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Hospitalized and outpatient kidney transplant recipients with covid-19

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ABSTRACT

Introduction: As the number of COVID-19 infection raise is expected that more kidney transplant (KT) recipients will be affected. More information is need about the clinic factors that determine severe presentation in KT recipients with COVID-19.

Methods: This is a retrospective observational single-center analysis of 18 KT recipients with confirmed SARS-CoV-2 infection between March to November of 2020.

Results: Ten patients (55.5%) needed hospitalization and 8 patients (44.4%) were managed as outpatient. Mean age was 45.3 ± 13.1 years and 61.1% were male. Hypertension was presented in 72.2%, diabetes in 33.3% and obesity in 22.1% of patients. Eleven patients (61.1%) had an identifiable sick contact. Hospitalized patients were older (52 ± 12.2 vs 37 ± 9.3 years; *p value* = 0.011), had lower baseline glomerular filtration rate (GFR) [39.0 (IQR 28.0 – 43.0) vs 59.0 ml/min/1.73m2 (IQR 41.3 – 101.0), *p value*= 0.021] and longer time since transplant (12.9 ± 6.9 vs 5.9 ± 6.5 years). Immunosuppression alteration occurred 90.0% of hospitalized patients vs 37.5% in outpatient (*p value*= 0.043). In hospitalized patients, 8 patients (80.0%) had acute kidney injury of which 2 patients needed renal replacement therapy. Recovery renal function was seen in 7 patients (70.0%) Hospitalized patients had a longer time to infection cure (35.6 ± 17.7 vs 21.6 ± 10.6 days).

Conclusion: Age, GFR at admission and time since transplant was associated with COVID-19 severity in kidney transplant recipients. Further research is needed to determine the impact of immunosuppression on the risk for COVID-19 infection and severity.

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARSCoV-2) is the causative agent of coronavirus disease 2019 (COVID-19). This has become a major global health concern and was declared a global pandemic by the World Health Organization (WHO) on 11th March 2020. As of November 2020, COVID-19 has affected more than 44 888 869 patients in 210 countries and territories around the world and caused 1 178 475 deaths worldwide.[1]

The clinical spectrum of COVID-19 appears to be wide, ranging from asymptomatic to severe pneumonia, acute respiratory syndrome, multiorgan failure and death with a combination of laboratory and imagiological findings.[2]

Innumerous factors have been related to the severity of COVID-19 as male gender, smoking, obesity, cancer, diabetes and hypertension[3] but clinical evidence is still controversial and there is little information about immunosuppression (IS) as a risk factor for COVID-19 severity. Although IS may predisposeto severe respiratory infection[4] some evidence suggested that these patients may be protected as IS diminished hyperinflammation or cytokine storm syndrome.[5]

Many reported cases of COVID-19 infection with worse clinical presentation require hospitalization. In specific populations such as KT patients, more information is need about the clinic factors that determine severe presentation. The purpose of this study was to compare hospitalized KT patients with KT recipients who did not require hospitalization with COVID-19 regarding clinical presentation and IS therapy and to identify potential factors that determine clinical severity of SARS-CoV-2 infection.

Methods

This is a retrospective observational analysis of consecutive kidney-only transplant recipients with confirmed SARS-CoV-2 infection followed in Transplant Unit of Centro Hospitalar Universitário Lisboa Norte (CHULN) between March to November of 2020. This study was approved by the Ethical Committee in agreement with institutional guidelines. Due to the retrospective and non-interventional nature of the study, informed consent was waived by the Ethical Committee.

Participants

Eligible patients were selected as patients older than 18 years of age, with a history of KT with positive SARS-CoV2 reverse real time polymerase chain reaction (RT-PCR) in nasopharyngeal exudate or bronchial secretions.

Variables and outcomes

Patient variables were collected from individual clinical records. The following variables were analyzed: patient demographic characteristics (age, gender and race); comorbidities [diabetes mellitus, hypertension, smoke habits, cardiovascular disease (CVD), lung disease, obesity and cerebrovascular disease], kidney disease aetiology, time on RRT before transplantation, type of organ donor, induction IS, maintenance IS, time since transplant, baseline serum creatinine (SCr), baseline estimated glomerular filtration rate (GFR), known sick contact, initial COVID-19 symptoms, duration of symptoms before diagnosis, alteration in IS, hospitalization in the previous 6 months, therapy with renin-angiotensin-aldosterone system inhibitors (RAASi). Outpatients were monitored by the medical team by phone calls every 24 to 48hours on the basis of the patient's symptom severity. The outcomes measured were time to infection cure. In hospitalized patients, recovery renal function (RRF) and hospital discharged were also analyzed.

Definitions

Diagnosis of COVID-19 was based on the WHO interim guidelines.[6] The Kidney Disease Improving Global Outcomes (KDIGO) classification according to serum creatinine (SCr) criteria and estimated glomerular filtration rate (GFR) was used to define and stratify AKI and CKD.[7,8] Diabetes mellitus was diagnosed according to the American Diabetes Association criteria[9] and hypertension was diagnosed according to the seventh report of the Joint National Committee.[10] Obesity was defined based on WHO criteria.[11] Lung disease comprised emphysema and chronic bronchitis. Cardiovascular disease was considered whenever a history of chronic heart failure of any cause and/or cardiac ischemic disease was documented, and, a previous diagnosis on clinical records was considered sufficient for the confirmation of this diagnosis. Previous diagnosis on clinical records was considered sufficient for the confirmation of cerebrovascular disease and smoke habits. Recovery renal function was defined as recovery of sufficient kidney function to discontinue dialysis during hospital stay and at hospital discharge.

Infection cure was defined when 2 consecutive RT-PCR test were negative.

Statistical methods

Categorical variables were described as the total number and percentage for each category. When normally distributed, continuous variables were described as the mean ± standard deviation or as median and interquartile range (IQR) when not normally distributed. Normally distributed continuous variables were compared with the Student's t-test, non-normally distributed continuous variables were compared with the Mann–Whitney U test and categorical variables were compared with the chi-square test.

Statistical significance was defined as a P-value <0.05. Statistical analysis was performed with the statistical software package SPSS for windows (version 21.0).

Results

We included a total of 18 KT patients with COVID-19 diagnosis confirmed by RT-PCR.

Mean age was 45.3 ± 13.1 years and 61.1% were male. Eight (44.4%) patients were Caucasian.

The causes of kidney disease were glomerular diseases in 6 patients (33.3%), hypertension in 3 patients (16.7%), unknown in 4 patients (22.2) and others in 5 patients (27.8%), which included dominant polycystic kidney disease in 2 patients, renal vein thrombosis in 2 patients and congenital anomalies of kidney and urinary tract in 1 patient.

Among all patients, the prevalence of hypertension was 72.2%, diabetes 33.3% and obesity 22.1%. More than half of the patients had an identifiable sick contact (n=11, 61.1%).

Median baseline SCr was 1.6 mg/dL (IQR 1.4 – 2.2) and median GFR was 41 ml/min/1.73m^2 (IQR 30 - 59). Mean time from RRT initiation to transplant was 4.7 ± 2.9 years. Sixteen (88.9%) patients had received kidney transplantation from deceased donors. Twelve (66.7%) were from standard criteria donor. The mean time since transplant was 9.8 ± 7.5 years.

Induction IS was with basiliximab in 7 patients, timoglobulin in 7 patients and others in 4 patients which included older induction IS regimens based only on cyclosporin, MMF and prednisolone. Maintenance IS regimen was a combination of prednisolone, mycophenolate mofetil (MMF) and tacrolimus (TAC) in 12 patients (66.7%); MMF and cyclosporine in one patient (5.6%); prednisolone, MMF and cyclosporin in two patients (11.1%); prednisolone and tacrolimus in one patient (5.6%); prednisolone, MMF and azathioprine in one patient (5.6%); and prednisolone, tacrolimus and everolimus in one patient (5.6%).

The mean time from symptom initiation to diagnosis was 5.1 ± 3.3 days. The most frequent symptoms were fever (n=12; 66.7%), cough (n=11, 61.1%), asthenia (n=7; 38.9%) and dyspnea (n=6; 35.3%).

Maintenance IS was altered in 12 patients (66.6%), namely antimetabolite reduction in 3 patients (25.0%) or withdrawal in 9 (75.0%). Four patients (22.2%) had been hospitalized in the 6 months prior and 4 patients (22.2%) were on RAASi. Mean time to cure was 29.4 ± 16.2 days. Patients' baseline characteristics are shown in table 1.

Hospitalized vs Outpatient Kidney Transplant Recipients

Ten patients (55.5%) needed hospitalization and 8 patients (44.4%) were managed as outpatient.

Hospitalized patients were older than outpatient (52.0 ± 12.2 vs 37.0 ± 9.3 years; *p value* = 0.011) with no difference in race or gender.

There were no differences in comorbidities or kidney etiology between groups. Identifiable sick contact, was more frequent in outpatient (87.5% vs 40.0%)

Hospitalized patients had lower baseline GFR [39.0 (IQR 28.0 – 43.0) vs 59.0 ml/min/1.73m2 (IQR 41.3 – 101.0), *p value*= 0.021].

There were no differences between groups regarding transplant characteristics and induction IS. Hospitalized patients had longer time since transplant (12.9 ± 6.9 vs 5.9 ± 6.5; *p value*= 0.043).

Although hospitalized patients had a longer time between symptom initiation and diagnosis (6.1 ± 3.3 vs 3.6 ± 2.9 days) this was not significantly different.

When comparing the two groups, hospitalized patients had a more diverse presentation which included chest pain and myalgias not present in outpatient.

IS alteration, was more frequent in hospitalized patients (90.0% vs 37.5%; *p value*= 0.043). In hospitalized patients, antimetabolite was withdrawn in 9 patients (90.0%). Reduction of antimetabolite occurred in 3 outpatient (37.5%).

The incidence in previous hospitalization in the 6 months was similar between groups (20.0% vs 25.0%). The main reason for hospitalization was respiratory failure with oxygen requirement in 5 patients (50.0%), acute kidney injure (AKI) in 3 patients (30.0%), and social isolation in two patients (20.0%). Two patients (20.0%) needed ICU admission. Eight patients (80.0%) had AKI, manly AKI KDIGO 1 in 4 patients, 2 patients had AKI KDIGO 2 and 2 patients needed renal replacement therapy (RRT). Six patients (60.0%) started lopinavir/ritonavir, 5 patients (50.0%) hydroxychloroquine and in 3 patients (30.0) corticosteroid dose was increased. Recovery renal function was seen in 7 patients (70.0%). Only 1 patient who need RRT remained hemodialysis dependent. All patients were discharged. Hospitalized patients had a longer time to infection cure (35.6 ± 17.7 vs 21.6 ± 10.6 days). Mean duration of hospitalization was 40.9 ± 32.6 days due to nosocomial infections which prolonged hospitalization after cure.

Discussion

As the COVID-19 pandemic continues to progress, it is expected an increasing number of KT recipients with COVID-19 infection. A better understanding of the disease course is needed to identify which patients are more likely to develop severe clinical presentation and require hospitalization.

We present a series of 18 cases of COVID-19 in KT which included 8 patients that were managed as outpatient.

Several reports in different populations identify older age, male sex, obesity, hypertension, diabetes, cardiovascular disease and chronic lung disease as risk factors for COVID-19.[12,16] A meta-analysis comparing the incidences of the comorbidities in severe and non-severe COVID-19 patients reveled that comorbidities greatly affect the prognosis of the COVID-19.[17]

It is thought that cardiovascular disease contributes to a weakened immunity which increases COVID-19 severity. In one of the largest reports on risk factors for mortality due to COVID-19, based on 44,672 confirmed cases from the CDC in China[18] a case fatality rate (CFR) of 6% was reported for patients with hypertension, 7.3% for patients with diabetes, 10.5% for patients with cardiovascular diseases, 6.3% for patients with chronic respiratory diseases, and 5.6% for cancer patients. These have also been reported as a risk factor for COVID-19 severity and mortality specifically in KT recipients.[19,20] Our population of KT recipients had a high prevalence of comorbidities and hospitalized KT patients were older than outpatient which may have contributed for COVID-19 severity.

In our study hospitalized patients had lower baseline GFR [39.0 (IQR 28.0 – 43.0) vs 59.0 ml/min/1.73m2 (IQR 41.3 – 101.0), *p value*= 0.021]. A study by Williamson et al.[21] Highlights CKD as a risk factor for COVID-19 mortality. In a large UK cross-sectional survey of 16,749 patients who were hospitalized with COVID-19, kidney disease, history of dialysis or end-stage renal failure were also associated with a higher risk of mortality.[22] A meta-analysis reported by Henry et al[23] recorded a higher risk of severe COVID-19 disease in CKD patients after analysing four studies including 1389 COVID-19 patients. Also, an analysis of 7162 laboratory-confirmed COVID-19 cases confirmed that CKD was 12-fold more frequent in those with ICU admission and 9-fold more frequent in hospitalized patients.[24] CKD causes significant changes in the immune system, including persistent systemic inflammation and acquired immunosuppression.[25]

The mean time between symptom initiation and diagnosis was 5.1 ± 3.3 days. Hospitalized patients had a longer time between symptom initiation compared to outpatient and had a more diverse presentation which included chest pain and myalgias. Patients need to be taught to promptly recognize COVID-19 symptoms and to alert medical teams, allowing close follow-up and IS management in order to improve diagnostic and treatment strategies. In fact, a substantial proportion of patients underwent an alteration in IS, mainly antimetabolite withdrawal in hospitalized patients.

The ideal treatment for KT patients with COVID-19 remains uncertain at present time. Timing and degree of IS

reduction were not uniform because patients first reported symptoms at varying time points during their illness and degree of IS was at each clinician's discretion based on illness severity and risk of IS reduction. This was based in reports of Italian and Spanish KT patients.[26]

Data regarding specific COVID-19 treatment in KT recipients is limited. In our study, five patients were treated with hydroxychloroquine, and as evidence was published, six patients started lopinavir/ritonavir for COVID-19 treatment and 3 patients initiated or increased dose of corticosteroid. According to the Grupo de Estudio GREAT[26] any of the previous therapy can be used in KT recipients although given the possibility of drug interactions, it is recommended to carefully review the therapeutic combinations well before starting any treatment.

There were no differences regarding the type of transplant, induction and maintenance IS. Hospitalized patients had longer time since transplant (12.9 ± 6.9 vs 5.9 ± 6.5; *p value*= 0.043). This may indicate that other factors may play a more prominent role in COVID-19 severity than the transplant itself and de degree of immunosuppression used.[27]

More than half of the patients had an identifiable sick contact. Although measures were implemented by the Portuguese Government[28] to avoid COVID-19 spread this may indicate that this sub-group of patients may benefit from specific measure to maintain isolation including at home.

Two patients needed hospitalization to keep social distancing. As hospitals reach overflow capacity it is important to have other places where patients who don't need close medical attention can be isolated.

Hospitalized patients had a longer time to infection cure (35.6 ± 17.7 vs 21.6 ± 10.6 days).

Li and colleges[29] found that the factors influencing the time of nucleic acid shedding were age, disease severity, the time from onset to hospitalization, maximum body temperature, and corticosteroid therapy. In another study, male sex, delayed hospital admission, and invasive mechanical ventilation were independent risk factors for prolonged SARS-CoV-2 RNA shedding.[30] In our cohort, hospitalized KT patients were older, had lower baseline GFR and had a more diverse and severe clinical presentation which could explain the longer time to infection cure.

We must consider some potential limitations of our study. First, this was a single-center cohort that limits the generalization of our results. Second, the retrospective design with a relatively small number of patients may contribute to overlooking some potential risk factors. Considering that we were only able to identify and include patients who contacted us to report symptoms, it is possible that additional asymptomatic cases of COVID-19 among our transplant recipients were not included in our study. Additionally, given that the majority of patients were managed remotely while remaining at home, we lack imaging or laboratory data.

Despite these limitations, our study has several noteworthy strengths. To the best of our knowledge, this is the first study comparing SARS-CoV-2 infection in hospitalized KT recipients versus patients who did not require hospitalization for SARS-CoV-2 infection confirmed by RT-PCR.

In conclusion, among 18 KT patients with COVID-19 the presence of comorbidities such as older age, lower GFR and longer time since transplant were a risk factor for COVID-19 severity determined by need for hospitalization. In hospitalized patients AKI were frequent indicating that these patients require close monitoring for clinical deterioration. Although many of our patients experienced a favorable outcome, a longer follow-up is required to better understand the prognosis and sequelae of COVID-19 in immunosuppressed KT recipients. Further research is needed to determine the optimal management of COVID-19, particularly regarding immunosuppression management and its impact on COVID-19 severity.

Declarations

Conflict of interest

There is no conflict of interest. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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ID, CO and AS made substantial contributions to the study concept and design, analysis and interpretation of data, and were involved in drafting the manuscript and revising it critically for important intellectual content. JG was involved in the critical revision of the manuscript.

Table 1. Patient's baseline characteristics

	Total (n=18)	Hospitalized patients (n=10)	Outpatients (n=8)
Baseline characteristics			
Age (years), mean ± SD	45.3 ± 13.1	52.0 ± 12.2	37.0 ± 9.3
Gender (male), n (%)	11 (61.1)	6 (60.0)	5 (62.5)

Race (caucasian), n (%)	8 (44.4)	4 (40.0)	4 (50.0)
Etiology of End-stage Renal Disease, n (%)			
Glomerular	6 (33.3)	2 (20.0)	4 (50.0)
Hypertension	3 (16.7)	3 (30.0)	0 (0.0)
Others	5 (27.8)	3 (30.0)	2 (25.0)
Unknown	4 (22.2)	2 (20.0)	2 (25.0)
Comorbidities, n (%)			
Hypertension	13 (72.2)	7 (70.0)	6 (75.0)
Diabetes mellitus	6 (33.3)	1 (10.0)	5 (62.5)
Cardiovascular disease	5 (27.8)	3 (30.0)	2 (25.0)
Cerebrovascular disease	1 (5.6)	1 (10.0)	0 (0.0)
Lung disease	4 (22.2)	3 (30.0)	1 (12.5)
Smoke habits	2 (11.1)	0 (0.0)	2 (25.0)
Obesity	4 (22.2)	2 (20.0)	2 (25.0)
Known sick contact	11 (61.1)	4 (40.0)	7 (87.5)
Baseline SCr, mg/dL, median (IQR)	1.6 (1.4 – 2.2)	1.8 (1.6 – 2.4)	1.4 (0.9 – 1.9)
Baseline GFR, mg/dL, median (IQR)	41 (30 - 59)	39.0 (28.0 – 43.0)	59.0 (41.3 – 101.0)
Time on RRT before transplant, mean (years)	4.7 ± 2.9	5.5 ± 3.6	3.7 ± 1.9
Type of Transplant, n (%)			
Deceased donor	16 (88.9)	9 (90.0)	7 (87.5)
Standard criteria	12 (66.7)	5 (50.0)	7 (87.5)
Time since transplant, years	9.8 ± 7.5	12.9 ± 6.9	5.9 ± 6.5
Induction Immunosuppression, n (%)			
Basiliximab	7 (38.8)	2 (20.0)	5 (62.5)
Timoglobulin	7 (38.8)	4 (40.0)	3 (37.5)
Other	4 (22.2)	4 (40.0)	0 (0.0)
Maintenance Immunosuppression, n (%)			
Pred, MMF, TAC	12 (66.7)	5 (50.0)	7 (87.5)
MMF, Cyclo	1 (5.6)	0 (0.0)	1 (12.5)
Pred, MMF, Cyclo	2 (11.1)	2 (20.0)	0 (0.0)
Pred, TAC	1 (5.6)	1 (10.0)	0 (0.0)
Pred, MMF, Aza	1 (5.6)	1 (10.0)	0 (0.0)
Pred, TAC, Everolimus	1 (5.6)	1 (10.0)	0 (0.0)
Duration of symptoms before diagnose, mean (days)	5.1 ± 3.3	6.1 ± 3.3	3.6 ± 2.9

Symptoms, n (%)			
Fever	12 (66.7)	8 (80.0)	4 (50.0)
Cough	11 (61.1)	7 (70.0)	4 (50.0)
Dyspnea	6 (35.3)	3 (30.0)	3 (37.5)
Chest pain	2 (11.1)	2 (20.0)	0 (0.0)
Asthenia	7 (38.9)	5 (50.0)	2 (25.0)
Myalgia	3 (16.7)	3 (30.0)	0 (0.0)
GI symptoms	4 (22.2)	3 (30.0)	1 (12.5)
IS alteration	12 (66.7)	9 (90.0)	3 (37.5)
Hospitalization in the previous 6 months, n (%)	4 (22.2)	2 (20.0)	2 (25.0)
IECA therapy, n (%)	4 (22.2)	4 (40.0)	0 (0.0)
Time to cure, mean ± SD (days)	29.4 ± 16.2	35.6 ± 17.7	21.6 ± 10.6

Pred, prednisolone; Cyclo; cyclosporin; MMF, mycophenolate mofetil; Aza, Azathioprine

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