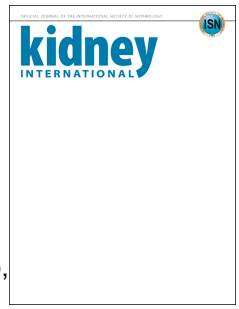

A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia.

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PII: S0085-2538(20)30365-3

DOI: https://doi.org/10.1016/j.kint.2020.04.002

Reference: KINT 2026

To appear in: *Kidney International*

Received Date: 28 March 2020

Revised Date: 3 April 2020

Accepted Date: 3 April 2020

Please cite this article as: Alberici F, Delbarba E, Manenti C, Econimo L, Valerio F, Pola A, Maffei C, Possenti S, Zambetti N, Moscato M, Venturini M, Affatato S, Gaggiotti M, Bossini N, Scolari F, A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia., *Kidney International* (2020), doi: https://doi.org/10.1016/j.kint.2020.04.002.

Early experience of COVID -19 infection in kidney transplant patients - Italian experience*

*Single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia

Population

20 kidney transplant patients admitted for SARS-CoV2 pneumonia

Median follow-up, 7 days

Transplant age	13 years
Immunosuppression	
CNIs	19/20 (95%)
MMF	14/20 (70%)
Glucocorticoids	13/20 (65%)
mTORi	2/20 (10%)

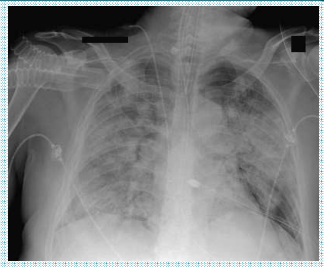
Management

Immunosuppression withdrawn

Commencement of:
Methylprednisolone 16 mg
Hydroxychloroquine (200 mg bid, to be reduced if eGFR<30ml/min): 19/20
Lopinavir/Ritonavir (200/50 mg 2 tabs bid): 15/19
Darunavir + Ritonavir (800+150 mg/daily) 4/19

13/15 (87%): Chest X-ray worsening

11/13 (85%): escalation of oxygen supplemental therapy



Dexamethasone in 11, Tocilizumab in 6 patients

Outcome

4/20 ICU Care
6/20 AKI
5/20 Deaths

CONCLUSION:

In this limited cohort of long-term kidney transplant patients, SARS-CoV-2 induced pneumonia is characterized by high risk of progression and significant mortality

kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Alberici F. et al., 2020

Editorial: Special Report

A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia.

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Conflict of interest: the authors declare no conflict of interest.

Word count: 1325/1500

Abstract

The outcome of SARS-CoV2 infection in patients who have received a kidney allograft and are being treated with immunosuppression is unclear. We describe 20 kidney transplant recipients (median age 59 years [inter quartile range 51-64 years], median age of transplant 13 years [9-20 years], baseline eGFR 36.5 [23-47.5]) with SARS-CoV2 induced pneumonia. At admission, all had immunosuppression withdrawn and were started on methylprednisolone 16 mg/day, all but one was commenced on antiviral therapy and hydroxychloroquine with doses adjusted for kidney function. At baseline, all patients presented fever but only one complained of difficulty in breathing. Half of patients showed chest radiographic evidence of bilateral infiltrates while the other half showed unilateral changes or no infiltrates. During a median follow-up of seven days, 87% experienced a radiological progression and among those 73% required escalation of oxygen therapy. Six patients developed acute kidney injury with one requiring hemodialysis. Six of 12 patients were treated with tocilizumab, a humanized monoclonal antibody to the IL-6 receptor. Overall, five kidney transplant recipients died after a median period of 15 days [15-19] from symptom onset. These preliminary findings describe a rapid clinical deterioration associated with chest radiographic deterioration and escalating oxygen requirement in renal transplant recipients with SARS-

Cov2 pneumonia. Thus, in this limited cohort of long-term kidney transplant patients, SARS-CoV-2 induced pneumonia is characterized by high risk of progression and significant mortality.

Keywords: transplantation, acute kidney injury, inflammation, tocilizumab

Introduction.

SARS-CoV-2 infection is posing challenges to all the health systems in the world. The ideal therapeutic approach is still debated and data on subgroups of patients at high risk still scarce(1). We have developed an internal treatment protocol for the management of renal transplant patients with SARS-CoV-2 pneumonia (2). Since the first days of March 2020 we re-organised our ward to admit kidney transplant patients with SARS-CoV2 pneumonia; we felt this rearrangement as necessary since our centre acts as referral for a population of 1200 kidney transplant patients. Due to the onset of the COVID-19 epidemic, acute transplantation surgery was suspended in our centre from the 20th of February 2020. The first admission of a transplant patient with SARS-CoV2 pneumonia occurred on the 27th of February 2020, the second one six days later and subsequently up to the 24thof March 2020 (day of when this analyses was performed and patients follow-up censored) an average rate of 1.2 kidney transplant patients were admitted per day . We describe here the clinical course and renal outcomes of the first 20 kidney transplant recipients admitted and followed in our unit with pneumonia secondary to SARS-CoV-2 infection.

Results

In this report we describe the progress of all kidney transplant patients with SARS-CoV2 pneumonia admitted up to the 24th of March 2020. These patients had a median inpatient stay of 7 days (IQR 4-15) and the main baseline clinical characteristics are shown in Table 1 and Table 2 . Briefly, all patients presented with fever, however only 1/20 complained of

dyspnoea; 50% of the transplant patients had radiographic changes of bilateral infiltrates on admission, while the remaining 50% showed unilateral changes or no infiltrates; 7/20 did not require supplemental oxygen.

All patients had their usual transplant immunosuppression withdrawn and were started on methylprednisolone 16 mg or equivalent dose of prednisone, 19/20 received antiviral therapy and hydroxychloroquine as per our protocol (2). As anti-viral therapy is known to interfere with calcineurin inhibitor metabolism, in four patients tacrolimus levels were monitored after these therapeutic changes were instituted. The median trough values before anti-viral therapy were 7.05 ng/ml(IQR 5.5-8.6); one patient had the level re-checked after 3 days with no change compared to baseline, one patient had the level rechecked 4 and 5 days after admission (-17% and -18% compared to baseline), one six days after admission (-12% compared to baseline) and one 8 days after admission (-21% compared to baseline). The median times from symptom onset and admission to these therapeutic changes were respectively 5 days (IQR 3-8.25) for antiviral therapy and 0 days (IQR 0-0) for hydroxychloroquine . During the follow-up one patient had hydroxychloroquine withdrawn due to toxicity (nausea, vomiting) but no prolongation of the cardiac QTc interval compared to baseline or cardiac arrhythmias were observed. Antibiotics were administered to 11/20 kidney transplant recipients (55%): cephalosporins in 64%, beta-lactams in 36%, fluoroquinolones in 25%, carbapenems in 10% and glycopeptides in 5%. During hospitalization chest radiographs were repeated in 15/20 patients and radiological findings worsened in 13/15 (87%). The changes of the main blood tests compared to baseline are shown in Supplementary Figure S1. In the individuals with worsening radiological findings, 11/13 (85%) required an escalation of the oxygen supplemental therapy; comprising: one patient switched from regular breathing to low oxygen requirement (LOR), 3/15 from regular

breathing to high oxygen requirement (HOR), 2/15 from HOR to non-invasive ventilation (NIV) and 2/15 from HOR to mechanical ventilation (MV).

Additional anti-inflammatory therapy comprising dexamethasone and tocilizumab were given to 11/20 (55%) and 6/20 (30%) patients, (see supplementary material for protocol details); in these patients, 4/11 (36%) and 2/6 (33%) subsequently died.

The characteristics of the patients treated with tocilizumab are shown in Table 3; among these patients, 3/6 (50%) experienced a reduction of the oxygen requirements and 2/6 (33%) showed amelioration of the radiological findings. Two out of the six patients who were treated with tocilizumab eventually died and one was discharged from hospital 9 days after the administration of tocilizumab.

In terms of kidney function, the medium creatinine level at admission was +17% (IQR 12-26%, range 0 – 143%) compared to baseline and the highest creatinine level observed during the follow-up was +33% (IQR 13-59%, range 0 - 157%) compared to baseline; 6/20 patients developed AKI and 1/6 required haemodialysis.

During follow-up, 4/20 (20%) patients required intensive care and three of these individuals subsequently died. Overall, 5/20 patients died after a median of 11 days from admission (IQR 11-14) and 15 days (IQR 15-19) from symptom onset; 4/5 patients died from complications of the respiratory failure secondary to SARS-Cov2 infection, 1/5 died of probable bacterial sepsis (fever, rise of CRP and procalcitonin) despite a satisfactory recovery from SARS-Cov2 pneumonia induced respiratory failure, need for ICU care and treatment with dexamethasone and tocilizumab.

Three patients were discharged, after 7 days in one case and after 16 in the 2 remaining cases; at discharge creatinine level compared to baseline was 3.6 vs 2.1, 2.3 vs 2.5 and 2.1 vs 1.5 mg/dl. In terms of immunosuppressive therapy, two patients were discharged receiving methylprednisolone 16 mg and one with methylprednisolone 12 mg per day.

Discussion

SARS-CoV2 infection is challenging health care systems around the world. The mortality of the disease has been proposed to be around the 2.3% with age and comorbidities such as cardiovascular diseases, diabetes, chronic respiratory diseases, hypertension and cancer being associated with worse prognoses (4, 5). Immunosuppression and CKD may represent additional risk factors, although specific data are not available at the moment. Here we reported the clinical characteristics and the outcomes of the first 20 kidney transplant patients affected by SARS-CoV2 pneumonia at our centre. Despite on average a relatively benign onset of the disease, a large proportion of the patients displayed worsening chest radiology and required an escalation of the supplemental oxygen. Of note, 25% of the patients died despite an aggressive approach to immunosuppression withdrawal and early commencement of antiviral therapy.

The role of lopinavir/ritonavir in SARS-CoV2 management is debated, with some data supporting a greater benefit with early start compared to a delayed commencement (1); our cohort was started on antiviral therapy a median of 5.5 days after symptom onset. Lopinavir/ritonavir may interact with CNIs impacting on their level: the four patients of our cohort with serial CNI monitoring confirmed that; of note none of these patients died and 3/4 have been discharged.

Reports suggest a role for hydroxychloroquine treatment in reducing the viral load(6). In our cohort, 19/20 patients received this drug although toxicity led to treatment withdrawal in one case.

Hydroxychloroquine and lopinavir/ritonavir may interact causing a prolongation of the cardiac QTc, interval however none of this series experienced this complication. Preliminary

data and understanding of the pathogenesis of the pneumonia secondary to SARS-CoV-2 infection suggest a central role of inflammatory cytokines in inducing the rapid clinical deterioration in association with worsening chest radiology and escalating oxygen requirement , observed in an average of 7-10 days from the symptom onset(7). In this context glucocorticoids and tocilizumab have been suggested to be a therapeutic strategy(8). Our subgroup of patients treated by this approach experienced a poor outcome, although encouraging signals in terms of potential beneficial effects were observed in the patients treated with tocilizumab: 50% reduced oxygen therapy requirement and 33% experiencing improvement of radiological changes. Despite that, two patients died. Our results are too preliminary and the sample size too small to draw firm conclusions.

The high mortality rate of this population suggests aggressive management is needed for kidney transplant patients with SARS-CoV2 infection, in particular early hospitalization should be considered in case of pneumonia; furthermore more effective treatment protocols need to be identified.

Our study has limitations: the sample size is small and the median follow-up short; findings are, therefore, preliminary and will need to be confirmed in bigger cohorts with longer follow-up. Some strengths may be acknowledged as well and in particular the monocentric approach and the homogeneity of the clinical treatment employed.

In conclusion, kidney transplant patients with SARS-CoV2 pneumonia may present with an unfavourable disease course and a poor outcome; hospitalization is required and repeat chest x-ray advisable. Clinical management needs to be improved in order to impact on these patients' prognosis.

Methods

All the kidney transplant patients with SARS-CoV-2 infection admitted in the Nephrology Unit of the Spedali Civili Hospital of Brescia have been included. The therapeutic approach followed our protocol already published on the website of the European Renal Association (ERA-EDTA)(2). In brief, all admitted patients had immunosupression withdrawn and were commenced on methylprednisolone 16 mg/daily. Antiviral therapy with Lopinavir/Ritonavir plus hydroxychloroquine (dose adjusted for kidney function) was considered in all patients if not contraindicated. In case of shortage of Lopinavir/Ritonavir, Darunavir and Ritonavir have been employed (*supplementary material*). Patients experiencing clinical deterioration after at least 7 days from symptom onset or no temperature for >72h but with escalating oxygen requirements or progression of the chest radiology and no signs of bacterial infection were considered for dexamethasone (20 mg/daily for 5 day, then 10 mg/daily for 5 days) and up to two tocilizumab infusions at intervals of 12-24 hours (8 mg/kg of body weight, maximum dose per infusion 800 mg). Details on the indications for dexamethasone and tocilizumab have been provided in the *supplementary materials*.

Oxygen requirements have been categorised as follow: no oxygen needs, low oxygen requirement (LOR), from nasal cannula up to Venturi mask with FiO2 of 0.5), high oxygen requirement (HOR, including Venturi mask with FiO2 of 0.6, reservoir mask with oxygen at 15l/min and high-flow nasal ventilation), non-invasive ventilation (NIV) and mechanical ventilation (MV). Acute kidney injury (AKI) was defined as per previous publications(3).

Considering the well documented effects of lopinavir/ritonavir and hydroxychloroquine on increasing the cardiac QTc interval , electrocardiograms were performed every 2-3 days; in case of prolongation compared to baseline, dose reduction was performed.

Due to the small sample size, only descriptive statistics have been performed, results are expressed as n(%) for categorical variables and median and interquartile range (IQR) for continuous variables.

According to the Italian regulations, ethical approval for the study has been obtained.

TABLES

Table 1. Baseline clinical characteristics of 20 kidney transplant patients affected by SARS-CoV-2 infection followed in our unit

Characteristics		
Male/Female		16/4
Age (years)		59 (IQR 51-64)
Comorbidities	Hypertension	85%
	Ischemic cardiac disease	15%
	Diabetes	15%
	HCV infection	10%
Kidney transplant age (years)		13 (IQR 9-20)
Time from symptoms onset to admission (days)		5.5 (IQR 3.3-8)
Baseline serum Creatinine (mg/dl)		1.95 (IQR 1.5-2.8)
Baseline eGFR (ml/min)*		36.5 (IQR 23-47.5)
Baseline immunosuppression		CNIs 19/20 MMF 14/20 Low dose glucocorticoid^ 13/20 mTORi 2/20
SARS-CoV-2 infection symptoms onset	Temperature (>37.5 °C)	100%
	Cough	50%
	Gastrointestinal symptoms	15%
	Pharyngitis	10%
	Shortness of breath	5%
	Myalgia	5%
Chest X ray at hospital admission	No infiltrates	15%
	Unilateral infiltrates	35%
	Bilateral infiltrates	50%
Blood tests at hospital admission	WBC (NV 4,00 – 10,80 x10^3/uL)	5470 (IQR 4115-6193)
	Neutrophils (NV 1,50 – 8,00 x10^3/uL)	3700 (IQR 2280-4500)
	Lymphocytes (NV 0,90 – 4,00 x10^3/uL)	1170 (IQR 620-1305)
	Platelets (NV 130 – 400 x10^3/uL)	196000 (IQR 119000-202000)

	LDH (NV 135 – 225 U/L)	231 (IQR 190-260)
	CPK (NV 39 – 308 U/L)	69 (IQR 44-121)
	AST (NV 18 – 54 U/L)	37 (IQR 26-35)
	ALT (NV 10 – 50 U/L)	23 (IQR 16-30)
	Bilirubin (NV < 1,20 mg/dl)	0.8 (IQR 0.4-0.9)
	CRP (NV < 5,0 mg/L)	49 (IQR 19-62)
	Procalcitonine (NV < 0,5 ng/mL)	0.22 (IQR 0.1-0.35)
	Ferritin (NV 30 – 400 ug/L)	831 (IQR 284-882)
	Fibrinogen (NV 170 – 410 mg/d)	461 (IQR 343-614)
	D-Dimer (NV < 232 ng/mL)	279 (IQR 277-563)
	Urea (NV 17 – 49 mg/dL)	46 (IQR 48-106)
	Creatinine (NV 0,70 – 1,20 mg/dL)	1.8 (IQR 1.7-3.5)
Antiviral therapy	Lopinavir/ritonavir	15/19
	Darunavir + ritonavir	4/19
Ventilation requirement at hospital admission	No oxygen	7/20
	LOR	8/20
	HOR	5/20
	NIV	0
	MV	0

Data are reported as n(%) for categorical variables and median (interquartile range) for continuous variables.

CNI: calcineurin inhibitors; MMF: mofetil mycophenolate; mTORi: mTOR inhibitors; LOR: low oxygen requirement; HOR: high oxygen requirement; NIV: non invasive ventilation; MV: mechanical ventilation; NV: normal value

*Determined with the CKD-EPI equation

^ Prednisone 5 mg/day or methylprednisolone 4 mg/day

Table 2: Clinical characteristics and outcome of twenty kidney transplant patients with COVID 19 infection

Table 3. Characteristics of 6 kidney transplant patients with SARS-CoV2 pneumonia treated with tocilizumab and outcome after treatment

	Day of tocilizumab administration	Oxygen requirement at tocilizumab	Follow up post tocilizumab (days)	Oxygen requirement after tocilizumab	Chest X ray improvement	Outcome
Patient 1	Day 6	NIV	11	HOR	No	Inpatient
Patient 2	Day 6	HOR	10	MV	No	Death
Patient 3	Day 7	LOR	9	Room air	No	Discharged
Patient 4	Day 3	HOR	4	HOR	Yes	Inpatient
Patient 5	Day 5	NIV	3	NIV	NA	Death
Patient 6	Day 4	HOR	3	LOR	Yes	Inpatient

LOR: low flux oxygen; HOR: high flux oxygen; NIV: non invasive ventilation; MV: mechanical ventilation

Supplementary Material

Supplementary Methods

Supplementary Figure S1: Changes of WBC, LDH, AST, ALT, CRP and creatinine compared to baseline.

Supplementary information is available on Kidney International's web site.

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Table 2 Clinical characteristics and outcome of twenty kidney transplant patients with COVID 19 infection

	Age/Sex	Tx date	Co-morbidities	Respiratory and renal involvement	Baseline creatinine µmol/L (eGFR ml/min/1.73 m^2)	Baseline immunosuppression and treatment (+/- tocilizumab)	ACEi or ARB	Outcome
1	70/F	12/2002	Hypertension	NIV	185 (23)	CNI/mTORi COVID treatment: lopinavir/ritonavir + hydroxychloroquine Dexamethasone	ACEi	Discharged
2	47/F	3/2011	None	ICU, AKI, ARDS	282 (16)	MMF/CNI/Low dose steroids COVID treatment: lopinavir/ritonavir + hydroxychloroquine Dexamethasone Tociliizumab	ACEi	Inpatient
3	71/M	1/2007	Ischemic cardiac disease	NIV, ARDS	159 (37)	MMF/CNI/Low dose steroids COVID treatment: lopinavir/ritonavir + hydroxychloroquine Dexamethasone	ARB	Death

4	57/M	8/2018	HCV infection	ICU, ARDS	141 (47)	MMF/CNI/Low dose steroids COVID treatment: lopinavir/ritonavir + hydroxychloroquine Dexamethasone Tocilizumab	NO	Death
5	51/M	3/1997	Hypertension HCV infection	NIV	221 (29)	MMF/CNI COVID treatment: lopinavir/ritonavir + hydroxychloroquine Dexamethasone Tocilizumab	NO	Discharged
6	46/M	9/ 2017	Hypertension	NIV	132 (55)	MMF/CNI COVID treatment: lopinavir/ritonavir + hydroxychloroquine Dexamethasone	NO	Discharged
7	59/M	2/2015	Hypertension	ICU, ARDS	256 (23)	MMF/CNI/Low dose steroids COVID treatment: lopinavir/ritonavir + hydroxychloroquine	ACEi	Death

						Dexamethasone		
8	70/F	7/2004	Hypertension	ICU, AKI, ARDS	300 (13)	CNI/Low dose steroids COVID treatment: lopinavir/ritonavir + hydroxychloroquine Dexamethasone	ACEi	Death
9	60/M	10/2011	Hypertension	Room air	150 (43)	MMF/CNI/Low dose steroids COVID treatment: lopinavir/ritonavir + hydroxychloroquine	ACEi	Inpatient
10	73/M	9/ 2013	Hypertension Diabetes	NIV, ARDS	132 (46)	MMF/CNI /low dose steroids COVID treatment: lopinavir/ritonavir + hydroxychloroquine	ACEi	Inpatient
11	59/M	3/2010	Hypertension Ischemic Cardiac disease Diabetes	NIV, AKI, ARDS	238 (25)	MMF/Low dose steroids COVID treatment: lopinavir/ritonavir + hydroxyhcloroquine Dexamethasone	ARB	Inpatient

						Tocilizumab		
12	63/M	8/2004	Hypertension	NIV, ARDS	203 (29 ml/min)	MMF/CNI COVID treatment: lopinavir/ritonavir + hydroxychloroquine Dexamethasone Tocilizumab	NO	Death
13	49/M	6/2018	Hypertension	NIV, AKI, ARDS	185 (36)	MMF/CNI/Low dose steroids COVID treatment: lopinavir/ritonavir + hydroxychloroquine Dexamethasone Tocilizumab	NO	Inpatient
14	60/F	6/2018	Hypertension	NIV, ARDS	106 (49)	MMF/CNI/Low dose steroids COVID treatment: lopinavir/ritonavir + hydroxychloroquine	NO	Inpatient

15	57/M	6/2009	Hypertension	Room air	106 (67)	MMF/CNI COVID treatment: lopinavir/ritonavir + hydroxychloroquine	NO	Inpatient
16	54/M	10/ 2002	Hypertension	NIV, AKI, ARDS	344 (16)	CNI/Low dose steroids COVID treatment: darunavir + ritonavir + hydroxychloroquine	ARB	Inpatient
17	60/M	4/ 2007	Hypertension Ischemic cardiac disease	Room air	141 (46)	CNI COVID treatment: lopinavir/ritonavir + hydroxychloroquine	NO	Inpatient
18	50/M	11/ 2010	Hypertension	Room air	123 (58)	MMF/CNI/Low dose steroids COVID treatment: darunavir + ritonavir + hydroxychloroquine	NO	Inpatient
19	69/M	7/ 1998	Hypertension Diabetes	AKI	309 (17)	CNI/Low dose steroids COVID treatment: darunavir + ritonavir + hydroxychloroquine	NO	Inpatient
20	44/M	7/2006	Hypertension	Room air	114 (66)	CNI mTORi COVID treatment: darunavir +	NO	Inpatient

						ritonavir + hydroxychloroquine		

Legend: Yr=year, M=male, F=female, Y=yes, N=No, Aza=azathioprine, MMF=mycophenolate mofetil, ITU=intensive therapy unit, NIV=non-invasive ventilation, CVVH-continuous veno-venous haemofiltration, AKI-Acute Kidney injury, ARDS-Acute Respiratory Distress Syndrome).