	4.5	3.1	3	3.6	3.2	3.4	2.7	3.3	3.9	3.4 ± 0.51
Na (mEq/l)	138	139	138	137	141	143	141	133	137	133	142	140	138.5 ± 3.2
K (mEq/l)	4.5	3.5	4.1	3.6	3.4	5	5	4.1	4	4.4	3.7	3.4	4.05 ± 0.57
Prothrombin time (s)	10.5	10.6	9.8	11.6	13.3	10	11.7	11.1	9.8	14.8	9.8	9.9	11.07 ± 1.58
Partial thromboplastin time (s)	20	20	20	22	27	20	23	69	20	37	26	20	27.05 ± 14.18
International normalized ratio	1.01	1.06	0.9	1.13	1.3	1.1	1.14	1.07	0.94	1.4	0.9	0.95	1.07 ± 0.15

SD = standard deviation.

assessed on CT scan images, including interlobular septal thickening, crazy-paving pattern, reverse halo sign, cystic changes, presence of cavitations, lymphadenopathy (defined as lymph node with short axis >10 mm), and pleural and pericardial effusion.

The initial CT scan on admission showed bilateral lung involvement in eight patients and unilateral involvement in four. The lower lobes were frequently involved, as observed in 11/12 of patients (Table 3). A combination of consolidation and GGO was the most predominant (75%) pattern, followed by GGO only (25%; Fig. 1). In terms of lesion distribution, a combination of peripheral plus central involvement was the most common. The mean lung involvement score was 9.5 ± 5.5 out of 20, which gives a mean estimate of 47.5 ± 27.8% for total lung involvement (Table 4).

We did not observe cavitation, cystic changes, or lymphadenopathy in any of the study population. Three patients had pleural or pericardial effusion or both. Four patients had a mildly elevated cardiothoracic ratio on chest CT. Pneumomediastinum was observed in two patients who had severe changes on chest CT, but neither was intubated or underwent noninvasive ventilation (NIV) before acquisition of the CT scan.

Table 3 – Frequency of chest computed tomography scan features in the 12 patients.

Parameter		Patients, *n* (%)
Lung involvement	Bilateral	8 (66.7)
	Unilateral	4 (33.3)
Lobar anatomy	Right upper lobe	9 (75)
	Right middle lobe	10 (83.3)
	Right lower lobe	11 (91.7)
	Left upper lobe	9 (75)
	Left lower lobe	11 (91.7)
Zonal anatomy	Upper	1 (8.3)
	Middle	3 (25)
	Lower	3 (25)
	Diffuse	5 (41.7)
Axial distribution	Peripheral	4 (33.3)
	Peripheral + central	8 (66.7)
Segmental distribution	Posterior	8 (66.7)
	Anterior	2 (16.7)
	Diffuse	2 (16.7)
Computed tomography features	Ground glass opacity	12 (100)
	Consolidation	9 (75)
	Interlobular septal thickening	5 (41.7)
	Dilated small vessels in the lesion	9 (75)
	Crazy-paving	2 (16.7)
	Pleural effusion	2 (16.7)
	Pericardial effusion	1 (8.3)

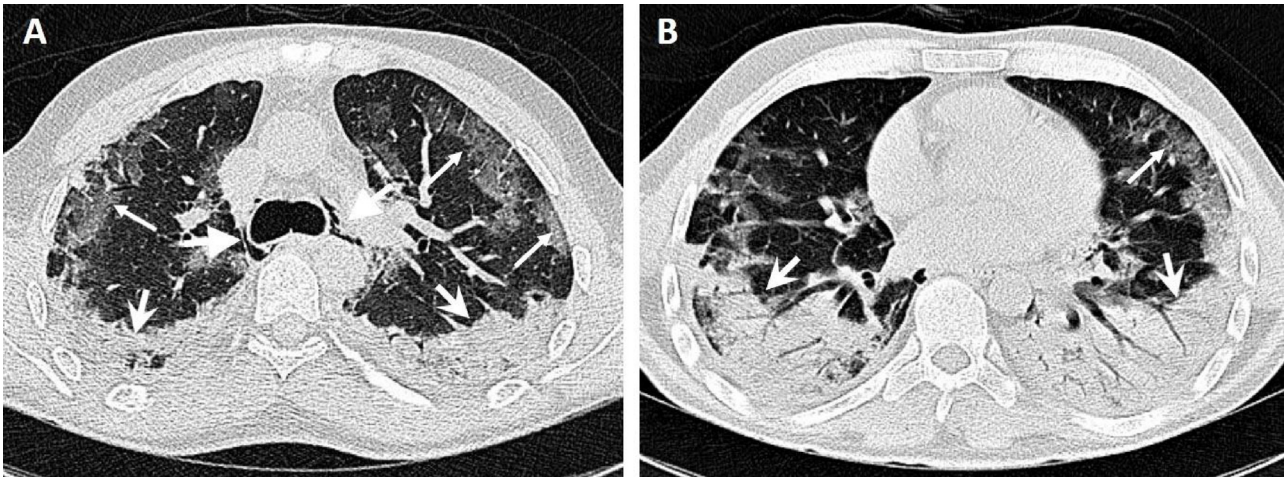

Fig. 1 – A 38-yr-old male patient presented with a dry cough and dyspnea and a history of kidney transplantation 15 yr previously. Computed tomography images show bilateral peripheral ground glass opacity (thin arrows) on the anterior side and an area of bilateral consolidation with air bronchogram (wide arrows) on the posterior side, predominantly in the lower lobes. Incidental pneumomediastinum is noted (thick-headed arrows). The patient died after 22 d in hospital.

Table 4 – Chest computed tomography scores for each lobe and total lungs.

Lobar anatomy	Ground glass opacity	Consolidation	Total score
Right upper lobe	1.5	0.16	1.66
Right middle lobe	1.66	0	1.66
Right lower lobe	1.41	0.91	2.32
Left upper lobe	1.41	0.08	1.49
Left lower lobe	1.58	0.75	2.33
Total lungs	7.58	1.9	9.46

Follow-up of the patients was performed to the study endpoints, which were death or complete recovery and discharge. Follow-up chest CT was carried out for three patients, while a portable chest X-ray was used for follow-up for the remaining nine. Follow-up imaging revealed progressive radiologic changes such as bilateral areas of air space opacity (Fig. 2).

Of the 12 patients, ten were admitted to an intensive care unit, nine were intubated, eight died of severe COVID-19 pneumonia and acute respiratory distress syndrome (ARDS), and four were discharged after complete recovery. Three patients required neither NIV nor intubation. The median hospital stay was 15 d (interquartile range [IQR] 8.0–21.5), with a longer stay for patients who died (18.0 d, IQR 12.3–21.5) than for those who were discharged (7.0 d, IQR 6.0–28.3), but the difference was not statistically significant.

2. Discussion

Owing to long-term immunosuppressive therapy, kidney transplant recipients are at higher risk of COVID-19 involvement in comparison to immunocompetent individuals. However, a few studies with small sample sizes have reported conflicting results for the characteristics of COVID-19 in these patients. In solid organ transplant recipients, the clinical presentation, imaging findings, laboratory data, and outcomes may differ from those for other adults and vary among patients.

On initial presentation, just one of our 12 cases had gastrointestinal symptoms; the most typical presentation was cough and fever, as for other adults [9,10]. Guillen et al [11] reported on a patient with a history of third kidney transplant who presented with vomiting and fever as a first symptom and was finally diagnosed with COVID-19 on follow-up.

Laboratory findings revealed that although the majority of COVID-19 patients in the general population have leukopenia and lymphocytopenia (70%) [12], normal white blood cell count was a more frequent finding in our series and leukopenia was detected in one-quarter of our subjects. On admission, lymphocytopenia was detected in 58.33% of our patients, whereas all cases had lymphocytopenia in another study [13]. In contrast to our results, Fishman and Grossi [14] reported that leukopenia and lymphopenia were the prevalent finding in immunocompromised transplant recipients.

According to CT images, the most common pattern of lung involvement was bilateral involvement with a diffuse pattern and a posterior segmental distribution. GGO, a feature highly suggestive of COVID-19, was observed in all cases and consolidation in the majority of cases. A crazy-paving pattern was observed in two patients, which is consistent with late-phase COVID-19. One-third of our cases had unilateral involvement; in other studies, one case had bilateral GGO [15] and one of five cases described by Zhang et al [13] had unilateral involvement.

All the initial CT scan findings were compatible with a normal immune function except for unilateral involvement and consolidation, which were slightly more frequent in our series than in a previous multicenter study of 101 COVID-19 patients [16]. Most patients in the later stages showed subpleural involvement as a less common finding. As the disease progresses, other uncommon findings include pleural/pericardial effusion, lymphadenopathy, cavitation,

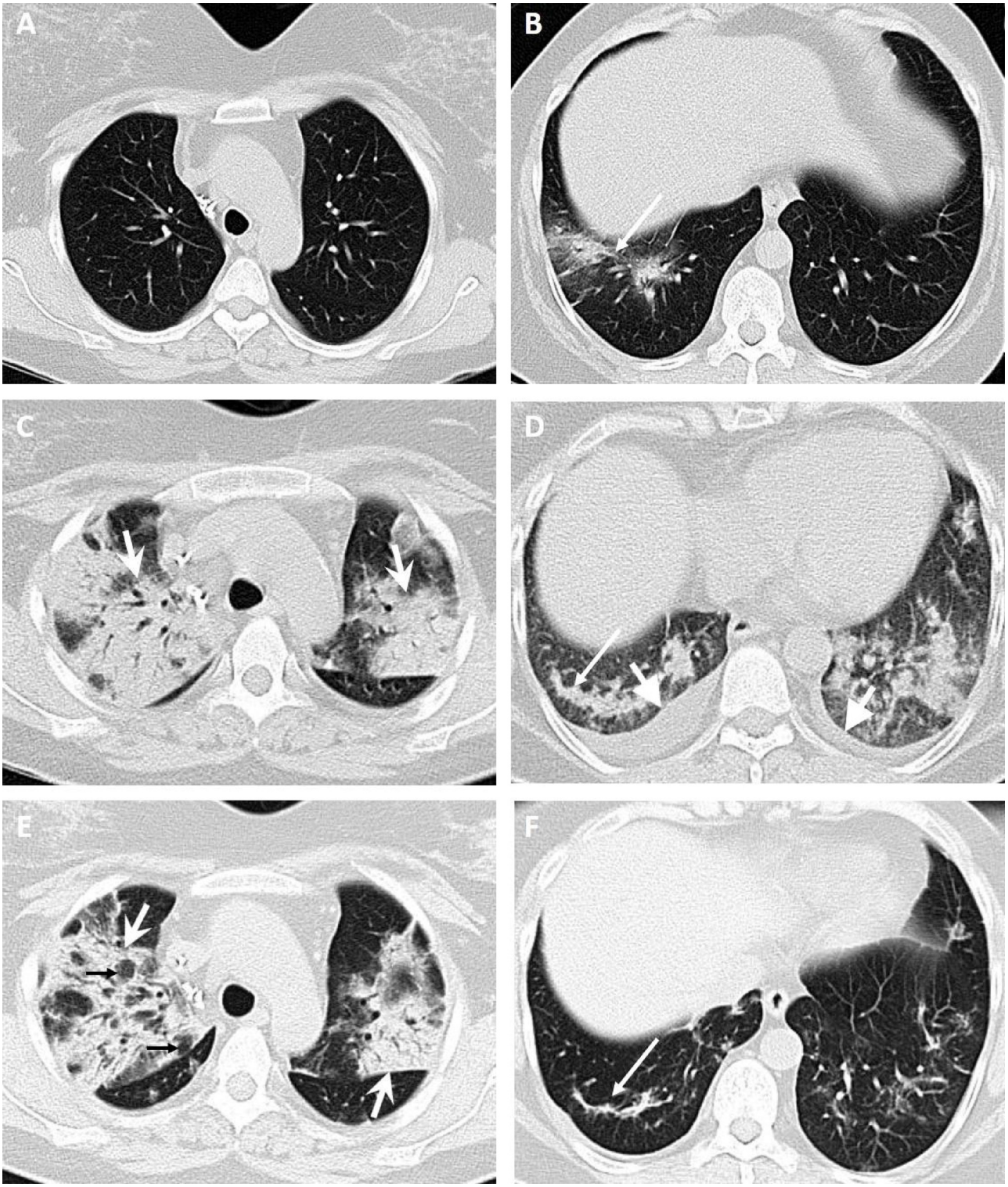

Fig. 2 – A 49-yr-old woman presented with a dry cough, sore throat, headache, and a history of kidney transplantation 17 yr previously. (A,B) Computed tomography (CT) images obtained 3 d after the onset of symptoms show patchy ground-glass opacity in the right inferior lobe with slight central consolidation (long arrows). (C,D) CT images obtained 25 d after the onset of symptoms with secondary superimposed bacterial pneumonia show diffuse bilateral ground-glass opacity and consolidation with air bronchogram (wide arrows) predominantly in the upper lobes and bilateral mild plural effusion (thick-headed arrows). (E,F) CT images obtained 28 d after the onset of symptoms and intravenous antibiotic therapy show evolution of the area of consolidation with vacuolar signs (small black arrows) in the right upper lobe and fibrotic bands (long arrow) in the right lower lobe. The patient was discharged after 37 d.

halo sign, and pneumothorax. The most common imaging features in severely ill patients were bilateral multilobar involvement and subsegmental consolidation [17].

Our study revealed that interlobular septal thickening, multilobar patterns, consolidative lesions, and a high score for lung involvement were more frequent among the patients with poor outcome and complicated cases with ARDS. In addition, all cases with pleural and pericardial effusion or a crazy-paving appearance had poor outcome. Interestingly, two cases had pneumomediastinum as a rare finding on chest CT at the time of presentation, without any history of intubation or other predisposing procedures. Patients who survived had a shorter hospital stay and a unilateral peripheral pattern limited to only one zone of the lung, with none of the other findings mentioned for patients with poor outcome.

In conclusion, CT imaging features may have an important role in predicting COVID-19 outcomes for kidney transplant recipients. However, the majority of the findings are similar to those from other adult studies for the general population.

Conflicts of interest: The authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.04.064.

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