

ORIGINAL ARTICLE

Induction immunosuppression and outcome in kidney transplant recipients with early COVID-19 after transplantation

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Received: 20.2.2022; Editorial decision: 26.4.2022

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ABSTRACT

Coronavirus disease 2019 (COVID-19) in kidney transplant recipients has a high risk of complications and mortality, especially in older recipients diagnosed during the early period after transplantation. Management of immunosuppression has been challenging during the pandemic. We investigated the impact of induction immunosuppression, either basiliximab or thymoglobulin, on the clinical evolution of kidney transplant recipients developing COVID-19 during the early period after transplantation. We included kidney transplant recipients with <6 months with a functioning graft diagnosed with COVID-19 from the initial pandemic outbreak (March 2020) until 31 July 2021 from different Spanish centres participating in a nationwide registry. A total of 127 patients from 17 Spanish centres developed COVID-19 during the first 6 months after transplantation; 73 (57.5%) received basiliximab and 54 (42.5%) thymoglobulin. Demographics were not different between groups but patients receiving thymoglobulin were more sensitized [calculated panel reactive antibodies (cPRAs) $32.7 \pm 40.8\%$ versus $5.6 \pm 18.5\%$] and were more frequently retransplants (30% versus 4%). Recipients >65 years of age treated with thymoglobulin showed the highest rate of acute respiratory distress syndrome [64.7% versus 37.1% for older recipients receiving thymoglobulin and basiliximab ($P < .05$), respectively, and 23.7% and 18.9% for young recipients receiving basiliximab and thymoglobulin ($P > .05$)], respectively, and the poorest survival [mortality rate 64.7% and 42.9% for older recipients treated with thymoglobulin and basiliximab, respectively ($P < .05$) and 8.1% and 10.5% for young recipients treated with thymoglobulin and basiliximab ($P > .05$), respectively]. Older recipients treated with thymoglobulin showed the poorest survival in the Cox regression model adjusted for comorbidities. Thus thymoglobulin should be used with caution in older recipients during the present pandemic era.

Keywords: basiliximab, COVID-19 infection, lymphocyte-depleting agents, renal transplantation

INTRODUCTION

Coronavirus disease 2019 (COVID-19) emerged as a pandemic in December 2019. The infection has spread quickly and renal transplant recipients receiving chronic immunosuppression have been considered a population at high risk of infection, complications and death. In these last months, a large amount of information from nationwide registries and multicentre and single-centre studies has been reported. Major complications such as acute kidney injury (AKI) and acute respiratory distress syndrome (ARDS) were very frequent in renal transplant patients with a high comorbidity burden [1]. Importantly, kidney transplant recipients have experienced a high mortality rate, especially among older recipients (>65 years) who acquired the infection during the early post-transplant period (<6 months) [2].

In this pandemic era, the management of induction and maintenance of immunosuppression has been challenging for clinicians treating kidney transplant recipients. Regarding the use of induction therapy with lymphocyte-depleting agents [antithymocyte globulins (ATGs), alemtuzumab and rituximab], a large study conducted in the USA showed that their use decreased during the first weeks after the outbreak as compared with the previous 3 years, while the use of basiliximab or no induction increased [3]. Importantly, while lymphocyte-depleting agents have been associated with a lower risk of acute rejection, no differences in mortality rates have been reported [3]. Additionally, a small, single-centre study reported that renal transplant patients treated with thymoglobulin who acquired COVID-19 early after transplantation display a modest risk for severe disease, especially using low doses [4]. Thus, it is necessary to investigate the potential differential impact of the type of induction therapy on patient and graft outcomes in larger cohorts of kidney transplant recipients who acquired COVID-19 during the initial months after transplantation.

Since the beginning of the pandemic, renal transplant units from Spain were requested to report all cases diagnosed with COVID-19 to the Spanish Organización Nacional de Trasplantes (ONT). This registry has contributed to characterizing the epidemiology and risk factors in the Spanish solid organ transplant

population [2, 5, 6]. For the present study, detailed information on renal transplant recipients diagnosed with COVID-19 during the early period after transplantation (<6 months) was recorded. The aim was to characterize the influence of antilymphocyte depleting agents (thymoglobulin) in the clinical course of infection compared with patients treated with interleukin-2 receptor antibodies (basiliximab).

MATERIALS AND METHODS

Patients

The data collection included recent kidney transplant recipients (<6 months) who had been diagnosed with COVID-19 from the start of the pandemic in Spain until 31 July 2021. Centres throughout the Spanish territory were requested to provide information on each case of COVID-19 confirmed by reverse transcription-polymerase chain reaction (RT-PCR) in a sample of the respiratory tract. The study was approved by the National Transplant Commission of the Interregional Council of the National Health System.

Variables

Data from donors (donor type, age and sex) and recipients [age, sex and comorbidities such as hypertension, diabetes mellitus, obesity (defined as a body mass index (BMI) $>30 \text{ kg/m}^2$), history of previous cancer, previous lung disease] and transplant-related variables, including date of transplantation; number of previous transplants; HLA A, B and DR mismatches; induction treatment (ATG or basiliximab); maintenance treatment [tacrolimus associated to mycophenolate and prednisone, tacrolimus associated to mammalian target of rapamycin inhibitors (mTORis) and prednisone or other combinations; delayed graft function and acute rejection] were recorded. Vaccination status with a messenger RNA (mRNA) vaccine, date of diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, hospitalization, nosocomial infection, ARDS, admission to the intensive care unit (ICU), mechanical ventilation, AKI, dialysis

Table 1. Clinical characteristics and lab tests at the time of COVID-19 diagnosis according to the induction treatment

Variables	Basiliximab (n = 73)	Thymoglobulin (n = 54)	P-value
Donor type (DBD/cDCD/LD), n/n/n	44/22/7	29/21/4	.575
Donor age (years), mean (SD)	60.7 (14.9)	59.7 (12.9)	.339
Donor sex (male/female), n/n	37/35	34/18	.120
Patient age (years), mean (SD)	59.4 (18.0)	58.2 (12.7)	.337
Patient age >65 years (yes/no), n/n	34/39	17/37	.086
Patient sex (male/female), n/n	46/27	31/23	.523
Arterial hypertension (yes/no), n/n	64/9	46/8	.684
Diabetes (yes/no), n/n	33/40	15/39	.045
BMI >30 kg/m ² (yes/no), n/n	17/56	12/41	.932
Previous cancer (yes/no), n/n	12/61	10/44	.759
Pneumopathy (yes/no), n/n	11/62	9/45	.807
Retransplant (yes/no), n/n	3/70	16/38	.000
cPRA (%), mean (SD)	5.6 (18.5)	32.7 (40.8)	.000
HLA mismatch, n (%)	3.7 (2.2)	4.2 (2.4)	.198
Maintenance immunosuppression (TAC + MMF + P/TAC + mTORi + P), n/n	62/11	50/4	.186
DGF (yes/no), n/n	28/45	17/37	.423
Acute rejection (yes/no), n/n	3/68	4/49	.428
Transplant to COVID-19 time (months), mean (SD)	2.5 (2.7)	3.2 (3.4)	.888
Hospitalization (yes/no), n/n	63/10	44/10	.461
Nosocomial infection (yes/no), n/n	33/40	23/30	.840
ARDS (yes/no), n/n	22/51	18/36	.701
ICU admission (yes/no), n/n	18/55	11/43	.569
Invasive mechanical ventilation (yes/no), n/n	13/60	9/45	.867
AKI (yes/no), n/n	32/36	22/30	.604
Haemodialysis requirement (yes/no), n/n	15/56	13/41	.654
Death (yes/no), n/n	54/19	40/14	.990
Survival time (months), mean (SD)	7.8 (6.3)	7.2 (5.8)	.289
Laboratory data at the time of diagnosis, mean (SD)			
Creatinine (mg/dL)	2.7 (2.1)	2.4 (1.8)	.465
Total lymphocytes (×10 ⁹ /L)	556 (389)	426 (361)	.016
D-dimer (ng/mL)	2961 (5459)	1591 (1405)	.327
Interleukin-6 (pg/mL)	113 (296)	105 (134)	.385
C-reactive protein (mg/dL)	26.1 (42.5)	21.6 (35.4)	.830

Comparison between groups was performed using Pearson's chi-squared test for categorical data, t-test was used for continuous normally distributed data and Mann-Whitney U test for non-normally distributed data. Statistically significant values are in bold.

DBD, donation after brain death; cDCD, controlled donation after circulatory death; LD, living donation; TAC, tacrolimus; MMF, mycophenolate; P, prednisone.

requirements (haemodialysis), graft failure and patient death were also recorded. In addition, different laboratory variables (serum creatinine, total lymphocyte count, D-dimer, interleukin-6 and C-reactive protein) at the time of diagnosis (day 0); 7, 14 and 21 days and at the end of follow-up were recorded.

Statistical analysis

Qualitative variables are described as absolute numbers and percentages and quantitative variables are presented as the mean and standard deviation (SD) or as the median and interquartile range (IQR), depending on the sample distribution. Categorical variables were compared by the chi-squared test and quantitative variables by the unpaired t-test or the non-parametric Mann-Whitney U test.

Kaplan-Meier survival curves were used to analyse patient survival with the log-rank test for comparisons. Univariate and multivariate Cox regression analysis was employed to analyse patient survival.

Linear mixed models for repeated measures were employed to analyse the evolution of the different lab values in patients treated with thymoglobulin and basiliximab.

Statistical analyses were performed using Stata version 16 (StataCorp, College Station, TX, USA).

RESULTS

Baseline patient characteristics

A total of 17/40 renal transplant units from Spain participated in the study and 127 patients with an early (<6 months) COVID-19 infection after transplantation were recorded. From this set of patients, 73 (57.5%) received induction treatment with basiliximab and 54 (42.5%) were treated with thymoglobulin. In Table 1 shows the clinical characteristics of donors and recipients as well as transplant-related variables according to induction therapy. Demographic data from donors and recipients were not significantly different between groups. Comorbidities among recipients were also not different between groups, except that diabetic recipients were more frequently treated with basiliximab (69% versus 51%; *P* = .045). As expected, patients receiving induction with thymoglobulin have higher calculated panel reactive antibodies (cPRAs) at the time of transplant (32.7±40.8% versus 5.6±18.5%; *P* < .001) and were more frequently recipients of a retransplant (30% versus 4%; *P*-value < .001). The rate of delayed graft function (DGF) was not different between groups (38% for basiliximab-treated patients versus 32% for thymoglobulin-treated patients) and the low rejection rate was also not different between groups (4.1% for basiliximab versus 7.4% for thymoglobulin).

Table 2. Clinical characteristics and lab tests at the time of COVID-19 diagnosis and survival

Variables	Recovered (n = 94)	Non-survivors (n = 33)	P-value
Donor type (DBD/cDCD/LD), n/n/n	54/29/11	19/14/0	.089
Donor age (years), mean (SD)	57.5 (14.6)	68.0 (8.6)	.000
Donor sex (male/female), n/n	51/41	20/12	.487
Patient age (years), mean (SD)	56.1 (13.9)	66.7 (18.7)	.000
Patient age >65 years (yes/no), n/n	26/68	25/8	.000
Patient sex (male/female), n/n	56/38	21/12	.681
Arterial hypertension (yes/no), n/n	79/15	31/2	.151
Diabetes (yes/no), n/n	28/66	20/13	.002
BMI >30 kg/m ² (yes/no), n/n	15/78	14/19	.002
Previous cancer (yes/no), n/n	13/81	9/24	.079
Pneumopathy (yes/no), n/n	13/81	7/26	.317
Retransplant (yes/no), n/n	11/83	8/25	.082
cPRA (%), mean (SD)	14.7 (31.0)	24.2 (36.3)	.076
HLA mismatch, n (%)	4.0 (2.5)	3.6 (1.8)	.845
Induction therapy (basiliximab/ATG), n/n	54/40	19/14	.990
Maintenance immunosuppression (TAC + MMF + P/TAC + mTOR-i + P), n/n	80/14	32/1	.069
DGF (yes/no), n/n	26/68	19/14	.002
Acute rejection (yes/no), n/n	7/87	34/0	.188
Transplant to COVID-19 diagnosis time (months), mean (SD)	3.0 (3.3)	2.2 (2.0)	.915
Hospitalization (yes/no), n/n	74/20	33/0	.004
Nosocomial infection (yes/no), n/n	37/56	19/14	.077
ARDS (yes/no), n/n	11/83	29/4	.000
ICU admission (yes/no), n/n	14/80	15/18	.000
Invasive mechanical ventilation (yes/no), n/n	8/86	14/19	.000
AKI (yes/no), n/n	33/56	21/10	.003
Haemodialysis requirement (yes/no), n/n	10/81	18/15	.000
Lab tests at diagnosis of COVID-19, mean (SD)			
Creatinine (mg/dL)	2.1 (1.5)	3.6 (2.4)	.011
Lymphocytes ($\times 10^9/L$)	510 (386)	479 (377)	.653
D-dimer (ng/mL)	1581 (1627)	4247 (7169)	.007
Interleukin-6 (pg/mL)	49 (62)	227 (390)	.002
C-reactive protein (mg/dL)	17 (30)	41 (53)	.002

Comparison between groups was performed using Pearson's chi-squared test for categorical data and t-tests for continuous normally distributed data. Statistically significant values are in bold.

DBD, donation after brain death; cDCD, controlled donation after circulatory death; LD, living donation; TAC, tacrolimus; MMF, mycophenolate; P, prednisone.

Only 19 transplant recipients from this cohort received at least one dose of an mRNA SARS-CoV-2 vaccine (12 receiving basiliximab and 9 receiving thymoglobulin) and only 12 patients completed a full vaccination 15 days before transplantation, precluding further analysis of this variable.

Evolution after COVID-19 diagnosis

COVID-19 was diagnosed at 3.0 ± 3.0 months in basiliximab-treated patients and at 2.2 ± 2.0 months in the thymoglobulin group ($P = .888$). The rate of hospitalization (86% and 83%), as well as the rate of nosocomial acquired infection (45% versus 43%), were high and not different between groups. Similarly, the rate of ARDS (30% versus 33%), intensive care unit admission (24.7% versus 20.4%) and respiratory failure requiring mechanical ventilation (17.8% versus 16.7%) were not different between groups. The AKI rate was high in both groups (43.4% versus 40.7%) and dialysis supportive treatment was also frequently required (20.5% versus 24.1%).

Patient survival

The mortality rate in the overall set of patients was 26% (33/127) and was not different between patients receiving basiliximab or thymoglobulin (Table 2). Kaplan–Meier analysis showed that the patient's age was closely associated with the patient's survival (Figure 1), while induction therapy was not (Figure 2). Since older recipients tended to receive less frequent thymoglobulin ($P = .086$), we analysed the outcome in young and older recipients categorized according to induction therapy. Transplant recipients <65 years of age treated with either basiliximab or thymoglobulin exhibited a similar survival. However, recipients >65 years of age had a poorer survival in the thymoglobulin-treated versus basiliximab-treated transplants (Figure 3). Noticeably, while 15/35 patients >65 years of age (42.9%) treated with basiliximab died, 11/17 (64.7%) patients >65 years of age treated with thymoglobulin died ($P < .05$). In the case of young recipients, these data were 4/38 patients (10.5%) treated with basiliximab and 3/37 (8.1%) patients treated with thymoglobulin. Similar data were observed if the analysis was done in recipients acquiring the infection during the first 3 months after trans-

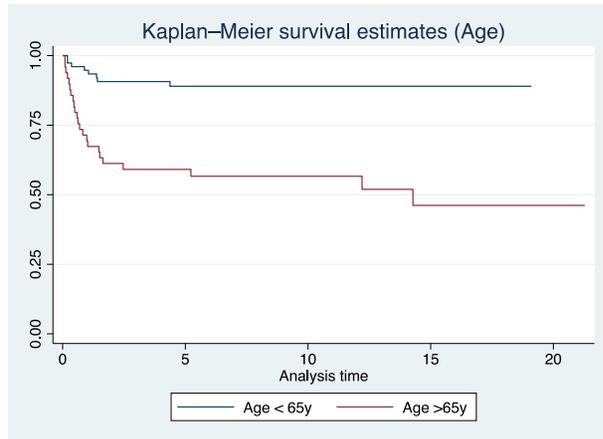


FIGURE 1: Kaplan-Meier analysis of patient survival in renal transplant recipients younger or older than 65 years ($P < .001$ by logrank test).

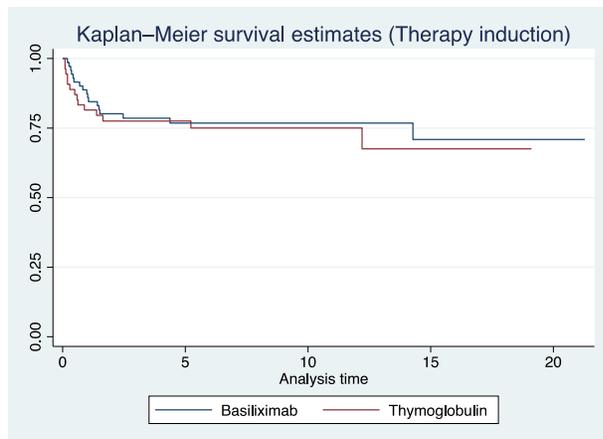


FIGURE 2: Kaplan-Meier analysis of patient survival in renal transplant recipients treated with basiliximab or thymoglobulin ($P > .05$ by logrank test).

plantation (death rates of 22% for young recipients treated with basiliximab, 10% for young recipients treated with thymoglobulin, 41% for older recipients treated with basiliximab and 78% for older recipients treated with thymoglobulin; $P = .005$). Among recipients who acquired the infection from the third to sixth month ($n = 39$), the mortality rate was 0% in recipients <65 years of age treated with either basiliximab or thymoglobulin, but it was significantly higher ($P = .0008$) in patients >65 years of age without statistically significant differences between thymoglobulin- and basiliximab-treated patients (62 and 43%, respectively).

ARDS was also more frequently observed in older recipients receiving thymoglobulin than in the other groups [64.7% versus 37.1% for older recipients receiving thymoglobulin and basiliximab, respectively ($P < .05$) and 23.7% for young recipients receiving basiliximab and 18.9% for young recipients receiving thymoglobulin ($P = \text{NS}$)].

Risk factors for patient death are summarized in Table 3. As previously described, comorbidities of the recipient (diabetes and obesity) were associated with survival. Maintenance immunosuppression with tacrolimus and mycophenolate tended to be associated with poorer survival than maintenance with tacrolimus and mTOR inhibitors, but the small number of pa-

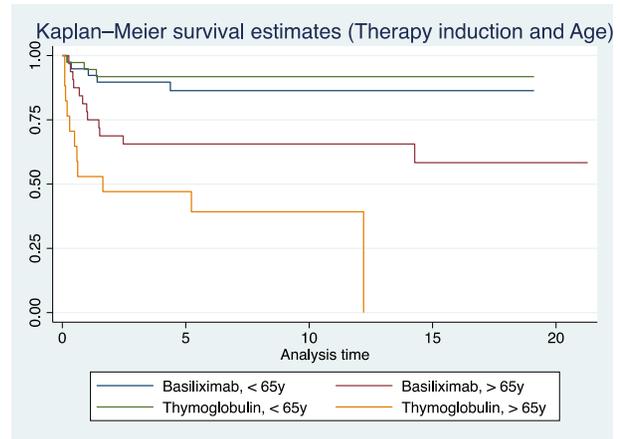


FIGURE 3: Kaplan-Meier analysis of patient survival in renal transplant recipients categorized according to patient's age older or younger than 65 years and induction immunosuppression with basiliximab or thymoglobulin ($P < .001$ by logrank test).

tients treated with tacrolimus and mTOR inhibitors ($n = 15$) precluded further analysis. Multivariate Cox regression analysis showed that older recipients treated with thymoglobulin had the poorest survival, adjusting for baseline comorbidities (Table 3). Furthermore, DGF also independently correlated with patient death.

Laboratory data

Patients treated with thymoglobulin showed a lower number of circulating lymphocytes at the time of diagnosis (Table 1). Linear mixed models for repeated measures showed that lymphopaenia tended to recover in both groups of patients as the infection evolved, but the recovery was slower in patients treated with thymoglobulin than in patients treated with basiliximab (Figure 4). Acute phase reactants and D-dimer were not different between groups at baseline (Table 1) and during the first month (data not shown). As expected, baseline acute phase reactants (interleukin-6 and C-reactive protein) and D-dimer levels were closely associated with survival.

DISCUSSION

In the present study, we analysed a cohort of renal transplant recipients with COVID-19 diagnosis early after transplantation (<6 months). As it has been previously reported, we confirmed that recipients >65 years of age with a higher comorbidity burden showed higher mortality than younger patients. Remarkably, among older recipients, thymoglobulin induction therapy was an independent factor predicting a higher risk of ARDS and death. As expected, lymphopaenia was significantly more profound in patients treated with thymoglobulin than in those treated with basiliximab.

In Spain, the standard of care for renal transplant recipients receiving a kidney from a brain dead or living donor is based on induction therapy with basiliximab, whereas thymoglobulin is restricted to high immunological risk transplants. However, the management of induction immunosuppression in the case of donors after controlled circulatory death is rather heterogeneous [7]. The standard of care for maintenance immunosuppression is tacrolimus, mycophenolate and steroids, but some centres have moved to a maintenance regimen based

Table 3. Risk factors associated with mortality in kidney transplant recipients with COVID-19 diagnosis during the initial 6 months after transplantation

Variable	Univariate analysis, hazard ratio (95% CI)	P-value	Multivariate analysis, hazard ratio (95% CI)	P-value
Patient age >65 years	0.985 (0.939–1.034)	.007		
Thymoglobulin induction	1.955 (0.880–4.342)	.100		
Patient age (years) and induction				
>65 and thymoglobulin	1 (reference)		1 (reference)	
>65 and basiliximab	0.397 (0.174–0.905)	.028	0.425 (0.187–0.967)	.041
<65 and thymoglobulin	0.049 (0.011–0.225)	.000	0.095 (0.026–0.349)	.000
<65 and basiliximab	0.111 (0.035–0.357)	.000	0.104 (0.032–0.340)	.000
Diabetes	2.809 (0.908–4.579)	.038	1.821 (0.541–2.584)	.674
BMI >30 kg/m ²	3.021 (1.511–6.024)	.002	2.439 (1.168–5.050)	.016
Previous cancer	2.049 (0.951–4.225)	.067		
Retransplant	1.989 (0.897–4.412)	.091		
cPRA (%)	1.007 (0.988–1.016)	.136		
TAC + MMF + P	4.871 (0.665–35.69)	.119		
DGF	2.915 (1.460–5.848)	.002	2.825 (1.383–5.780)	.004

CI, confidence interval; TAC, tacrolimus; MMF, mycophenolate; P, prednisone.

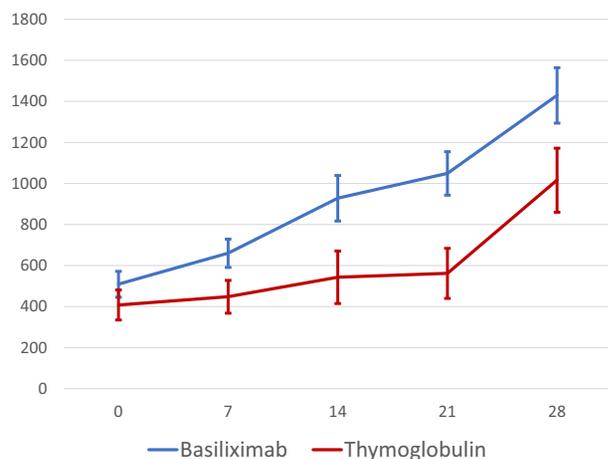


FIGURE 4: Linear mixed models for repeated measures for the evolution of circulating lymphocytes (y-axis, number of cells × 10⁹/L) in basiliximab- and thymoglobulin-treated patients during the first month after infection (x-axis, days) ($P < .001$ for time and $P = .008$ for intergroup differences).

on tacrolimus and mTOR inhibitors [8]. Our set of patients, containing one-third of transplants from donors after circulatory death, reflects these heterogeneous policies and includes a significant number of patients treated with both induction regimens. In this study cohort, nosocomially acquired infection was highly prevalent (44%), especially during the first and second waves, indicating that infection was acquired during the first admission or after readmission due to transplant-related complications.

Since the beginning of the pandemic, patient age and comorbidities associated with ageing have been repeatedly associated with outcomes after COVID-19 in both the general population [9] and renal transplant recipients [10]. Different case-control studies with propensity score matching tried to elucidate whether chronic immunosuppression received by solid organ transplant recipients is a risk factor for COVID-19 complications and death. A number of studies concluded that the increased risk in solid organ transplant recipients is related to the high burden of comorbidities [11–15], despite others observing higher COVID-19-

related mortality compared with a matched non-transplant hospitalized cohort [16]. However, in these large nationwide or multicentre studies, the proportion of patients who acquired the infection during the initial months after transplantation was low and was not specifically analysed. It is well known that the strong immunosuppression employed during the first months after transplantation is associated with the highest risk of viral infections and severity during this early period. Initial reports with a small number of patients [17], and confirmed later in larger studies, have shown that the fatality rate related to COVID-19 is higher among elderly recipients acquiring the infection during the early period after transplantation, approaching 50% of cases [2]. Our set of patients containing patients included in previous studies confirms these data in a larger sample size.

The transplant community agrees that during the current COVID-19 pandemic, the benefit-harm of immunosuppression should be well balanced. Among immunosuppressants, administration of lymphocyte-depleting agents during the peri-transplant period might increase the risk of COVID-19-related complications. In our study, recipients <65 years of age have a similar clinical evolution as in patients treated with basiliximab or thymoglobulin, suggesting that these patients may safely receive both induction therapies without increasing the risk of major complications in case of early COVID-19 infection. Conversely, recipients >65 years of age receiving thymoglobulin show a significantly higher risk of ARDS and COVID-19-related mortality than patients treated with basiliximab. Among the increasingly older population receiving a renal transplant [18, 19], it has been described that immune senescence and frailty increase the risk for infections during the first months when transplant recipients are receiving a greater degree of immunosuppression. [20]. Thus, combined with age-related immune senescence, delivery of immunosuppressive therapy remains a challenging issue given the delicate balance between rejection and infections in older recipients. Despite current transplantation guidelines providing no specific recommendations for induction or maintenance of immunosuppression for older recipients, ATG induction immunosuppressive therapy in older recipients has been associated with an increased risk of infectious complications [21]. In this regard, Bae et al [3], using data from the Scientific Registry of Transplant Recipients, studied kidney-only transplant recipients during the pre-pandemic era

(1 January 2017–12 March 2020; $n = 5035$) and the pandemic era (13 March 2020–31 July 2020; $n = 5035$) and compared the use of lymphocyte-depleting agents versus basiliximab or no induction. Interestingly, the use of lymphocyte-depleting agents was associated with a decreased risk of rejection, but with no significant difference in mortality during the pandemic era. However, mortality risk among the infected elderly population was not analysed. Similarly, a single-centre concluded that thymoglobulin use either as an induction protocol or as antirejection treatment during the COVID-19 pandemic appears to be safe, although the number of patients with COVID-19 was very low (only two cases) and a limited number of patients >65 years of age were included [22]. In our study, the number of patients >65 years of age receiving thymoglobulin was relatively low ($n = 17$), but the fatality rate was very high (64.7%), suggesting that this treatment should be employed with caution in this population.

It is very important to note that most patients included in the present study were transplanted before the SARS-CoV-2 vaccines were available. Thus these outcomes may not fully reflect the current clinical situation where most transplant candidates have been actively immunized before transplantation [23].

In summary, in this retrospective, nationwide Spanish registry cohort study we show that renal transplant recipients >65 years of age developing COVID-19 during the early post-transplant period have high mortality, especially if they received thymoglobulin as induction therapy. Thus these data suggest that thymoglobulin induction among elderly transplant recipients should be well balanced and used with caution during the present pandemic era, especially among patients not previously vaccinated against SARS-CoV-2.

ACKNOWLEDGEMENTS

We thank all the medical doctors working in the participating renal transplant units for their contributions.

CONFLICT OF INTEREST STATEMENT

None declared.

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