



COVID-19 Infection in Kidney Transplant Recipients: Single-Center Study

Kastali Mourad¹, Benkacimi Nouara¹, Saad Djaballah Djihad¹,

Boudlal Malika², Rahim Abd-El-Kader²,

Bellatache Hanane² and Mameri Imane²

¹Département de médecine- Faculté de médecine - Université Blida 1. Algérie

²EHS. T.O.T. Blida

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ABSTRACT: *Introduction :* Renal transplant recipients receiving chronic immunosuppression have been considered a population at high risk for infections, complications and death related to COVID-19 infection. **Results:** The average age of the patients was 37.3 ± 12.1 years, with a male predominance (65.9%). At least one comorbidity was observed in 41% of patients; obese (27.3%), diabetics (20.5%), cardiovascular diseases (6.8%), and cancers (2.2%). 90.1% of patients were hospitalized, of which 10% were admitted to the intensive care unit. Of the hospitalized patients, 10% died. Antimetabolites were reduced in 91% and stopped in 9% of patients. Calcineurin inhibitors were discontinued in 11.3% of patients. Hydroxychloroquine was administered in 23 patients (52.3%), antivirals in one patient (2.3%) and antibiotics in 56.8% of cases. **Conclusion:** Close monitoring of kidney transplant recipients is required during a pandemic due to a high mortality rate. The management of kidney transplant recipients has been difficult for clinicians and strategies are not based on high quality evidence.

KEYWORDS : COVID-19, Infection, Kidney Transplant



INTRODUCTION

In December 2019, a viral pneumonitis due to a coronavirus was declared in a Chinese city, Wuhan, and which quickly spread throughout the world [1]. Kidney transplant recipients (**KTR**) are considered a high-risk population for developing severe COVID-19 infection [2]. The immunosuppressive therapy taken by these patients could make them more susceptible to serious infections and increased viral loads [3], justifying the importance of mortality compared to the general population with COVID-19 (20% to 28% versus 1% to 5%) [4, 5, 6]. A faster clinical progression than in the general population has been noted in KTR with COVID-19 [7]. We describe in this study the prevalence of infection, risk factors and survival of KTR with COVID-19.

Patients and Methods

This was a single-center retrospective study of KTR with COVID-19 infection, carried out in the nephrology department between April 1, 2020 and September 1, 2022.

1. Inclusion Criteria:

All kidney transplant patients regularly followed in the department until April 1, 2020 were included in the study.

2. Exclusion Criteria:

Kidney transplant patients were excluded in other centers, and those who had lost their graft or died before April 1, 2020.

METHODOLOGY

KTR patients were included if they were clinically suspected of having COVID-19, whose diagnosis of infection was confirmed by a positive Reverse Transcriptase Polymerase Chain Reaction (**RT-PCR**) on nasopharyngeal samples. A thoracic computed tomography (**CT**) was performed and the parenchymal lesion is graded into 5 stages, based on the percentage of injured lung: absent or minimal lesion (<10%), moderate (10–25%), extensive (25–50%), severe (50–75%) or critical (> 75%) [8]. In case of strong suspicion and negative RT-PCR test, a new test must be repeated after 48 hours and the patient is considered positive in the interval [9]. A biological assessment was carried out on admission of the patient and the therapeutic management of confirmed cases is done according to the established protocol [10].

- Hydroxychloroquine: 200 mg x 3 per day for 10 days.
- Azithromycin: 500 mg the first day followed by 250 mg per day for the following 4 days

The alternative treatment was:

- Lopinavir/Ritonavir: (200/50 mg tablet) at the rate of 400 mg x 2 per day for 14 days.
- For severe or critical forms: The prescription of a short corticosteroid therapy (dexamethasone 0.1 to 0.2 mg/kg/d).



The parameters studied were age, gender, body mass index (BMI), duration of dialysis before transplantation, duration of follow-up after transplantation until infection, existing comorbidities, the initial and current function of the renal graft (creatinine, GFR) and current immunosuppressive treatments. For infected patients, data collection included initial clinical manifestations, biological assessments, lung damage on chest CT, medications prescribed to patients, evolution and prognosis.

Statistical Analysis

Continuous variables were expressed as mean \pm SD or median and IQR and categorical variables as total number (n) and percentage (%). Comparison between groups was performed using Pearson's χ^2 test for categorical data or Fisher's exact test was applied when the number of cases were < 5 . Univariate and multivariate logistic regression methods were used to explore risk factors associated with death. Statistical significance was considered as a two-sided p value < 0.05 .

RESULTS

Forty-four KTR (34.6%) were diagnosed positive for COVID-19 infection between April 1, 2020 and April 1, 2022. The infection had occurred 101.9 ± 72.5 months (3 - 342 months) after transplantation, only 18.1% of patients were in their first year of transplantation. Twenty-nine patients (65.9%) were men. The average age of patients with COVID-19 was 34.1 ± 11.6 years, compared to the uninfected patients which was 37.3 ± 12.1 years ($p = 0.8$). Patients positive for COVID-19 were more often obese (27.3%) compared to uninfected patients (8.4%; $p=0.02$), and diabetics (20.5% vs 7.2%; $p=0.0009$); hypertension was comparable among the two groups (61.3% vs 60.2%; $p=0.9$). History of cardiovascular disease was 4.5% vs 3.6% ($p=0.8$). The history of cancers was greater among not infected patients than the COVID-19 positive patients (4.8% vs 2.2%; $p=0.5$) (**Table I**). Clinical manifestations and results of COVID-19 positive patients are summarized in **Table II** and their main characteristics were asthenia (61.3%), fever (56.8%), cough (43.2%), dyspnea (20.4%), diarrhea (15.9%), headache (6.8%), arthralgia (6.8%), myalgia (2.2%) and ageusia (2.2%). Chest CT was ground glass opacities (88%), crazy paving (8%) and condensation (8%) images. These injuries were classified as minimal (2.3%), moderate (27.3%), extensive (59.1%), severe (4.6%) and critical (6.8%). The biological assessment carried out on admission showed leukopenia (43.2%), lymphopenia (63.6%), thrombocytopenia (4.5%) and transaminases: Alanine transaminase (ALT) at 26.0 ± 21.1 U/ml (2 – 93 U/ml) and Aspartate transaminase (AST) at 22 ± 16.2 U/ml (7 – 85 U/ml). On admission, seventeen patients (38.6%) presented acute kidney injury (AKI) with serum creatinine at 1.73 ± 0.57 mg/dl (0.9 – 2.9 mg/dl), no patient had required dialysis. One patient had co-infection COVID-19 and cytomegalovirus infection (CMV). According to the initial symptomatology, four patients (9.1%) had minor symptoms and were treated in ambulatory, while forty patients (90.1%) were hospitalized, of which four patients (9.1%) were transferred to the intensive care unit (ICU) for intubation and mechanical ventilation. Antimetabolites were reduced in 91% and stopped in 9% of patients. Anticalcineurins were stopped for 5 patients (11.3%). Intravenous glucocorticoids were administered for 8 patients (18.2%).



The therapeutic prescription was based on hydroxychloroquine for 23 patients (52.2%), antivirals for one patient (2.2%). Cefotaxime (56.8%) and azithromycin (43.2%) were the most frequently administered antibiotics. During the evolution, we have unfortunately counted four deaths (9.1%) on 15 ± 1.4 days of hospitalization (14 – 17 days), residual renal insufficiency persisted in two patients (4.5%) and the patient who had presented with COVID-19-CMV coinfection had required chronic dialysis after 6 months of infection.

In univariate analysis, factors associated death were age > 50 years ($p=0.05$), obesity ($p=0.04$), dyspnea ($p=0.000$) and the severity of pulmonary parenchymal damage at chest CT ($p=0.000$) **table III**.

DISCUSSION

The incidence of patients with COVID-19 in Algeria was 612.03 cases per 100,000 inhabitants [11]. We diagnosed forty-four KTR with COVID-19 (34.6%). Our study confirms the impact observed on the prevalence of COVID-19 in kidney transplant recipients (**KTR**) or chronic hemodialysis patients (34.6% vs 7.8%) [12]. The frequency of SARS-CoV-2 infection was approximately 1.8% of KTR patients and 4.9% of dialysis patients in the REIN cohort [13], while this incidence was 1.9% in the study of Ismail [14]. Some studies have shown that most KTR with COVID-19 worldwide are men with an average age of over 50 years [15, 16]. The average age of our patients was 34.1 ± 11.6 years (31.8% were aged ≥ 50 years), of which 29 patients (69.5%) were men. In Molaei's study [16], 20% of patients were women with an average age of 59.6 ± 7.7 years. Age was an independent risk factor of disease severity in our cohort. Indeed, age has been considered to have an unfavorable prognostic significance in previous studies on the general population [17, 18] and on the population of solid organ transplant recipients [19]. Male gender has previously been associated with severe COVID-19 disease [18]; however, a significant association between male gender and disease severity or mortality was not observed in either our series or in Caillard [19]. The symptomatology in KTR patients with COVID-19 was similar to that reported in the general population, with a predominance of cough (56.5%) and fever (52.2%). This is what results from studies [19, 20, 21] showing that fever varies between 77% - 94% and cough between 68% - 79% of cases. Digestive disorders, especially diarrhea, were less frequent in our study (17.4%) than in those reported by Caillard [19] (36.3%) and Crespo [22] (36.7%). In our cohort, four patients (9.1%) progressed to acute respiratory distress syndrome (ARDS) requiring their transfer to the ICU; however, Favà et al. [23] described that half of their patients progressed to ARDS, and 50% of them died.

The incidence of AKI increased in patients with COVID-19 and is associated with increased ICU mortality [24]. Aziz et al. [25] showed that the incidence of AKI was higher in KTR patients compared to the general population (27.5% versus 13.3%), while the mortality rate was similar between the groups. According to Marinaki et al. [26], 44% of hospitalized KTR patients developed AKI and 23% required dialysis.

AKI was observed in 38.6% in our cohort, probably functional because patients were frequently admitted with diarrhea and high fever. AKI was observed in 5.1% of patients hospitalized with COVID-19 in Cheng's study [27]. In our study, the severity of COVID-19 was not associated



with elevated serum creatinine levels 1.68 ± 0.56 mg/dl vs 1.97 ± 0.67 mg/dl ($p=0.4$), hence these results were similar to those reported in KTR patients with COVID-19 [16, 28].

In renal transplant recipients, CMV infection is frequent; it does not only induce endothelial activation and rejection by well-identified cellular mechanisms [29], but also leads directly to allograft damage [30]. In Molaei's cohort [16], 40% of patients presented CMV-COVID-19 co-infection. The most widely used drugs with presumed antiviral activity were hydroxychloroquine, antibiotics (azithromycin) and protease inhibitors, showing no benefit for prevention or treatment in general populations or solid organ transplant recipients [31, 19, 32]. Regarding immunosuppressants, the trend was reduction or suspension of antimetabolite or mTOR inhibitors, while calcineurin inhibitors were suspended in patients at risk of interaction with protease inhibitors. In vitro, the efficacy of cyclosporine A and tacrolimus on inhibiting the replication of SARS-CoV-1 and other human coronaviruses has been reported [33]. Obesity and dyspnea were risk factors independent of disease severity in our cohort. The association of obesity and the severity of COVID-19 in KTR has been shown in the Caillard cohort [19].

Four patients (9.1%) whose symptomatology was minor were followed at home with a good evolution as described in some studies [19, 34, 35], while 40 patients (86.9%) were hospitalized. Transfer to the ICU was necessary in 9.1% of our patients. They were five patients (71.4%) to be hospitalized in the Banerjee cohort [36]. In some studies [3, 37, 38, 39, 19, 40], this rate was between 6% and 50% of hospitalized patients. This percentage was slightly higher than that reported for immunocompetent subjects (16%-33%) [17, 20]. The vulnerability of KTR and/or the added comorbidities cause a high mortality rate in these patients with COVID-19. In general, compared to the general population, KTR has a higher mortality including between 18% and 43% [41]. De Meester [42] showed similar mortality to that reported in the general population (14% versus 15.3%). The mortality rate of our KTR patients with COVID-19 was 9.1%. Previous data obtained in small series of transplant patients indicated a mortality rate of between 6% and 28% [37, 3, 38, 39, 19, 40]. In the multicenter TANGO study, the mortality rate was 32% and it appears that older age, lower lymphocyte count, higher levels of lactate dehydrogenase, procalcitonin and IL-6 and eGFR lower were associated with mortality [43]. In Favà's study [23], advanced age, the elevation of serum lactate dehydrogenase, and ARDS at admission were independently associated with a higher risk of death, and the mortality rate was 28%. The study (ERACODA) involving several European countries [44], mortality in KTR patients at 28 days of hospitalization was 21.3% compared to 25% in dialysis patients, and advanced age was the major risk factor prevalence of mortality.

Our study has certain limitations. The notable limitation is the small sample. The fact that we included in our study only symptomatic patients (with positive COVID-19 swab), on the one hand, prevents any conclusion regarding the prevalence of COVID-19 in patients without clinical manifestations and, on the other hand, can lead to possibly missing false negative patients. Also, during the period of confinement, due to the absence of online consultations, different diagnostic approaches when suspected of infection were applied. Therefore, our results only reflect those observed on a homogeneous cohort of KTR patients who came to our center.

In conclusion, KTR is a population at a high risk of developing severe forms of COVID-19. The collaborative work has the advantage of developing prevention and screening strategies in these immunocompromised patients, often with added comorbidities.

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APPENDIX

Table 1. Demographic characteristic kidney transplant recipients' patients

Demographic Characteristics	COVID-19– Positive Patients (N=44)	COVID-19– Negative patients (N=83)	p
Age, yr	34.1± 11.6	37.3 ± 12.1	0.7
Sex (male), no. (%)	29 (65.9)	58 (69.9)	0.8
Time on dialysis, (mo),	42.7 ± 35.4	43.9 ± 44.4	0.9
BMI (kg/m ²)	26.42 ± 4.99	25.28 ± 4.96	0.9
Comorbidities			
Hypertension, no. (%)	27(61.3)	50 (60.2)	0.9
Diabetes, no. (%)	9 (20.5)	6 (7.2)	0.0000
Obesity (BMI>30), no. (%)	12 (27.3)	7 (8.4)	9
Cancers, no. (%)	1 (2.2)	4 (4.8)	0.02
Cardiovascular disease, no. (%)	2(4.5)	3(3.6)	0.5
Time on dialysis, (mo),	42.7 ± 35.4	43.9 ± 44.4	0.8
Donor, LD/DD, no. (%)	42/2 (95.5/4.5)	80/3 (96.4/3.6)	0.1 0.9
Immunosuppressive therapies, no. (%)	29 (65.9)	45 (54.2)	
Cyclosporine, no. (%)	10 (22.7)	30 (36.1)	0.5
Tacrolimus, no. (%)	44 (100)	82 (98.8)	0.2
Glucocorticosteroids, no. (%)	1 (2.2)	2 (2.4)	0.9
Sirolimus, no. (%)	43 (97.7)	81 (97.6)	0.9
MMF, no. (%)	3 (6.8)	2 (2.4)	0.9
Azathioprine, no. (%)	101.9 ± 72.5	90.9 ± 66.5	0.3
Duration of transplantation (mo)			0.5

mo: months, **yr:** years, **BMI:** body mass index; **LD:** living donor; **DD:** Deceased donor, **MMF :** Mycophenolate mofetil; **KT:** Kidney transplantation

**Table II: Clinical characteristics and outcomes of kidney transplant recipients with COVID-19**

Parameters	Number	%
Symptoms/signs		
Cough	19	43.2
Asthenia	27	61.3
Dyspnea	9	20.4
Fever	25	56.8
Diarrhea	7	15.9
Headache	3	6.8
Arthralgia	3	6.8
Myalgia	1	2.2
Ageusia	1	2.2
AKI	17	38.6
Laboratory tests		
Admission creatinine (mg/dl)	1.73 ± 0.57 (9 – 29)	
Admission eGFR (ml/mn/1.73m ²)	47.03 ± 15.53 (24.17- 75.22)	
Control creatinine (mg/dl)	1.56 ± 0.81 (9 – 61)	
Control eGFR (ml/mn/1.73m ²)	53.10 ± 15.20 (8.24 – 81.86)	
Chest CT		
Minimal	1	2.2
Moderate	12	27.2
Extensive	26	59.1
Severe	2	4.4
Critical	3	6.8
Traitement		
Hydroxychloroquine	23	52.2
Antiviral treatment	1	2.2
Azithromycin;	20	45.4
Evolution		
ICU	4	9.1
Full recovery	40	90.9
Died	4	9.1

Chest CT, Chest computed tomography, **eGFR**: estimated glomerular filtration rate; **ICU**: intensive care units; **AKI**: acute kidney injury



Table III: Comparison between Living and Died kidney transplant renal Patients from COVID -19 Infection

Parameters	Living patients (N= 40)	Deceased patients (N= 4)	p
Age > 50 y; no, (%)	11 (27.5)	3 (75)	0.09
Sex men; no, (%)	27 (67.5)	2 (50)	0.5
Obesity; no, (%)	8 (20)	3 (75)	0.04
Hypertension; no, (%)	25 (62.5)	2 (50)	0.6
Diabetes; no, (%)	5 (12.5)	1 (25)	0.5
Fever; no, (%)	22 (55)	3 (75)	0.5
Dyspnea; no, (%)	5 (12.5)	4 (100)	0.0009
Leucopenia; no, (%)	16 (40)	3 (75)	0.2
Lymphopenia; no, (%)	25 (62.5)	3 (75)	0.7
Pulmonary CT scan			
Extensive	25 (62.5)	1 (25)	0.2
Severe	2 (5)	3 (75)	0.003
AKI no, (%)	14 (35)	3 (75)	0.1
Graft function			
Admission creatinine (mg/dl)	1.68 ± 0.56	1.97 ± 0.67	0.5
Admission eGFR	48.18 ± 15.58	36.11 ± 11.29	0.6
Traitment			
Ciclosporine; n, (%)	27 (67.5)	2 (50)	0.5
Tacrolimus; n, (%)	9 (22.5)	1 (25)	0.8
Sirolimus n, (%)	0	1 (25)	
Hydroxychloroquine; n, (%)	20 (50)	3 (75)	0.4

AKI: acute kidney injury, **eGFR:** estimated glomerular filtration rate