COVID-19 in kidney transplant recipients: what have we learned one year later? A cohort study from a tertiary center

COVID-19 em receptores de transplante renal: o que aprendemos um ano depois? Um estudo de coorte a partir de um centro terciário

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Submitted on: 11/12/2021.
Approved on: 04/10/2022.
Published on: 07/04/2022.

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DOI: https://doi.org/10.1590/2175-8239-JBN-2021-0257en

ABSTRACT

Introduction: Kidney transplant (KT) recipients have a high risk for adverse outcomes from infections, such as COVID-19. **Methods:** We have retrospectively reviewed all KT recipients with documented COVID-19 between March 1, 2020, and March 15, 2021, and analyzed patients' characteristics, clinical course, treatment, and outcomes. **Results:** We identified 123 patients, 72% were male, with a mean age of 54.5±13.0 years. Twenty percent were asymptomatic, 7% had a nosocomial transmission, and 36% of the remainder required hospitalization. Almost all admitted patients received oxygen, 30% required invasive mechanical ventilation (IMV), more than a half had acute kidney injury, with 10% requiring dialysis, and 20% died. Incidence was comparable to that of the Portuguese population, but the mortality rate was almost four times higher (SMR of 3.768 (95% CI:1.723-7.154). Higher body mass index (OR 1.275, P=0.001), lower baseline graft function (OR 0.968, P=0.015), and nosocomial transmission (OR 13.836, P=0.019) were associated with oxygen demand, whereas female gender (OR 3.801, P=0.031) and lower baseline kidney graft function (OR 0.955, P=0.005), but not body mass index, were associated with IMV and/or death. **Conclusion:** Mortality rate in KT patients was higher than in the general population and lower baseline kidney function was the most consistent marker for adverse outcomes.

Keywords: Acute Kidney Injury; Renal Insufficiency, Chronic; COVID-19; Immunosuppression; Kidney Transplantation.

RESUMO

Introdução: Os receptores de transplante renal (TR) apresentam um alto risco para desfechos adversos de infecções, tais como a COVID-19. **Métodos:** Revisamos retrospectivamente todos os receptores de TR com COVID-19 documentada entre 1º de Março de 2020 e 15 de Março de 2021, e analisamos as características, curso clínico, tratamento e desfechos dos pacientes. **Resultados:** Identificamos 123 pacientes, 72% do sexo masculino, com uma média de idade de 54,5±13,0 anos. Vinte por cento eram assintomáticos, 7% apresentaram transmissão nosocomial, e 36% do restante necessitaram de internação. Quase todos os pacientes internados receberam oxigênio, 30% necessitaram de ventilação mecânica invasiva (VMI), mais da metade apresentou lesão renal aguda, com 10% necessitando de diálise, e 20% foram a óbito. A incidência foi comparável à da população portuguesa, mas a taxa de mortalidade foi quase quatro vezes superior (TMP de 3,768 (IC 95%: 1,723-7,154). Maior índice de massa corporal (OR 1,275; P=0,001), menor função do enxerto basal (OR 0,968; P=0,015), e transmissão nosocomial (OR 13,836; P=0,019) foram associados à demanda de oxigênio, enquanto sexo feminino (OR 3,801; P=0,031) e menor função do enxerto renal basal (OR 0,955; P=0,005), mas não índice de massa corporal, foram associados à VMI e/ou óbito. **Conclusão:** A taxa de mortalidade em pacientes com TR foi mais elevada do que na população em geral e a função renal basal mais baixa foi o marcador mais consistente para desfechos adversos.

Descritores: Injúria Renal Aguda; Insuficiência Renal Crônica; COVID-19; Imunossupressão; Transplante Renal.

INTRODUCTION

Kidney transplant (KT) recipients are highly susceptible to infections, such as COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), a new form of coronavirus

that was identified in December 2019 and quickly became a worldwide pandemic[1].

Previous reports of COVID-19 infections in KT recipients have described high mortality rates[2-4]. In the ERA-EDTA registry, the mortality rate associated with COVID-19 in KT patients was 19.9.% compared to 0.2% in the control group[5]. Moreover, both chronic kidney disease (CKD) and acute kidney injury (AKI) were associated with a more severe disease course and mortality rate[6,7]. Whether the increased risk of adverse outcomes in KT patients is due to immunosuppression itself or to impaired kidney function remains to be elucidated.

We aim to describe the impact of COVID-19 in our KT population one year after the onset of the pandemic and compare it with the general population and identify potential risk factors for adverse outcomes.

Methods

Study population

We conducted a retrospective, single-center study of adult kidney transplant (KT) recipients with a positive reverse-transcriptase polymerase chain reaction (RT-PCR) test for SARS-CoV2, from March 1st, 2020, to March 15th, 2021, at a tertiary care center. Informed consent was obtained in accordance with the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.

Data collection and definitions

General information on the Portuguese population, such as incidence by age group and gender, and deaths, was collected from the official data of the Portuguese Ministry of Health[8] from the start of the pandemic to March 15th, 2021.

At the time of data collection, 1786 KT recipients were followed up at our center. We defined adult KT recipients with a PCR-confirmed SARS-CoV2 infection, registered in the Portuguese National System of Epidemiology Surveillance (SINAVE) as cases.

Data collection was obtained from electronic medical reports, and telephone contact was made in case of missing information.

Demographic and clinical data, including transplant characteristics, comorbidities, symptoms at presentation, hospital admission, analytical data, oxygen need, admission in the ICU, specific treatment, AKI, renal replacement therapy (RRT), and all-cause mortality rates were registered. All cases were followed up for at least 60 days after diagnosis.

Disease severity was classified according to the COVID-19 Treatment Guidelines Panel of the National Institutes of Health[9] as:

- *Mild*: Any sign/symptom of COVID-19 but with no shortness of breath or abnormal thoracic imaging.
- *Moderate*: Evidence of low respiratory disease (clinical/imaging) but the oxygen saturation is ≥94% on room air at sea level.
- *Severe*: If oxygen saturation is <94% on room air at sea level, respiratory insufficiency (a ratio of partial pressure of oxygen to fraction of inspired oxygen <300 mm Hg), respiratory frequency above 30 cycles per minute or more than 50% of lung infiltrates.
- *Critical*: Acute respiratory distress syndrome (ARDS), septic shock and/or multiple organ dysfunction.

Asymptomatic patients were identified after contact tracing of patients who had high-risk exposure to COVID-19 cases and in patients who underwent PCR testing for hospital admission for elective procedures.

Patients were divided into three groups according to hospital admission: outpatient group and non-ICU or ICU inpatient groups. Comorbidities and clinical presentation were collected in all patients and compared between the three groups. Because laboratory results were available only in the inpatient groups, the results were compared between the latter two groups, as were hospital treatments and outcomes.

Baseline creatinine was defined as the last value registered before infection and it was used to calculate the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[10]. AKI was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines[11].

All laboratorial data were expressed according to the international system of units (SI).

Immunosuppression management was made in all COVID-19 KT patients that notified our transplant unit, and it consisted in antimetabolite withdrawal

and suspension of the calcineurin inhibitor (CNI) for patients with critical disease. Additionally, steroid dose was increased from 5 to 10 mg/dL[12]. This approach was in line with the expert opinion later published by the ERA-EDTA DESCARTES working group[13]. We would like to point out that some patients did not notify the transplant unit and the diagnosis of the COVID-19 disease was not established until after the screening was performed.

The specific COVID-19 treatment depended on the timing of the pandemic, which affected our hospital protocol at each time. In the first wave, patients with documented pneumonia or respiratory failure started hydroxychloroquine 400 mg twice-daily on day 1, followed by 200 mg twice-daily until day 5-10. An electrocardiogram to access corrected QT interval was performed in all patients. By May 2020, hydroxychloroquine was shown to have no benefit on mortality rate and its side effects were non-negligible[14]. Its use was discontinued and replaced by dexamethasone, 6 mg per day for 5 to 10 days, in severe to critical disease. All admitted patients received prophylaxis with low-molecular-weight heparin adjusted to kidney function, unless a contraindication was present, and a therapeutic dose if they were previously anticoagulated or at high risk of thrombosis. Our institution defined patients with active neoplasms or inflammatory diseases, d-dimers higher than 3000 ng/mL, and d-dimers higher than 1000 ng/mL, plus fibrinogen higher that 5 g/L as patients at high thrombotic risk.

Finally, risk factors for adverse outcomes as oxygen need, invasive mechanical ventilation (IMV), and/or death were identified.

Statistical analysis

Continuous data were described using mean (standard deviation, SD) or median (interquartile range, IQR) and categorical data were expressed as numbers (frequencies). The distribution of continuous variables were analyzed using Shapiro-Wilk normality test. As appropriate, categorical data were compared using Pearson $\chi 2$ test or Fisher's exact test and continuous variables were compared with Student t-test or Mann-Whitney U test.

Age and gender distribution of transplant recipients was substantially different from that of the general population, thus indicating the necessity of standardization. Due to a relatively small number of events, leading to rather imprecise age-/gender-specific rates, we used the indirect method of standardization with the age and gender structure of the general population as reference. Standardized incidence ratio (SIR) and standardized mortality ratio (SMR) were calculated as the ratio of observed to expected number of events. The calculation of their 95% confidence intervals (95% CIs) was done by assuming a Poisson process[15]. A 95% CI not including the null value of one indicates a significant excess or deficit mortality rate.

Significant risk factors for two major adverse outcomes (oxygen need and IMV and/or death) were explored by univariate and multivariable logistic regression. In all multivariable models, independent risk factors were identified using a backward elimination method, with a P value <0.05 required to remain in the model[16].

A two-sided P-value of <0.05 was considered statistically significant. Statistical calculations were performed using Stata/MP, version 15.1 (Stata Corp, College Station, TX).

Results

General characteristics and comparison with the portuguese population

One hundred twenty-three (6.9%) of our KT patients tested positive for SARS-CoV2. Most (72%) were male, with a mean age of 54.5 ± 13 years. The infection rate in women was higher in the general population (8.2%), but lower in the KT group (5.1%).

The cumulative incidence of KT recipients (Figure 1) paralleled the cumulative incidence of the Portuguese population, until about February 2021, after which it started to be higher in the general population.

Age- and gender-standardized incidence of COVID-19 in our transplant population was 7.1% (95% CI:5.9-8.4%), similar to the Portuguese population, a SIR of 0.892 (95% CI: 0.741-1.064). However, age- and gender-standardized mortality rate was of 7.7% (95% CI:3.6-16.6%), representing a SMR of 3.8 (95% CI:1.7-7.2) in relation to the general population (Table 1).

Comorbidities and transplant characteristics

Table 2 describes patients' comorbidities and transplant characteristics, according to the outpatient and inpatient groups.

Female gender (p=0.03) and higher BMI (p=0.029) were associated with admission. No statistically

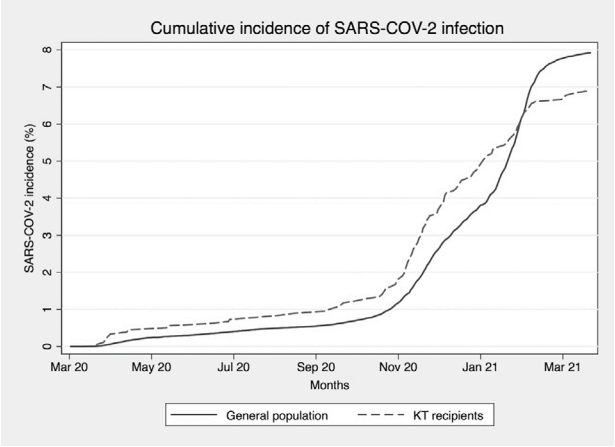

Figure 1. Cumulative incidence of SARS-CoV2 infection in KT recipients and in the general Portuguese population.

significant differences for other comorbidities were detected.

As for transplant characteristics, the median time between transplant and COVID-19 disease was 7.0 (2.9-14.2) years. No significant differences were observed in time since transplant, isolated or combined KT, number of immunosuppressors, or type of CNI. The mean baseline eGFR was significantly higher in the outpatient group.

Twenty-four per cent received a graft from a living donor, with most of these patients (80%) not requiring hospitalization (p=0.02).

Clinical presentation

From the total of 123 patients, 44 patients (36%) were admitted in hospital, with 8 patients having COVID-19 secondary to nosocomial transmission. Immunosuppression regimen was changed in all patients of the inpatient group.

At the time of diagnosis, fever, myalgia, and respiratory symptoms were more frequent in the inpatient group. The patients managed in ambulatory were either asymptomatic (20%) or had mild disease. There was one asymptomatic patient in the inpatient group who was admitted due to the impossibility of self-isolation, but most patients (80%) presented a severe to critical disease.

Analytical parameters at admission are described in Supplementary Table 1, with median lymphopenia and procalcitonin values being, respectively, lower (P=0.006) and higher (P=0.046) in the ICU group. A trend towards higher D-dimers values was also observed.

Treatment and outcomes in inpatients

The median time of hospital stay was 12 (7-20) days. Most patients (84%) received COVID-19 specific treatment and fewer (9%) received remdesivir. Other treatments, such as anticoagulation, were given to more than half (64%) of the admitted patients and to the majority (87.5%) of the patients treated in the ICU. Antibiotics were also needed in 88% of ICU patients due to concurrent bacterial infections.

Oxygen therapy was administered to 80% of the patients and 30% of them needed IMV. These values increased to 100% and 88%, respectively, in the ICU group.

Table 1 Crude incidence of COVID-19 in KT recipients versus the general Portuguese population

	KT recipients		General Portuguese population	
	Positive/Total	%	Positive/Total	%
Total	123/1786	6.9	814513/10280909	7.9
Age group				
0-20	1/29	3.5	120661/1942307	6.2
20-50	44/659	6.7	368729/3911097	9.4
50-70	57/903	6.3	203799/2785993	7.3
70+	21/195	10.8	121324/1641512	7.4
p value between age group	0.160		<0.001	
Gender				
Female	35/690	5.1	444919/5420932	8.2
Male	88/1096	8.0	369594/4859977	7.6
p value between gender group	0.016		<0.001	
Death	9/123	7.3	16694/814513	2.0

Table 2 Patient characteristics and comparison according to the outpatient and the non-ICU and ICU inpatient groups

	Total	Outpatient	Non-ICU inpatient	ICU inpatient	*P*
Recipient	n = 123	n = 79	n =28	n = 16	
Age mean±SD	54.5±13.0	53.3±13.2	57.9±13.2	54.6±11.2	0.267
Age, n (%)					0.249
< 50	45 (37)	32 (41)	8 (29)	5 (31)	
50-59	31 (25)	21 (27)	6 (21)	4 (25)	
60-69	26 (21)	15 (19)	5 (18)	6 (38)	
≥ 70	21 (17)	11 (14)	9 (32)	1 (6)	
BMI, median (IQR)	26.1 (24.1-28.7)	25.7 (24.2-27.9)	27.7 (22.5-30.2)	28.8 (26.5-30.1)	0.029*
Female, n (%)	35 (28)	19 (24)	7 (25)	9 (56)	0.030*
Comorbidities					
HTN, n (%)	102 (83)	66 (84)	23 (82)	13 (81)	0.941
ACEi/ARB, n(%)	57 (46)	42 (53)	9 (32)	6 (38)	0.119
DM, n (%)	34 (28)	21 (27)	8 (29)	5 (31)	0.923
CVD, n (%)	32 (26)	19 (24)	9 (32)	4 (25)	0.682
Smoking, n (%)					
No	104 (85)	67 (85)	22 (79)	15 (94)	
Ative	2 (2)	1 (1)	1 (4)	0	0.631
Past history	17 (14)	11 (14)	5 (18)	1 (6)	
Cancer, n (%)	9 (7)	7 (9)	2 (7)	0	0.684
Respiratory disease, n (%)	15 (12)	9 (11)	5 (18)	1 (6)	0.600
OAC, n (%)	13 (11)	8 (10)	4 (14)	1 (6)	0.682
Transplant					
Type of KT, n (%)					1
Isolated	108 (88)	69 (87)	25 (89)	14 (88)	
Combined	14+1 (12)	10+0 (13)	2+1 (11)	2+0 (13)	
LD, n (%)	30 (24)	24 (30)	6 (21)	0	0.020*
Years of KT, median (IQR)	7.0 (2.9-14.2)	7.2 (3.2-12.5)	6.3 (2.3-16.2)	5.7 (0.9-13.6)	0.664
Retransplant, n (%)	15 (12)	7 (9)	4 (14)	4 (25)	0.141
Triple IS, n (%)	102 (83)	64 (81)	23 (82)	15 (94)	0.562
CNI, n (%)					
TAC	108 (88)	72 (91)	22 (79)	14 (88)	0.177
CsA	15 (12)	7 (9)	6 (21)	2 (13)	
Last sCr, median (IQR)	1.3 (1.1-1.7)	1.2 (0.9-1.5)	1.4 (1.2-1.6)	1.3 (1.2-1.9)	0.055
Last eGFR, mean±SD	57.5±22.3	62.1±20.0	51.6±25.6	45.0±21.3	0.005*
Last eGFR category, n (%)					0.004*
≥60	52 (42)	40 (51)	7 (25)	5 (31)	
30-59	54 (44)	34 (43)	14 (50)	6 (38)	
<30	17 (14)	5 (6)	7 (25)	5 (31)	

*$p<0.05$

ACEi – Angiotensin converting enzyme inhibitor, ARB – Angiotensin receptor blocker, BMI – Body mass index, CNI – Calcineurin inhibitor, CsA – Cyclosporine CVD – Cardiovascular disease, DM- Diabetes mellitus, eGFR – Estimated glomerular filtration rate, HTN – Hypertension, ICU – Intensive care unit, IS – Immunosuppression, KT – Kidney transplant, LD – Living donor, OAC – Oral anticoagulation, sCr – Serum creatinine, TAC – Tacrolimus, SD – Standard deviation IQR – Interquartile range.

Table 3 Treatment and outcomes in the inpatient groups

	Total N=44	Non-ICU inpatient N=28	ICU inpatient N=16	*P*
Specific COVID-19 Treatment				
Dexamethasone, n (%)	31 (70)	17 (61)	14 (88)	0.089
Hydroxychloroquine, n (%)	6 (14)	4 (14)	2 (13)	1
Remdesivir, n (%)	4 (9)	2 (7)	2 (13)	0.614
Other treatments				
Antibiotics, n (%)	23 (52)	9 (32)	14 (88)	0.001*
Anticoagulation, n (%)				0.023*
No	16 (36)	14 (50)	2 (13)	
Prophylactic dose	15 (34)	9 (32)	6 (38)	
Therapeutic dose	13 (30)	5 (18)	8 (50)	
Max respiratory support				
OxTx, n (%)	35 (80)	19 (68)	16 (100)	0.016*
OxTx, HFNC, n (%)	10 (23)	0	10 (63)	<0.001*
OxTx, NIV, n (%)	9 (20)	0	9 (56)	<0.001*
OxTx, IMV, n (%)	13 (30)	0	13 (81)	<0.001*
Clinical course				
Length of stay, days Median (IQR)	12 (7-20)	10 (6-13)	27 (16-45)	<0.001*
Days from admission to ICU, Median (IQR)	-	-	2 (1-4)	-
Other infection, n (%)	20 (48)	9 (32)	11 (79)	0.008*
Missing	*2*	*0*	*2*	
AKI, n (%)	28 (64)	13 (46)	15 (94)	0.003*
Peak sCr, mg/dL, Median (IQR)	1.93 (1.40-3.03)	1.57 (1.30-2.61)	3.01 (1.51-5.0)	0.019*
Missing	*2*	*1*	*1*	
Peak sCys ng/mL, Median (IQR)	3.04 (2.46-5.0)	2.68 (2.30-3.91)	4.51 (2.54-5)	0.115
Missing	*15*	*14*	*1*	
RRT, n (%)	5 (11)	1 (4)	4 (25)	0.051
Days of RRT, Median (IQR)	6 (1-11)	-	-	-
HD dependency, n (%)	1	-	-	-
In-hospital mortality rate				
Death, n (%)	9 (20)	1 (4)	8 (50)	0.001*
Days from admission to death, Median (IQR) [Min-Max]	15 (13-21) [10-46]	-	-	-

*$p<0.05$

AKI – Acute kidney injury, HD – Hemodialysis, HFNC – High-flux Nasal Canula, ICU – Intensive Care Unit, IMV – Invasive Mechanical Ventilation, NIV – Non-invasive Ventilation, OxTx – Oxygen therapy, RRT – Renal replacement therapy, sCr – Serum creatinine, sCys – Serum Cystatin C IQR – Interquartile range, Min – Minimum, Max - Maximum.

AKI was present in 64% of admitted patients, of whom 11% required RRT. Peak serum creatinine (sCr), but not serum cystatin C, was significantly higher in patients admitted in the ICU. In the ICU group, almost all patients (94%) had AKI and 25% needed dialysis. The patient who remained dialysis-dependent had a baseline sCr of 4.5 mg/dL.

The all-cause mortality rate was 20% in hospitalized patients, reaching 50% in the ICU. The median time between admission and death was 15 (IQR:13-21, min-max:10-46) days.

Supplementary Table 2 describes the characteristics and clinical course of each deceased patient. Five patients (56%) were female. Patients' age ranged from 51 to 73 years, and KT time span ranged from 1 month to almost thirteen years, with two cases within the first year after transplantation. Almost all patients went to the ICU and received IMV, with the exception of one frail patient for whom it was decided not to scale up care. All patients developed AKI and two patients (22.2%) needed RRT. Besides bacterial infections, other complications such as hypertensive

Table 4 Multivariable analysis of risk factors for oxygen need and IVM and/or death

A. Oxygen need	OR (95% CI)	*P*	B. IVM and/or Death	OR (95% CI)	*P*
BMI	1.275 (1.103-1.473)	0.001	Female Gender	3.801 (1.132-12.760)	0.031
Last eGFR	0.968 (0.944-0.994)	0.015	Last eGFR	0.955 (0.926-0.986)	0.005
Retransplant	6.237 (1.008-38.595)	0.049			
Fever	5.877 (1.680-20.559)	0.006			
Myalgia	5.045 (1.402-18.147)	0.013			
Cough	8.549 (1.985-36.817)	0.001			
Nosocomial	13.836 (1.532-124.998)	0.019			

BMI – Body mass index, eGFR – Estimated glomerular filtration rate; IVM – Invasive Mechanical Ventilation. CI – Confidence interval, OR – Odds ratio.

pneumothorax and superior vena cava syndrome were observed.

In the survival group, no cases of graft rejection were detected until the end of the follow-up.

In univariate analysis (Supplementary Table 3), risk factors for oxygen need were BMI [OR 1.193 (1.073-1.327), p=0.001] and symptoms such as fever [OR 9.529 (3.370-26.946), p<0.001], myalgia [OR 4.012 (1.737-9.265), p=0.001], cough [OR 5.541 (2.093-14.670), p=0.001], and dyspnea [OR 93.630 (23.800-368.345), p<0.001]. Due to strong correlation between dyspnea and oxygen need, this variable was removed from the multivariate analysis. In this analysis (Table 4A), the significant risk factors identified were BMI [OR 1.275 (1.103-1.473), p=0.001], last eGFR [OR 0.968 (0.944-0.994), p=0.015], retransplant [OR 6.237 (1.008-38.595), p=0.049], fever [OR 5.877 (1.680-20.559), p=0.006], myalgia [OR 5.045 (1.402-18.147), p=0.013], and cough [OR 8.549 (1.985-36.817), p=0.004], as well as hospital-acquired infection [OR 13.836 (1.532-124.998), p=0.019].

Considering the composite outcome IMV and/or 60-day all-cause mortality rate, the univariate analysis showed as risk factors, female gender [OR 4.049 (1.289-12.717), p=0.017], last eGFR [OR 0.953 (0.923-0.984), p=0.003] and dyspnea [OR 16.552 (3.492-78.457), p<0.001]. Again, due to the strong correlation with this outcome, dyspnea was removed from multivariate analysis. Female gender and last eGFR remained as significant risk factors for IMV and/or death (Table 4B).

Discussion

The present study describes a one-year experience of COVID-19 disease in KT recipients from a tertiary center in a country with a high incidence and mortality rate of SARS-CoV2 infection. We have thoroughly reviewed all cases from both inpatient and outpatient groups.

The COVID-19 incidence in our KT recipients, after standardization, was comparable to the general population (~7%), but the mortality rate was almost 4 times higher. These results contrast with preliminary data from 46 Flemish patients, in which the incidence in KT recipients was 2.5 times higher, with comparable death rates[17]. A recent nationwide study from Sweden reported similar 30-day all-cause mortality rates between the general population and overall solid organ transplant recipients, of whom approximately 70% were KT patients[18].

Although we describe an increased risk of death in KT recipients, the overall 60-day all cause-mortality rate was lower (7.7%) than previously reported[3-5] and similar to the 9% reported in the Swedish study[18]. We believe that this lower value is due to an extensive review of all infected patients and a longer period of follow-up, with an increasing number of patients (64%) managed at home. Nevertheless, the death rate rises to 20% in the inpatient group and to 50% in the ICU group.

No age difference was detected between groups, and age was not identified as a risk factor for adverse outcomes. The region-wide Flemish study has also reported that older age was associated with increased mortality rate in the general population but not in patients on RRT[17]. Still, older age (>60 years old) has been associated to critical disease and death, both in the general population[19] and in transplant patients[18,20]. A closer look at these studies revels that most of them were performed on groups of hospitalized patients. We hypothesize that the fact

that we included a larger group of outpatients may have reduced the age difference between the groups. Moreover, in our population, the overall percentage of patients older than 60 years is low compared with the younger group (38% vs. 62%), which also might have contributed for these results.

There are conflicting data about gender predominance. In previous publications, the incidence in males varies from 46% to values closer to our reality (72%), of 79%[20,21]. Even though we report a higher incidence in men, female gender was associated with ICU admission and death. These data are in concordance with those from the ERA-EDTA Registry[5] but not with other reports[18,22]. Moreover, high BMI, which was soon associated as a critical risk factor for COVID-19[23], was associated with admission and oxygen need, but not with IMV and/or death in our study.

Considering immunosuppression, only the role of corticosteroids is well established after the results of the RECOVERY trial[24]. CNI has been attributed an inhibitory *in vitro* effect on viral replication of SARS-CoV-2, due to its effects in previous forms of coronavirus[25], and a possible beneficial effect in suppressing the cytokine storm. An initial study suggested that tacrolimus should be substituted for cyclosporine because of a possible benefit for patients under cyclosporine[26]. In contrast, a multicenter European study in liver recipients found an increased survival probability in patients using tacrolimus and encouraged clinicians to maintain it during COVID-19 infection[27]. In our study, no differences were seen when comparing the type of CNI used. We eagerly await the results of the TACROVID trial protocol, a randomized, open-label, single center, phase II trial that will evaluate the efficacy and safety of adding tacrolimus to standard treatment[28]. All our admitted patients changed the immunosuppression regimen, with both prednisolone increase and antimetabolite withdrawal in most of them, and no cases of rejection were registered.

Baseline graft function (last eGFR) was the only factor associated with all the adverse outcomes explored (admission, oxygen need, and the composite outcome IMV and/or death). A French nationwide retrospective study comparing hospitalized KT patients with a non-transplant control cohort reported a higher mortality rate for patients with higher sCr compared with normal range values. That difference persisted after adjusting for age and comorbidities. In fact, in the multivariate analysis, KT was not independently associated with mortality rate, while a sCr above 1.3 mg/dL was an independent risk factor for death[29]. This data is consistent with early reports that CKD is associated with higher mortality rate[6,7].

COVID-19-associated AKI is common, and has been associated with higher mortality rate and is an independent risk factor for all-cause-in-hospital death in COVID-19 patients[30]. This is in concordance with our results, in which AKI was present in half of the admitted patients, in 94% in the ICU, and in all deceased patients.

The strengths of this study include a long-term, one-year follow-up of COVID-19 disease in KT recipients, with a thorough review of all notified cases. This resulted in a reduction in selection bias of more severe cases and consequently in reduction of adverse outcomes overall.

We acknowledge the weaknesses of this study. Because of its retrospective nature, it was not possible to establish an analytical protocol since the beginning of the pandemic, resulting in missing laboratorial values, and the therapeutic approach was wave-dependent and guided by the recommendations at each time. Moreover, the relatively small number of adverse events hampered our ability to identify risk factors for these events. A multicenter prospective study would increase the number of patients and events and allow standardized data collection and management.

In conclusion, KT recipients with COVID-19 have an increased risk of death compared to the general population, which doubles if hospitalization is required. This group of patients requires special attention and the assistant nephrologist should be consulted to manage immunosuppression.

Final eGFR was the most consistent marker of adverse outcomes, being associated with admission, oxygen need, IMV, and/or death. Given the higher risk observed in patients with previous graft dysfunction, the threshold for intervention in this group should be lowered. Moreover, AKI, as a marker of disease severity, should also be an indication for immediate treatment. On the other hand, factors associated with the baseline immunosuppression alone did not seem to affect outcomes.

Abbreviations

AKI - Acute kidney injury
ARDS - Acute respiratory distress syndrome
BMI - Body mass index
CI - Confidence interval
CKD - Chronic kidney disease
CNI - Calcineurin inhibitor
COVID-19 - Coronavirus disease 2019
eGFR - Estimated glomerular filtration rate
ICU - Intensive care unit
IQR - Interquartile range
IMV - Invasive mechanical ventilation
KT - Kidney transplant
OR - Odds ratio
RRT - Renal replacement therapy
RT-PCR - Reverse transcription polymerase chain reaction
SARS-CoV-2 - Severe acute respiratory syndrome coronavirus 2
sCr - Serum creatinine
SD - Standard deviation
SIR - Standardized incidence ratio
SMR - Standardized mortality ratio

Acknowledgments

No funding was provided for the preparation of this manuscript.

Authors' Contribution

All authors contributed to the study conception and design. Material preparation and data collection was performed by JT, JPO, PR, BR and FS. Data analysis was performed by JM. The first draft of the manuscript was written by JT. JM, MA, LSM, LD, ACH and AC provided intellectual content of critical importante to the work described. All authors read and approved the final manuscript.

Conflict of Interest

None declared. The results presented in this article have not been published previously in whole or part, except in abstract format.

Supplementary Material

The following online material is available for this article:

Supplementary Table 1 - Laboratory findings at admission.

Supplementary Table 2 - Clinical characteristic and management of the KT recipients who died of COVID-19.

Supplementary Table 3 - Univariable analysis of risk factors for oxygen need and IVM and/or death.

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