Immunosuppressive therapy reduction and early post-infection graft function in kidney transplant recipients with COVID-19

Articoli originali

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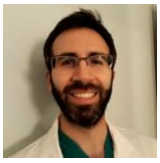
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ABSTRACT

Background: Kidney transplant (KT) recipients with COVID-19 are at high risk of poor outcomes due to the high burden of comorbidities and immunosuppression. The effects of immunosuppressive therapy (IST) reduction are unclear in patients with COVID-19.

Methods: A retrospective study on 45 KT recipients followed at the University Hospital of Modena (Italy) who tested positive for COVID-19 by RT-PCR analysis.

Results: The median age was 56.1 years (interquartile range, [IQR] 47.3-61.1), with a predominance of males (64.4%). Kidney transplantation vintage was 10.1 (2.7-16) years, and 55.6 % of patients were on triple IST before COVID-19. Early immunosuppression minimization occurred in 27 (60%) patients (reduced-dose IST group) and included antimetabolite (88.8%) and calcineurin inhibitor withdrawal (22.2%). After SARS-CoV-2 infection, 88.9% of patients became symptomatic and 42.2% required hospitalization. One patient experienced irreversible graft failure. There were no differences in serum creatinine level and proteinuria in non-hospitalized patients before and post-COVID-19, whereas hospitalized patients experienced better kidney function after hospital discharge (P=0.019). Overall mortality was 17.8%. without differences between full- and reduced-dose IST. Risk factors for death were age (odds ratio [OR]: 1.19; 95%CI: 1.01-1.39), and duration of kidney transplant (OR: 1.17; 95%CI: 1.01-1.35). One KT recipient developed IgA glomerulonephritis and two ones experienced symptomatic COVID-19 after primary infection and SARS-CoV-2 mRNA vaccine, respectively.

Conclusions: Despite the reduction of immunosuppression, COVID-19 affected the survival of KT recipients. Age of patients and time elapsed from kidney transplantation were independent predictors of death. Early kidney function was favorable in most survivors after COVID-19.

KEYWORDS: COVID-19, kidney transplant, immunosuppressive therapy, graft function, proteinuria, mortality, transplant, SARS-COV-2, reinfection

Introduction

Since SARS CoV-2 infection was first identified in December 2019, the pandemic spread quickly around the world, with a disruptive impact on social and economic life. This virus yielded several new challenges to our healthcare systems that had to cope with an increased rate of morbidity and mortality among the most vulnerable populations [1]. Kidney transplant (KT) recipients are a subset of the population at high risk of severe COVID-19 due to the high burden of comorbidities and the cumulative side effects of immunosuppressive therapy (IST) [2]. Data collected so far show that transplant recipients are extremely susceptible to the SARS-CoV-2 infection, much more than the general population [3, 4]. The causes are multiple, but principally revolve around the use of long-term IST.

Despite the great emphasis on early IST reduction to face the potentially lethal consequences of COVID-19, no confirming data supports its beneficial effect in terms of survival or clinical manifestations. Additional uncertainty arises from the recent literature reporting that a tempered immune response is thought to prevent COVID-19–induced systemic inflammatory syndrome. To date, data regarding early graft outcomes after COVID-19 are scarce [5]. It is worth noting that graft survival may be threatened by non-reversible episodes of kidney injury [6, 7]. Lastly, a concerning issue may be the hyporesponsiveness to anti-SARS-CoV-2 vaccination [8, 9]. Numerous studies have confirmed that KT recipients have a blunted immune response to mRNA vaccines [10]. Only 48% of patients were able to develop a protective serologic response to SARS-CoV-2 [11]. Caillard et al [12] reported that about one-third of kidney transplant patients had severe manifestations, including a fatal outcome, despite COVID-19 vaccination. This group of patients is therefore expected to remain vulnerable to the severe complications of COVID-19 until new strategies will be implemented to reduce the susceptibility of these subjects.

Considering all the uncertainties in the management of KT recipients and the high risk of severe COVID-19 manifestations within this cohort of patients, we report our experience in managing KT recipients with COVID-19. In particular, we focus on the impact of early IST reduction, and early graft function after the resolution of the infection.

Material and methods

Kidney transplant outpatient clinic

This kidney transplant outpatient clinic follows more than 500 KT recipients, including combined liver and pancreas-kidney transplantation. Outpatient service was delivered by a senior nephrologist with experience in kidney transplantation, one fellow and three nurses. A 24-h, 7/7 days per week service was available for KT recipients in case of kidney-related pathologic processes (anuria, fluid overload) or infections. This service was also offered to the subjects transplanted in our Center but living far away from it.

During COVID-19 all the patients were instructed to call the clinic in case of COVID-19 symptoms. Despite the reduction of non-essential healthcare services, our outpatient clinic continued to deliver care to KT recipients, adopting all the containment measures (triage at entry, masking, social distancing and hands hygiene) to prevent COVID-19 diffusion. A telephonic triage was performed for all patients before reaching the hospital to intercept paucisymptomatic patients.

Patients with symptoms were invited to perform nasal swabs using RT-PCR and were visited in a dedicated room to assess vital parameters and clinical conditions. According to the severity of the symptoms, patients were sent home or to the emergency room.

To reduce the workload of the emergency room, patients were managed as outpatients unless they developed severe symptoms that required hospital admission. The monitoring of noncritical patients was mostly performed via phone calls and emails.

According to our internal protocol and taking into account the opinions of European experts [13, 14], immunosuppression was modulated as follow:

- for **asymptomatic** or **mild COVID-19** patients (i.e., mild upper respiratory and/or gastrointestinal symptoms, temperature <38°C without dyspnea) in triple therapy (calcineurin-inhibitors [CNI] + mycophenolate acid [MPA]/azathioprine [AZA] + steroids), MPA or AZA was withdrawn, and a dual therapy (CNI + steroid) was continued. If the patients were on dual therapy (CNI + mammalian target of rapamycin inhibitor [mTOR-i] or CNI + MPA), MPA/mTOR was withdrawn and replaced with a low dose of steroids (i.e., methylprednisolone 4 or 8 mg once-daily).
- for **moderate** (signs and symptoms of lower respiratory disease or saturation of oxygen [SpO2] ≥94% on room air at sea level) and **severe COVID-19** (SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO2/FiO2] <300 mm Hg, respiratory frequency >30 breaths per minute, or lung infiltrates >50%) all immunosuppressors, but steroids, were stopped. The prescription of anti-inflammatory and immunomodulant steroid therapy for symptomatic COVID-19 patients (dexamethasone at a dose of 6 mg once daily for up to 10 days) was not part of the anti-rejection therapy and was administered by COVID-19 experts.

COVID-19 population

The study population was comprised of kidney transplant recipients with COVID-19 with a complete follow-up, including death or discharge from hospital.

We retrospectively reviewed the electronic charts of all KT recipients with COVID-19 from March 7, 2020, to June 25, 2021. During this period we performed 144 nasopharyngeal swabs. The diagnosis of COVID-19 was performed through reverse transcriptase-polymerase chain reaction (RT-PCR) assay on a nasopharyngeal swab. We excluded patients aged <18 years. Kidney function was estimated by glomerular fraction rate (eGFR) using the CKD-EPI equation. Occasionally, some data were missing for patients admitted to a hospital located far from our Center.

This study has been authorized by the local Ethical Committee of Emilia Romagna (n. 839/2020). The study protocol complies with the guidelines for human studies and includes evidence that the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Statistical analysis

Baseline characteristics were described using median (interquartile range [IQR]) or frequencies, as appropriate. The chi-square or Fisher's test, and student's t-test were used to compare categorical and continuous variables between groups, respectively. Univariate and multivariate logistic regressions were performed to test the association between mortality and baseline patient characteristics. Variables that were significant on univariate analysis (P=<0.05) were entered into the multivariate model to identify independent predictors. Results were expressed as odds ratios (OR) and 95% confidence intervals (CI). Univariate and multivariate logistic regression analysis determined risk factors for death. A P value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS® statistical software.

Results

Characteristics of COVID-19 population

From the beginning of the COVID-19 pandemic in Italy, 45 KT recipients followed in our center contracted COVID-19. The demographic and clinical characteristics of these patients are detailed in Table I. This group of patients included two (4.4%) combined liver-kidney and one (2.2%) heart-kidney transplant recipient. Seven (15.5%) patients were hospitalized in another structure because they lived far from our Center.

Variable	All patients (n.=45)	Reduced-dose IST (n.=27)	Full-dose IST (n.=18)	p-value
Age, year	56.1 (47.3-61.1)	55.9 (47.6-61.2)	56.1 (44.4-62)	0.85
Range	19.2-83.5	19.2-79.8	28.1-83.5	
Males, n. (%)	29 (64.4)	18 (66.7)	110 (61.1)	0.75
Race/ethnicity				0.61
White, n. (%)	41 (91.1)	26 (92.6)	16 (88.9	
Black, n. (%)	4 (8.9)	2 (7.4)	2 (11.1)	
Transplant vintage, year	10.1 (2.7-16.01)	7.8 (2.4-15.2)	11.1 (4.7-21.1)	0.29
sCr pre-COVID-19, mg/dl	1.45 (1.18-1.84)	1.44 (1.18-1.81)	1.28 (1.14-1.82)	0.68
eGFR pre-COVID-19, ml/min	48.4 (36-64)	47.7 (35-64)	49.5 (38.6-67.9)	0.83
24-h proteinuria, mg/dl	87.4 (0.52-188.5)	72 (0.25-183)	145.5 (6.2-205)	0.69
Immunosuppressive therapy, n. (%)				
CNI	39 (86.7)	24 (88.9)	15 (83.3)	0.67
mTOR-i	8 (17.8)	4 (14.8)	4 (22.2)	0.69
MPA	31 (68.9)	24 (88.9)	7 (38.9)	**0.01**
Steroid	36 (80)	23 (85.2)	13 (72.2)	0.44
IS regimen				**0.001**
Triple therapy	25 (55.6)	21 (77)	4 (22.2)	
Double therapy	19 (42.2)	6 (22.2)	13 (72.2)	
Monotherapy	1 (2.2)	0 (0)	1 (5.6)	
Reduction IS therapy, n. (%)	27 (60)	27 (100)	0 (0)	N/A
MPA withdrawal	24 (53.3)	24 (88.9)	0 (0)	N/A
CNI or mTOR-i withdrawal	6 (13.3)	6 (22.2)	0 (0)	N/A
Increase steroid	9 (5,4)	8 (29.6)	1 (5.6)	0.064
Comorbidities, n. (%)				
HIV, HCV or HBV	6 (13.3)	3 (11.1)	3 (16.7)	0.65
Diabetes	5 (11.1)	4 (14.8)	1 (5.6)	0.63
Neoplasia	10 (22.2)	7 (25.9)	3 (16.7)	0.71
Graft rejection	4 (8.9)	1 (3.7)	3 (16.7)	0.13
CVD	12 (26.7)	7 (25.9)	4 (22.2)	77
Autoimmune disease	4 (8.9)	1 (3.7)	3 (16.7)	0.13
Previous severe infection	13 (28.9)	8 (29.6)	5 (27.7)	1
Symptomatic COVID-19, n. (%)	40 (88.9)	27 (100)	13 (72.2)	0.45
Hospitalization, n. (%)	19 (42.2)	14 (51.9)	5 (27.8)	0.13
Graft failure, n. (%)	1 (2.2)	1 (3.7)	0 (0)	1
ICU admission, n. (%)	9 (20)	4 (14.8)	5 (27.8)	0.28
Mortality, n (%)	8 (17.8)	4 (14.8)	4 (22.2)	0.69
Post-COVID-19 follow-up, day	70.5 (51-109)	76 (50.5-116.5)	69 (66-76)	0.57

Notes: eGFR denotes estimated glomerular filtration rate; CNI, calcineurin inhibitor; CVD, cardiovascular disease; HCV, hepatitis C; HBV, hepatitis B; IST, immunosuppressive therapy; MPA, mycophenolate acid; mTOR-I, mammalian target of rapamycin inhibitor; sCr, serum creatinine.

Table I: Demographics and clinical characteristics of KT recipients

The age of patients ranged from 19.2 to 83.5 years and the median was 56.1 (IQR, 47.3-61.1) years. COVID-19 was more prevalent in males than in females (64.4% vs 35.6%) and occurred after a median of 10.1 (2.7-16.01) years from transplantation.

Before the COVID-19 infection, serum creatine (sCr) was 1.45 (IQR 1.1-1.8) mg/dl corresponding to a median eGFR of 48.4 (IQR 36-64) ml/min. At the time of the COVID-19 diagnosis, more than half of the patients were in triple standard IST. Forty patients (88.9%) developed symptoms of COVID-19

and 19 of them (42.2%) required hospitalization. One patient returned to dialysis following acute kidney injury. Overall, nine patients (20%) were admitted to ICU for severe manifestations of COVID-91 and eight (17.8%) died.

Reduced- vs full-dose IST group

The entire population was subdivided into two groups: reduced-dose (n.=27; 60%) and full-dose IST (n.=18; 40%). There were no significative statistical differences in terms of demographic and clinical characteristics between the two groups. Statistical analysis detected significant differences in the prescription of IST. Patients who underwent reduction of immunosuppression (reduced-dose IST) were treated with a higher dose of IST before COVID-19; indeed, the rate of prescribed triple-drug IST was higher in this group than in full-dose IST patients (77% vs. 22.2%; P=<0.001).

In the reduced-dose IST group, MPA (88.8%) and CNI or mTOR-i (22.2%) were the most frequent discontinued agents. Conversely, the dose of steroids was increased in a third of patients and, in all of them, the administration of steroids changed from alternate days (methylprednisolone 2/0 or 4/0) to a daily regimen. Hospitalization, ICU admission and death rate in patients who underwent IST reduction were 51.8%, 14.8% and 14.8%, respectively. However, despite IST reduction, hospitalization (P=0.13), ICU admission (P=0.28) and death (P=0.69) rates were not different from those of the full-dose IST group.

Outcomes of KT recipients with COVID-19

Univariate and multivariate logistic regression was performed to detect predictors of mortality (Table II). Multivariate analysis found that age (OR=1.19 [95%CI 1.01-1.39]; P=0.034) and years spent on immunosuppressive therapy (OR=1.17 [95%CI 1.01-1.35]; P=0.040) were associated with mortality in this group of patients.

	Univariate				Multivariate			
Variable	**OR**	**CI (95%)**		**p-value**	**OR**	**CI (95%)**		**p-value**
Sex								
Male	4.40	0.78	24.81	0.09				
Age (1-yr increase)	1.11	1.02	1.22	0.016	1.19	1.01	1.39	**0.034**
KT vintage (1-yr increase)	1.10	1.00	1.21	0.053	1.17	1.01	1.35	**0.040**
Steroid-based IST	1.93	0.21	18.08	0.56				
Reduction IST	1.33	0.26	6.869	0.74				
Increase of steroid	0.52	0.06	4.85	0.56				
Triple IST	0.51	0.10	2.620	0.42				
Double IST	1.96	0.38	10.026	0.42				
GFR	0.99	0.95	1.026	0.57				
GFR< 45ml/min	1.47	0.32	6.80	0.62				
GFR 45-59 ml/min	0.68	0.15	3.16	0.62				
sCr	1,33	0,26	6.87	0.73				
Graft rejection	1.52	0.14	16.91	0.73				
Autoimmune disease	0.00	0.00		0.99				
HIV/HCV/HBV	2.58	0.38	17.43	0.33				
Previous sever infection	0,73	0.13	4.19	0.72				
Diabetes	1.11	0.11	11.49	0.93				
Neoplasm	1.12	0.19	6.70	0.89				
Cardiovascular disease	1.73	0.34	8.76	0.50				

Notes: eGFR denotes estimated glomerular filtration rate; HCV, hepatitis C; HBV, hepatitis B; IST, immunosuppressive therapy; MPA, mycophenolate acid; mTOR-I, mammalian target of rapamycin inhibitor; sCr, serum creatinine.

Table II: Univariate and multivariate predictors of mortality through logistic regression analysis

Among the survivors (82.2%), one patient with a CKD stage 4 (GFR=20 ml/min) before SARS-CoV-2 infection developed irreversible graft failure requiring HD. One patient (2.7%) manifested de-novo proteinuria (4100 mg/die) after the resolution of COVID-19 and graft biopsy revealed IgA glomerulonephritis (the lack of data on the cause of CKD did not allow us to classify these histological

findings as either de-novo or recurrent IgA glomerulonephritis). Lastly, one patient experienced symptomatic COVID-19 reinfection after the primary infection and another one following the SARS-CoV-2 mRNA vaccine. Early post-COVID-19 follow-up of 25 out of the 37 survivors showed that pre- and post-COVID variations of sCr, eGFR and 24-hour proteinuria were not statistically significant in outpatients after the resolution of COVID-19. A significantly lower sCr level (P=0.019) and eGFR (P=0.028) were measured after hospital discharge in hospitalized patients. No differences were noted in the level of daily proteinuria (Table III). The early follow-up of KT recipients after COVID-19 resolution did not show any new episodes of graft rejection.

	Non-hospitalized patients			Hospitalized patients		
	Pre-COVID-19	**Post-COVID-19**	**p-value**	**Pre-COVID-19**	**Post-COVID-19**	**p-value**
sCr, mg/dl	1.31 (1.2-1.76)	1.33 (1.08- 1.7)	0.85	1.49 (1.1-1.8)	1.21 (0.9-2.1)	**0.019**
eGFR, ml/min	48.8 (40.5-62.1)	56.7 (41.5-67)	0.25	46.7 (36-64)	56.7 (41.5-67)	**0.028**
24-h proteinuria, mg/die	102 (6.2-205)	89.4 (37.2-246.4)	0.08	13(2.5-183)	44.7 (10.8-1141)	0.29
Notes: eGFR, estimated glomerular filtration rate; sCr, serum creatinine.						

Table III: Early graft function post-COVID-19 in hospitalized and non-hospitalized KT recipients

Discussion

Numerous reports have alerted the scientific community regarding the unfavorable outcome of COVID-19 in patients with a reduced immune response [1, 15]. The results of this study confirmed that COVID-19 poses KT recipients at high risk of severe consequences.

In our cohort of KT recipients, COVID-19 carried with it a higher rate of symptoms, hospitalization and mortality compared to the general population [16, 17]. We found that in this cohort (45 KT recipients with COVID-19, median age 56.1), 40% of patients developed severe symptoms requiring hospitalization. Overall mortality was 17.8%, higher than the mortality reported in the general population, which ranges between 0.1-19.2% around the world and accounts for about 2.02% globally [18].

In an attempt to reconstitute the immune system against SAR-CoV-2 infection, we minimized the burden of IST in these patients. All KT recipients who communicated their COVID-19 positivity to our center, were advised to discontinue the antimetabolite agents (i.e., MFA or AZA) (88.9%) and CNI or m-TOR-I (22.2%). In the hospitalized patients, IST was further reduced or suspended, according to the clinical conditions of the patient. Nevertheless, hospitalization and death rates in the reduced-dose IST group were not dissimilar from the full-dose IST group.

At first glance, these results show that the reduction of immunosuppression did not confer any advantage in terms of patient survival. However, some considerations should be considered before drawing firm conclusions. Most patients who underwent IST reduction carried a significantly higher burden of IST compared to KT recipients whose therapy was left unmodified. The higher prevalence of triple-drug immunosuppressive regimen in patients who underwent IST minimization (77% vs. 22.2%; P=<0.001) has probably increased the vulnerability to COVID-19. Conversely, patients with a full-dose IST spent more time (11.2 vs 7.8 years) on kidney transplantation compared to the reduced-dose IST group. Lastly, we believe that the slight increase of steroid therapy (from alternate days to a daily administration) in the reduced-dose IST group (P=0.064) was too small to mitigate the inflammatory response driven by COVID-19.

Although the reduction of IST did not lead to a favorable outcome, it is worth mentioning that the overall mortality in our cohort was tendentially lower than that reported in other studies, where this approached up to 32.5% [19–26]. Our results are in line with the population-based data on 1013 KT

recipients affected by COVID-19 collected by the French and Spanish national registries, which reported a 28-day mortality of 20% [27]. In Italy, Bossini et al. [24] reported a higher overall mortality rate (28%) during the first wave of COVID-19 in the city of Brescia. Similarly to our therapeutic strategy, they discontinued immunosuppression in all hospitalized patients and introduced or increased the dose of steroids. The causes underlying these different mortality rates are unknown. The different timing of enrollment made the two cohorts not perfectly comparable. All patients in the Brescia cohort were enrolled during the first wave of COVID-19 in Europe, in an overwhelmed and unprepared hospital setting, within a timespan characterized by a high rate of experimental regimens and relative side effects [28, 29]. Lastly, a lower median age (56.1 vs. 60 years) in our cohort of patients probably contributed to the better prognosis.

Multivariate analysis showed that the predictors of death were age and time elapsed on IST, in line with previous studies. Age is widely associated with COVID-19 severity and death in KT recipients [30, 31] as well as in the general population [32]. The Centers for Disease Control (CDC) claims that 8 out 10 COVID-19 deaths in the U.S. occurred in adults over 65 and that the risk of hospitalization and death increases enormously with age [33].

The effect of immunosuppression is still controversial in KT recipients [34]. Immunosuppression is known to dysregulate innate and adaptive immunity, exposing the patients to severe infections. On the other hand, severe COVID-19 infection has been associated with a dysregulated inflammatory response (IL-6, IL-1, and chemokines) leading to ARDS and sepsis. The new insights support a promising role of immunosuppressants (i.e., tocilizumab, steroid) in tempering the immune response of patients with severe manifestations of COVID-19 [35].

Lastly, we report a short-term good graft function in patients who survived COVID-19. These data indicate a stable early graft function (sCr and 24-hour proteinuria) in outpatients who were not hospitalized. Conversely, hospitalized KT recipients had a statistically significant improvement in renal function. As stated also by Dacina et al. [5], we speculate that lower sCr after SARS-CoV-2 is due to the minimization or withdrawn of CNI, a ‘drug holiday’ apparently without dire consequences in terms of graft rejection.

Finally, the limitations of the study should be enumerated. It is a retrospective study, with a small sample size and a short follow-up after COVID-19. The small number of patients and the short observation period may have reduced the probability to observe an underlying difference between these two groups.

Long-term follow-up is required to verify if the early improvement of kidney function after COVID-19 is maintained in the survivors. Furthermore, we cannot exclude that, in some cases, the reduction of IST occurred with a short delay after the diagnosis of COVID-19; however, all patients with symptoms underwent nasopharyngeal swabs as fast as possible in an ambulatory setting.

Conclusion

In our cohort of patients, the reduction of immunosuppression did not decrease the risk of severe COVID-19 or death. COVID-19 was associated with hospitalization (42%), graft failure (2.2%), IgA glomerulonephritis (2.2%) and death (17.8%). Age and time elapsed from kidney transplantation were independent predictors of death in our patients. Short-term follow-up after COVID-19 showed an excellent graft function in most survivors. Primary infection or vaccination did not exclude the risk of SARS-CoV-2 infection in KT recipients.

Authorship credit

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Acknowledgments

Special thanks are due to Marco Ballestri, Elisabetta Ascione, Roberto Pulizzi and Francesca Facchini, skilled and experienced nephrologists involved in the “Kidney Transplant Program”, and to Laura Bonaretti and all nurses of the “Kidney Transplantation Outpatient Clinic” at the University Hospital of Modena for their precious support in managing KT recipients.

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