Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COVID-19 in transplant recipients: The Spanish experience

Elisabeth Coll[1] | Mario Fernández-Ruiz[2,3] | J. Emilio Sánchez-Álvarez[4,5] | José R. Martínez-Fernández[1] | Marta Crespo[6,7,8] | Jorge Gayoso[1] | Teresa Bada-Bosch[9] | Federico Oppenheimer[10] | Francesc Moreso[11] | María O. López-Oliva[12] | Edoardo Melilli[13] | Marisa L. Rodríguez-Ferrero[14] | Carlos Bravo[15] | Elena Burgos[16] | Carme Facundo[17] | Inmaculada Lorenzo[18] | Íñigo Yañez[19] | Cristina Galeano[20] | Ana Roca[21] | Mercedes Cabello[22] | Manuel Gómez-Bueno[23] | MªDolores García-Cosío[24,25] | Javier Graus[26] | Laura Lladó[27] | Alicia de Pablo[28] | Carmelo Loinaz[29] | Beatriz Aguado[30] | Domingo Hernández[31,32,33] | Beatriz Domínguez-Gil[1] | the Spanish Group for the Study of COVID-19 in Transplant Recipients

[1]Organización Nacional de Trasplantes (Spanish National Transplant Organization), Madrid, Spain

[2]Unit of Infectious Diseases, Hospital Universitario 12 de Octubre. Instituto de Investigación Sanitaria, Hospital Universitario 12 de Octubre (imas12), President of the Group for the Study of Infection in Transplantation and the Immunocompromised Host (GESITRA-IC) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), Madrid, Spain

[3]Group for the Study of Infection in Transplantation and the Immunocompromised Host (GESITRA-IC) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), Madrid, Spain

[4]Department of Nephrology, Hospital Universitario de Cabueñes, Gijón, Spain

[5]Spanish Society of Nephrology (SEN), Gijón, Spain

[6]Department of Nephrology, Hospital del Mar, Barcelona, Spain

[7]Transplant Working Group of the Spanish Society of Nephrology (SEN), Barcelona, Spain

[8]REDinREN (RD16/0009/0013), Barcelona, Spain

[9]Department of Nephrology, Hospital Universitario 12 de Octubre, Madrid, Spain

[10]Department of Nephrology, Hospital Clinic, Barcelona, Spain

[11]Kidney Transplant Unit, Department of Nephrology, Hospital Universitario Vall d´Hebrón, Barcelona, Spain

[12]Department oof Nephrology, Hospital Universitario La Paz, Madrid, Spain

[13]Kidney Transplant Unit, Department of Nephrology, Hospital Universitario de Bellvitge, Barcelona, Spain

[14]Department of Nephrology, Hospital General Universitario Gregorio Marañón, Madrid, Spain

[15]Department of Pulmonology, Lung transplant Unit, Hospital Universitario Vall d´Hebrón, Barcelona, Spain

[16]Department of Nephrology, Hospital Germans Trias i Pujol, Badalona, Spain

[17]Kidney Transplant Unit, Fundación Puigvert, Barcelona, Spain

[18]Department of Nephrology, Complejo Hospitalario Universitario de Albacete, Albacete, Spain

[19]Department of Nephrology, Hospital Universitario de Cruces, Barakaldo, Spain

[20]Kidney Transplant Unit, Hospital Universitario Ramón y Cajal, Madrid, Spain

[21]Department of Nephrology, Complejo Hospitalario Universitario de Toledo, Toledo, Spain

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval; COVID-19, coronavirus disease 2019; DTAC, Disease Transmission Advisory Committee; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range; mTOR, mammalian target of rapamycin; ONT, Spanish National Transplant Organization (Organización Nacional de Trasplantes); OR, odds ratio; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SEMICYUC, Spanish Society of Intensive and Critical Care and Coronary Units; SEN, Spanish Society of Nephrology; SOT, solid organ transplantation.

The members of the Spanish Group for the Study of COVID-19 in Transplant Recipients are listed in Appendix 1.

[22]Department of Nephrology, Hospital Regional Universitario de Málaga, Málaga, Spain
[23]Department of Cardiology, Hospital Universitario Puerta de Hierro, Madrid, Spain
[24]Cardiology Service, Hospital Universitario 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain
[25]Centro de Investigación Biomédica en Red Cardiovascular (CIBERCV), Madrid, Spain
[26]Department of Gastroenterology, Hospital Universitario Ramón y Cajal, Madrid, Spain
[27]Liver Transplant Unit, Hospital Universitario de Bellvitge, Barcelona, Spain
[28]Lung Transplant Unit, Department of Pneumology, Hospital Universitario 12 de Octubre, Madrid, Spain
[29]Transplant Unit, Department of General Surgery, Digestive Tract and Abdominal Organ Transplantation, Hospital Universitario 12 de Octubre, Madrid, Spain
[30]Transplant Unit. Department of Hematology, Hospital Universitario La Princesa, Madrid, Spain
[31]Department of Nephrology, Hospital Regional Universitario, Málaga, Spain
[32]Instituto de Investigación Biomédica de Málaga (IBIMA), Málaga, Spain
[33]Spanish Society of Transplantation (SET), Málaga, Spain

Correspondence
Beatriz Domínguez-Gil
Email: bdominguez@sanidad.gob.es

We report the nationwide experience with solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) recipients diagnosed with coronavirus disease 2019 (COVID-19) in Spain until 13 July 2020. We compiled information for 778 (423 kidney, 113 HSCT, 110 liver, 69 heart, 54 lung, 8 pancreas, 1 multivisceral) recipients. Median age at diagnosis was 61 years (interquartile range [IQR]: 52-70), and 66% were male. The incidence of COVID-19 in SOT recipients was two-fold higher compared to the Spanish general population. The median interval from transplantation was 59 months (IQR: 18-131). Infection was hospital-acquired in 13% of cases. No donor-derived COVID-19 was suspected. Most patients (89%) were admitted to the hospital. Therapies included hydroxychloroquine (84%), azithromycin (53%), protease inhibitors (37%), and interferon-β (5%), whereas immunomodulation was based on corticosteroids (41%) and tocilizumab (21%). Adjustment of immunosuppression was performed in 85% of patients. At the time of analysis, complete follow-up was available from 652 patients. Acute respiratory distress syndrome occurred in 35% of patients. Ultimately, 174 (27%) patients died. In univariate analysis, risk factors for death were lung transplantation (odds ratio [OR]: 2.5; 95% CI: 1.4-4.6), age >60 years (OR: 3.7; 95% CI: 2.5-5.5), and hospital-acquired COVID-19 (OR: 3.0; 95% CI: 1.9-4.9).

KEYWORDS
clinical research/practice, infectious disease, infection and infectious agents - viral, antibiotic: antiviral, clinical decision-making, complication: infectious

1 | INTRODUCTION

Since first described in Wuhan, China, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causal agent of coronavirus disease 2019 (COVID-19), has rapidly become an international pandemic.[1–4] The body of knowledge about the natural history of the disease and risk factors for poor outcomes is progressively increasing.[5,6] However, there is limited information on the incidence of COVID-19, the course of the infection and its prognostic factors among transplant patients. Since the outbreak of the pandemic, a number of case reports[7–12] and case series[13–23] have been published, suggesting a higher rate of complications in this particular patient population. The more aggressive course of posttransplant COVID-19 would be supported by the poor outcomes reported for endemic human coronaviruses among immunocompromised hosts[24,25] and solid organ transplant (SOT) recipients.[26,27] On the other hand, it has been proposed that the long-term use of immunosuppression could mitigate the hyperinflammatory status secondary to the cytokine storm syndrome triggered by SARS-CoV-2 that leads to most COVID-19-attributable deaths.

The risk of transmission of COVID-19 through transplantation remains theoretical, although no case of donor-derived infection has been reported to date. This has led to apply the principle of maximum precaution in international guidance on the evaluation and screening of donors for SARS-CoV-2 infection.[28–30]

Spain is one of the countries most affected by the COVID-19 pandemic in terms of absolute number of cases, incidence *per* 1,000 inhabitants, and number of COVID-19-attributable deaths.[3]

On 13 March 2020, the Spanish Government declared a national state of alarm, comprising nationwide lock-down, social confinement and restricted mobility to control the spread of the infection. The country as a whole entered into epidemiological scenarios 3 (sustained community transmission) and 4 (intensive care capacity saturated and healthcare system overwhelmed), as described by the European Centre for Disease Control and Prevention.[31] On April 29, 2020, a national de-escalation plan was put in place, in coincidence with a decreasing number of new cases and a relieved healthcare system. The state of alarm ended by the end of June 2020.

In the above-described scenario, the Spanish Organización Nacional de Trasplantes (ONT) promoted a centralized data collection on SOT and hematopoietic stem cells transplant (HSCT) recipients diagnosed with COVID-19. The aim of this initiative was to investigate the impact of the SARS-CoV-2 infection in the transplant population. In particular, we aimed at evaluating the incidence of COVID-19 in transplant recipients, characterizing clinical features and patient management in terms of antiviral and immunomodulatory therapies as well as adjustment of baseline immunosuppression, describing clinical outcomes, and exploring factors predictive of death. The Spanish Society of Nephrology (SEN) had initiated in parallel a similar data collection on patients under renal replacement therapy, including kidney transplant recipients.[32] Intending to increase the comprehensiveness of the national data collection, both ONT and SEN joined efforts to better assess the previously mentioned objectives.

2 | PATIENTS AND METHODS

2.1 | Study design and patient management

Data collection comprised all SOT and HSCT (either autologous or allogeneic) recipients who had been diagnosed with COVID-19 in Spain until 13 July 2020. Centers across the Spanish territory were requested to provide information on every COVID-19 case confirmed by reverse transcription polymerase chain reaction (RT-PCR) in a respiratory tract sample, although patients with a highly suggestive clinical and radiological picture could be also included. The study was approved by the National Transplant Committee of the Inter-Regional Council of the Spanish National Health-Care System.

At the beginning of the outbreak, ONT published guidance for the evaluation and testing of potential deceased and living donors, which entailed universal screening for SARS-CoV-2 by RT-PCR in respiratory tract samples obtained within 24 hours prior to organ recovery.[29] ONT also recommended screening of SARS-CoV-2 by RT-PCR of transplant candidates immediately before transplantation. Donation and transplantation would not proceed in case of a positive RT-PCR result or high clinical suspicion of COVID-19. National scientific societies released recommendations on the treatment and management of immunosuppression in SOT and HSCT recipients with COVID-19, based on the limited evidence available at the time and aligned with the guidelines issued by the Spanish Ministry of Health.[33–35] In general terms, recipients diagnosed with COVID-19 were admitted to the hospital in case of pneumonia and/or clinical instability. However, definitive decisions about hospital and intensive care unit (ICU) admission, as well as intubation and initiation of invasive mechanical ventilation (IMV), were ultimately made by treating teams on the basis of perceived life expectancy and available resources. Patients with mild-to-moderate disease could be treated with hydroxychloroquine, either alone or in combination with azithromycin. In the presence of more severe forms of the disease, co-formulated lopinavir/ritonavir or remdesivir were administered as compassionate care. The off-label use of tocilizumab and/or corticosteroids was also considered as immunomodulatory therapy in recipients with elevated inflammatory markers (ie, C-reactive protein or interleukin-6 [IL-6]) and progressive respiratory failure.

2.2 | Data collection

For each SOT and HSCT recipient diagnosed with COVID-19, a notification form was completed by the treating team including demographics, baseline clinical characteristics, date of transplantation, date of diagnosis of COVID-19, and information on whether the infection had been acquired in the hospital or in the community and on whether the case was suspected to be donor-derived. In case of a suspected donor-derived COVID-19, the Disease Transmission Advisory Committee (DTAC) tool was used to assess the likelihood that the SARS-CoV-2 infection derived from the donor.[36]

An additional follow-up form was filled in with details on intermediate outcomes (hospital admission, ICU admission, IMV, acute distress respiratory syndrome [ARDS] defined according to the Berlin criteria,[37] septic shock, or multiorgan failure), therapeutic approaches, and outcomes (resolution of the infection [ie, clinical improvement with or without virologic evidence of clearance] or death [including whether death was potentially attributable to COVID-19]).

To provide more accurate information on the incidence of COVID-19 among kidney transplant recipients, we additionally identified cases reported to the SEN that had not been notified to ONT. To exclude duplicates, the following variables were used: reporting center, date of transplantation, date of birth, and gender. Due to the lack of certain key variables in the SEN registry (eg, occurrence of ARDS), these additional cases were not taken into account for the remaining descriptive analysis contained in this paper.

2.3 | Statistical analysis

Quantitative variables are presented as the mean and standard deviation or the median and interquartile range (IQR), depending on the distribution of the sample. Qualitative variables are described as absolute numbers and percentages (of cases with available information). Kaplan-Meier curves were used to analyze patient survival from diagnosis of infection, with the log-rank test for comparisons. To assess patient- and infection-related factors associated with COVID-19-attributable mortality, the χ^2 test was used, with the Fischer correction

where applicable. Univariate associations are expressed as unadjusted odds ratios (OR) with 95% confidence intervals (CI). In addition, an exploratory analysis on the association between specific therapeutic approaches and mortality was performed. Given the descriptive nature of the present research and the level of detail of data, which do not allow for adequately controlling for potential confounders influencing the choice of therapy, no multivariate modeling was attempted. Nevertheless, univariate analyses were stratified by the development of ARDS as a proxy to disease severity. The statistical analysis was performed with SPSS version 25.0 (IBM Corp., Armonk, NY).

3 | RESULTS

3.1 | Study population and baseline characteristics

A total of 778 SOT and HSCT recipients diagnosed with COVID-19 between 20 February and 13 July 2020 in Spain were reported to ONT by 61 centers. The diagnosis was confirmed by RT-PCR in 93% of cases. Cases notified included 423 kidney (54%), 113 HSCT (15%), 110 liver (14%), 69 heart (9%), 54 lung (7%), 8 pancreas (1%), and 1 multivisceral (0.1%) transplant patients. Within the HSCT group, 42 and 71 patients had received autologous and allogenic grafts, respectively. The number of reported cases according to the date of presentation reached its maximum in the second fortnight of March, to progressively decrease thereafter (Figure 1).

Considering the number of patients with a functioning graft in Spain as of 1 January 2020 (based on data derived from National Transplant Registries) and adding those cases of kidney transplant recipients who had been reported to SEN, but not to ONT (N = 198), the cumulative incidence of COVID-19 among SOT recipients was 11.9/1,000 persons at risk (17.7/1,000 for kidney, 8.3/1,000 for liver, 19.1/1,000 for heart, 22.5/1,000 for lung, 5.5/1,000 for pancreas, and 13.7/1,000 for small bowel recipients). The cumulative incidence of COVID-19 in the Spanish general population was 5.5/1,000 persons at risk by 13 July 2020.

Baseline characteristics of SOT and HSCT recipients with COVID-19 are shown in Table 1.

Ninety-nine patients (13%) were considered to have acquired COVID-19 in the hospital. The median interval between transplantation and diagnosis for this group of recipients was 20 months (IQR: 1-123), whereas the median interval for community-acquired cases was 65 months (IQR: 23-133). In detail, 19 out of 99 patients with hospital-acquired SARS-CoV-2 infection were in the first posttransplant month.

Only 25 patients (3%) acquired SARS-CoV-2 infection in the immediate posttransplant period (ie, first month after transplantation), 20 of them being SOT recipients. These 20 cases represent 1.5% of the 1,300 SOT procedures performed in the country between 20 February and 13 July 2020. There were only two notified SOT recipients with COVID-19 who had received the transplant after the declaration of the national state of alarm.

At the time of this analysis, no suspected cases of donor-derived COVID-19 have been reported.

3.2 | Therapeutic management

Information on the management of COVID-19 was available from 657 (84%) cases at the time of submission of this paper. A description of the antiviral and immunomodulatory therapies used is shown in Table 1, globally and according to the type of transplant. No specific antiviral therapy was administered in 80 (12%) patients, of whom 50% were managed as outpatients. The agent with presumed antiviral activity most commonly used was hydroxychloroquine, which was administered in 555 (84%) patients. A protease inhibitor-containing regimen was used in 246 (37%) patients. Of note, available agents were used in a great variety

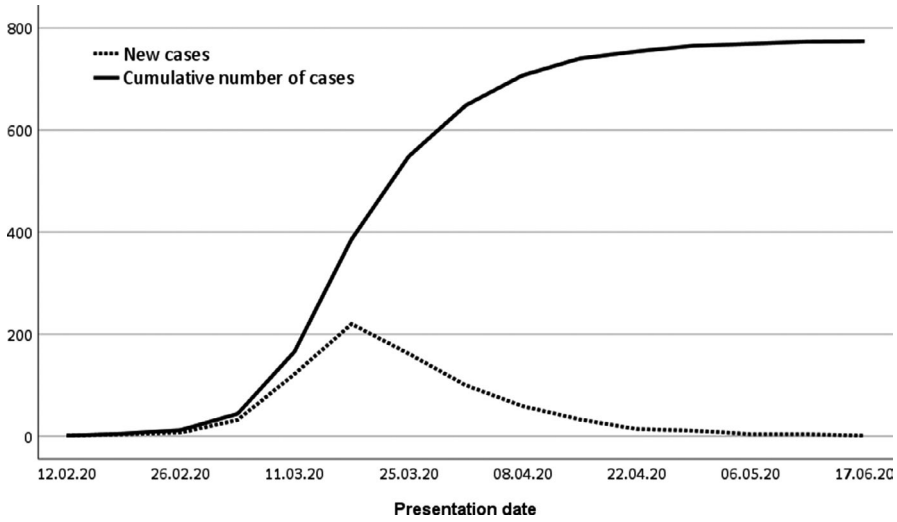

FIGURE 1 Evolution of notified cases of COVID-19 in solid organ and hematopoietic stem cell transplant recipients according to presenting date

TABLE 1 Baseline characteristics of solid organ and hematopoietic stem cell transplant recipients with COVID-19 and therapies used, overall and according to the transplant type[a]

Baseline data	Overall (N = 778)	Kidney (N = 423)	Liver (N = 110)	Heart (N = 69)	Lung (N = 54)	Pancreas (N = 8)	Multivisceral (N = 1)	Allo-HSCT (N = 71)	Auto-HSCT (N = 42)
Baseline characteristics									
Male gender, n (%)	512 (66)	277 (65)	78 (71)	54 (79)	33 (61)	5 (63)	1 (100)	40 (57)	24 (57)
Age at diagnosis									
Years, median (IQR)	61 (52-70)	62 (52-71)	65 (56-72)	64 (52-72)	62 (55-67)	48 (43-50)	31 (-)	48 (34-61)	60 (55-64)
>60 years, n (%)	404 (52)	225 (54)	73 (66)	40 (59)	29 (56)	0 (0)	0 (0)	19 (27)	18 (43)
Hospital-acquired SARS-CoV-2, n (%)	99 (13)	55 (13)	15 (14)	6 (9)	5 (9)	2 (25)	1 (100)	10 (14)	5 (12)
Time since transplantation									
Months, median (IQR)	59 (18-131)	66 (28-132)	95 (25-161)	122 (34-209)	43 (7-79)	132 (101-171)	20 (-)	15 (7-37)	18 (4-53)
First month, n (%)	25 (3)	12 (3)	3 (3)	3 (4)	2 (4)	0 (0)	0 (0)	2 (3)	3 (7)
>1 year, n (%)	631 (82)	367 (87)	89 (82)	63 (93)	39 (74)	7 (100)	1 (100)	42 (60)	23 (56)
Baseline immunosuppression									
Calcineurin inhibitor, n (%)	606 (78)	384 (91)	74 (67)	62 (90)	54 (100)	8 (100)	1 (100)	21 (30)	2 (5)
Antimetabolite, n (%)[b]	456 (59)	297 (70)	59 (54)	50 (72)	40 (74)	6 (75)	0 (0)	4 (6)	0 (0)
mTOR inhibitors, n (%)	161 (21)	101 (24)	22 (20)	11 (16)	17 (31)	2 (25)	0 (0)	7 (10)	1 (2)
Corticosteroids, n (%)	528 (68)	336 (79)	26 (24)	59 (86)	54 (100)	8 (100)	1 (100)	29 (41)	15 (36)
Therapeutic management	**Overall (N = 657)**	**Kidney (N = 376)**	**Liver (N = 75)**	**Heart (N = 57)**	**Lung (N = 52)**	**Pancreas (N = 7)**	**Multivisceral (N = 1)**	**Allo-HSCT (N = 58)**	**Auto-HSCT (N = 31)**
Antiviral therapy[c]									
None, n (%)	80 (12)	38 (10)	10 (13)	11 (19)	5 (10)	3 (43)	0 (0)	8 (14)	5 (16)
Hydroxychloroquine, n (%)	555 (84)	323 (86)	62 (83)	46 (81)	45 (87)	4 (57)	1 (100)	48 (83)	26 (84)
Azithromycin, n (%)	346 (53)	216 (57)	38 (51)	29 (51)	27 (52)	3 (43)	0 (0)	23 (40)	10 (32)
Protease inhibitors, n (%)	246 (37)	141 (37)	25 (33)	10 (18)	20 (38)	3 (43)	0 (0)	28 (48)	19 (61)
Interferon-β, n (%)	31 (5)	17 (5)	2 (3)	2 (4)	5 (10)	1 (14)	0 (0)	1 (2)	3 (10)
Other antiviral, n (%)[d]	9 (1)	3 (1)	1 (1)	1 (2)	0 (0)	0 (0)	0 (0)	2 (3)	2 (6)
Immunomodulatory therapy[c]									
None, n (%)	342 (52)	167 (44)	58 (77)	30 (53)	20 (38)	5 (71)	1 (100)	40 (69)	21 (68)
Corticosteroids, n (%)[e]	272 (41)	183 (49)	16 (21)	26 (46)	24 (46)	1 (14)	0 (0)	15 (26)	7 (23)
Tocilizumab, n (%)	138 (21)	81 (21)	4 (5)	11 (19)	22 (42)	1 (14)	0 (0)	11 (19)	8 (26)
Anakinra, n (%)	14 (2)	8 (2)	1 (1)	0 (0)	2 (4)	0 (0)	0 (0)	2 (3)	1 (3)

Abbreviations: Allo-HSCT, allogeneic hematopoietic stem cell transplantation; auto-HSCT, autologous hematopoietic stem cell transplantation; COVID-19, coronavirus disease 2019; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Percentages are calculated according to the available information for each variable.

[b]Mostly mycophenolate.

[c]Some patients received more than one antiviral or immunomodulatory agent.

[d]Other antivirals include: remdesivir (6 patients), ribavirine (1 patient), acyclovir (1 patient), and oseltamivir (1 patient).

[e]Defined as the administration of boluses of corticosteroids, initiation of corticosteroids or increase of baseline doses.

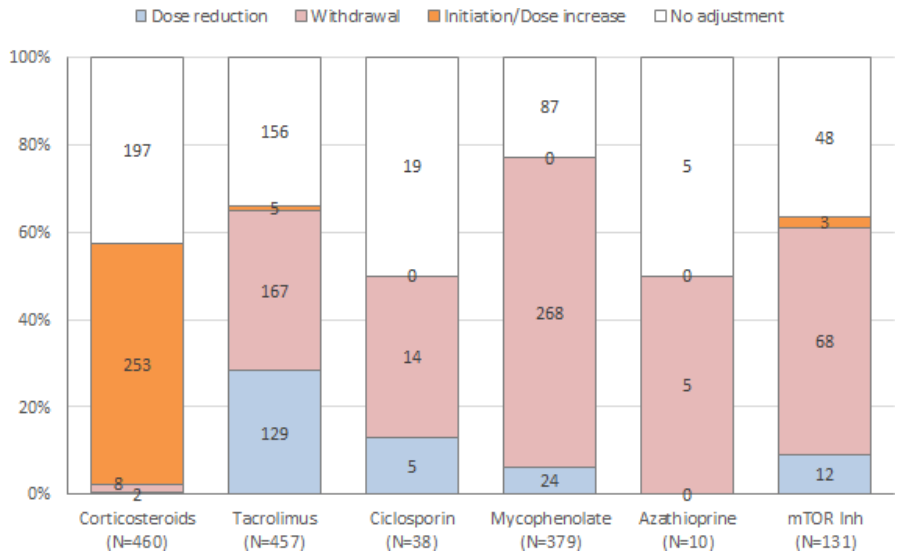

FIGURE 2 Adjustment of baseline immunosuppression in solid organ transplant recipients with COVID-19. mTOR inh, mammalian target of rapamycin inhibitors [Color figure can be viewed at wileyonlinelibrary.com]

of combinations, being hydroxychloroquine alone or in combination with azithromycin (316 patients [48%]) the most common regimen. Immunomodulatory therapy was administered in 48% of patients, mainly consisting on boluses or increased baseline dose of corticosteroids, whereas tocilizumab was used in 138 (21%) recipients.

Among SOT recipients, some adjustment of the baseline immunosuppressive regimen was performed in 85% cases. Although variable depending on the transplant type, this modification generally consisted of the withdrawal or dose reduction of calcineurin inhibitors, antimetabolites and mammalian target of rapamycin (mTOR) inhibitors, as well as the initiation or increase of corticosteroid dose (Figure 2). Sixty-four out of the 113 HSCT patients were receiving immunosuppressive treatment at the time of diagnosis of COVID-19, consisting of one drug in 34 patients and two or more drugs in 30 patients. Immunosuppression was modified in 31 and continued without changes in the remaining 33 HSCT recipients.

3.3 | Clinical outcomes

Patient outcomes are displayed in Table 2. Complete follow-up information was available for 652 (84%) of the reported cases at the time of submitting. The median interval between the diagnosis of COVID-19 and the resolution of infection or death was 16 (IQR: 10-25) and 13 (IQR: 7-20) days, respectively. Among patients admitted to the hospital, the median duration of hospital stay was 12 days (IQR: 7-21).

Overall, 174 patients died, accounting for a case-fatality rate of 27%. Death was considered to be attributable to COVID-19 in 93% of cases. The probability of survival at 10 and 20 days following the diagnosis of COVID-19 was 89% and 80%, respectively.

There were no significant differences between recipients with laboratory-confirmed SARS-CoV-2 infection and those in which the diagnosis was only based on clinical and radiological features in terms of case-fatality rate (26% versus 30%, respectively; *P*-value = 0.579). On the other hand, the rates of ICU admission (14% versus 6%; *P*-value = 0.128) and ARDS (36% versus 27%; *P*-value = 0.195) were numerically higher among patients with RT-PCR-confirmed COVID-19, who were in turn less likely to be managed as outpatients (10% versus 18%; *P*-value = 0.100).

3.4 | Analysis of mortality

Table 3 details mortality rates in patients with complete follow-up according to baseline features and intermediate outcome variables. Mortality significantly differed across transplant types, the probability of death being significantly higher for lung transplant versus other transplant recipients (OR: 2.5 [95% CI: 1.4-4.6]). The risk of death increased with age (OR for recipients >60 years: 3.7 [95% CI: 2.5-5.5]). Mortality was higher among patients with hospital-acquired SARS-CoV-2 infection (OR: 3.0 [95% CI: 1.9-4.9]). No significant differences in mortality were observed in terms of gender or type of baseline immunosuppression. Mortality was higher among recipients who had received the graft within the previous year, although the difference did not reach statistical significance (OR: 1.5 [95% CI: 0.9-2.3]). As expected, mortality was more frequent among recipients who were admitted to the hospital (OR: 4.4 [95% CI: 1.9-10.4]) and to the ICU (OR: 5.2 [95% CI: 3.2-8.4]), as well as in those who required IMV (OR: 6.9 [95% CI: 3.9-12.4]). The mortality rate within the subgroup of patients who developed ARDS was 64% (OR: 28.9 [95% CI: 17.6-47.4]). Most patients who developed septic shock [OR: 12.2 [95% CI: 5.9-25.4]) or multiorgan failure (OR: 30.3 [95% CI: 14.0-65.4]) died. Similar

TABLE 2 Evolution of solid organ and hematopoietic stem cell transplant recipients with COVID-19 with complete follow-up, overall and according to the transplant type[a]

	Overall (N = 652)	Kidney (N = 375)	Liver (N = 76)	Heart (N = 59)	Lung (N = 50)	Pancreas (N = 6)	Multivisceral (N = 1)	Allo-HSCT (N = 56)	Auto-HSCT (N = 29)
Hospital admission, n (%)	581 (89)	338 (90)	67 (88)	51 (86)	48 (96)	4 (67)	0 (0)	45 (80)	28 (97)
ICU admission, n (%)	84 (13)	57 (16)	3 (4)	7 (12)	6 (12)	2 (33)	0 (0)	4 (7)	5 (17)
Invasive mechanical ventilation, n (%)	58 (10)	36 (11)	3 (6)	3 (6)	6 (12)	2 (33)	0 (0)	4 (8)	4 (14)
ARDS, n (%)	224 (35)	134 (37)	16 (21)	16 (27)	29 (58)	3 (50)	0 (0)	14 (25)	12 (43)
Septic shock, n (%)	44 (7)	28 (8)	4 (5)	2 (3)	3 (6)	1 (17)	0 (0)	3 (6)	3 (11)
Multiorgan failure, n (%)	64 (10)	31 (9)	6 (8)	6 (10)	10 (20)	1 (17)	0 (0)	6 (11)	4 (14)
Death, n (%)	174 (27)	103 (28)	17 (22)	13 (22)	23 (46)	0 (0)	0 (0)	11 (20)	7 (24)

Abbreviations: Allo-HSCT, allogeneic hematopoietic stem cell transplantation; ARDS, acute respiratory distress syndrome; auto-HSCT, autologous hematopoietic stem cell transplantation; COVID-19, coronavirus disease 2019; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Percentages are calculated according to the available information for each variable.

TABLE 3 Mortality of solid organ and hematopoietic stem cell transplant recipients with COVID-19 according to baseline features and intermediate outcomes (N = 652)

	N	Number of deaths	% deaths	*p*-value
Baseline features				
Type of transplant				.035
Kidney	375	103	28%	
Liver	76	17	22%	
Heart	59	13	22%	
Lung	50	23	46%	
Pancreas	6	0	0%	
Multivisceral	1	0	0%	
Allogeneic hematopoietic stem cell	56	11	20%	
Autologous hematopoietic stem cell	29	7	24%	
Gender				.432
Male	431	111	26%	
Female	220	63	29%	
Age at diagnosis				<.001
≤15 years	11	2	18%	
16-45 years	87	5	6%	
46-60 years	202	35	17%	
61-70 years	196	61	31%	
71-80 years	135	63	47%	
>80 years	17	7	41%	
Time since transplantation				.099
≤ 1 year	109	36	33%	
> 1 year	540	137	25%	
Hospital-acquired SARS-CoV–2 infection				<.001
Yes	77	37	48%	
No	570	133	23%	
Baseline calcineurin inhibitor				.443
Yes	519	142	27%	
No	133	32	24%	
Baseline antimetabolite				.462
Yes	397	110	28%	
No	255	64	25%	
Baseline mTOR inhibitor				.578
Yes	137	34	25%	
No	515	140	27%	
Intermediate outcomes				
Hospital admission				<.001
Yes	581	168	29%	
No	71	6	9%	
ICU admission				<.001
Yes	84	49	58%	
No	557	118	21%	

(Continues)

Table 3 (Continued)

	N	Number of deaths	% deaths	*p*-value
Invasive mechanical ventilation				<.001
Yes	58	38	66%	
No	521	112	22%	
ARDS				<.001
Yes	224	143	64%	
No	417	24	6%	
Septic shock				<.001
Yes	44	34	77%	
No	593	129	22%	
Multiorgan failure				<.001
Yes	64	56	88%	
No	575	108	19%	

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit; mTOR, mammalian target of rapamycin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

results were obtained when HSCT recipients were excluded from the analysis (Table S1 in Data S1). Figure 3 represents the Kaplan-Meier survival curves according to the type of transplantation, age at diagnosis, hospital- versus community-acquired SARS-CoV-2 infection, and development of ARDS.

Finally, Table 4 displays an exploratory analysis of mortality according to the different antiviral and immunomodulatory therapies administered. Data are presented in the overall cohort of SOT and HSCT recipients and stratified by the development of ARDS, in order to account for the severity of COVID-19. Similarly, mortality rates according to the management of immunosuppression are shown in Table 5. The mortality of patients with ARDS was lower among those who received hydroxychloroquine (either alone or associated with azithromycin) as compared to other regimens or no antiviral treatment, as well as among those in whom the antimetabolite agent (mainly mycophenolate) was discontinued. This set of analyses was also repeated in the specific group of SOT recipients (Tables S2 and S3 in Data S1).

4 | DISCUSSION

To the best of our knowledge, this is the largest series published on SOT and HSCT recipients with a diagnosis of COVID-19, providing a nationwide picture of the disease burden and the natural history of SARS-CoV-2 infection in the Spanish transplant population.

In our experience, transplant patients presented a higher non-adjusted incidence of COVID-19 than that reported for the general population in Spain. There are different potential explanations for this finding. Transplant recipients may be at a higher risk of infection by SARS-CoV-2 due to the baseline use of immunosuppression, underlying comorbidities, and frequent contact with healthcare systems. On the other hand, they may be more likely of being diagnosed when they present symptoms, either because of a more overt symptomatology than immunocompetent individuals, or because of a closer follow-up at the transplant center.

As in other studies on posttransplant COVID-19, recipients in our series were usually in their sixth decade of life, predominantly males, and with a long history of transplantation prior to the diagnosis.[13,17–20,22,23] Although the majority of cases were acquired in the community, there was a relevant proportion of hospital-acquired infections, with 3% of patients developing COVID-19 in the immediate posttransplant period, similarly to what was reported by Pereira et al.[17] When analyzing cases with early posttransplant COVID-19 in further detail, donor-derived COVID-19 was not suspected in any of the patients. None of the donors exhibited a clinical picture compatible with COVID-19 and all had tested negative for SARS-CoV-2 by RT-PCR in respiratory tract samples prior to organ recovery, in alignment with national recommendations.[29] Of note, none of these infected recipients shared the same donor. Most importantly, professionals in charge considered that the infection had more likely resulted from a cross-contamination within the hospital. Based on the algorithm developed by DTAC, these findings made a donor-derived infection unlikely. These results reveal either the appropriateness of current guidelines for donor testing, or the decreased likelihood that the infection is transmitted through transplantation. Indeed, no cases of donor-derived transmission of SARS-CoV-2 or other epidemic coronaviruses have been reported to date in the literature.

Recipients who acquired COVID-19 during the immediate posttransplant period were infected within the first weeks of the outbreak, presumably in coincidence with the saturation of hospitals and ICU capacities. The transplantation activity subsequently decreased with a selected number of procedures being undertaken and priority given to urgent and critically ill patients, as well as to highly sensitized recipients provided an appropriate organ became available during the epidemic.[29] Similar decisions have been made in other countries, always prevailing the best interests of patients on the waiting list. The negligible proportion of COVID-19 cases diagnosed during the immediate posttransplant period following the declaration of the national state of alarm might be explained by the efforts to ensure "clean" healthcare circuits in hospitals.

Several potential therapeutic targets based on the replicative cycle of SARS-CoV-2 have dictated treatment approaches for COVID-19 in the absence of robust supporting evidence.[38] In view of their presumed *in vitro* activity, hydroxychloroquine[39–42] and ritonavir/lopinavir[43] were commonly administered during the early phase of the pandemic, as illustrated by our experience. Nevertheless, the use of protease inhibitors poses significant challenges due to drug-drug interactions with immunosuppressive agents.[34] Remdesivir has been recently granted conditional marketing authorization by the European Medicines Agency.[44] Access to this antiviral agent in our country has been largely limited to ongoing clinical trials, and its use in the present cohort was anecdotal (only 6 patients). Preliminary results suggesting a potential benefit from immunomodulatory therapy with dexamethasone[45,46] or anti-IL-6 agents[47] for the

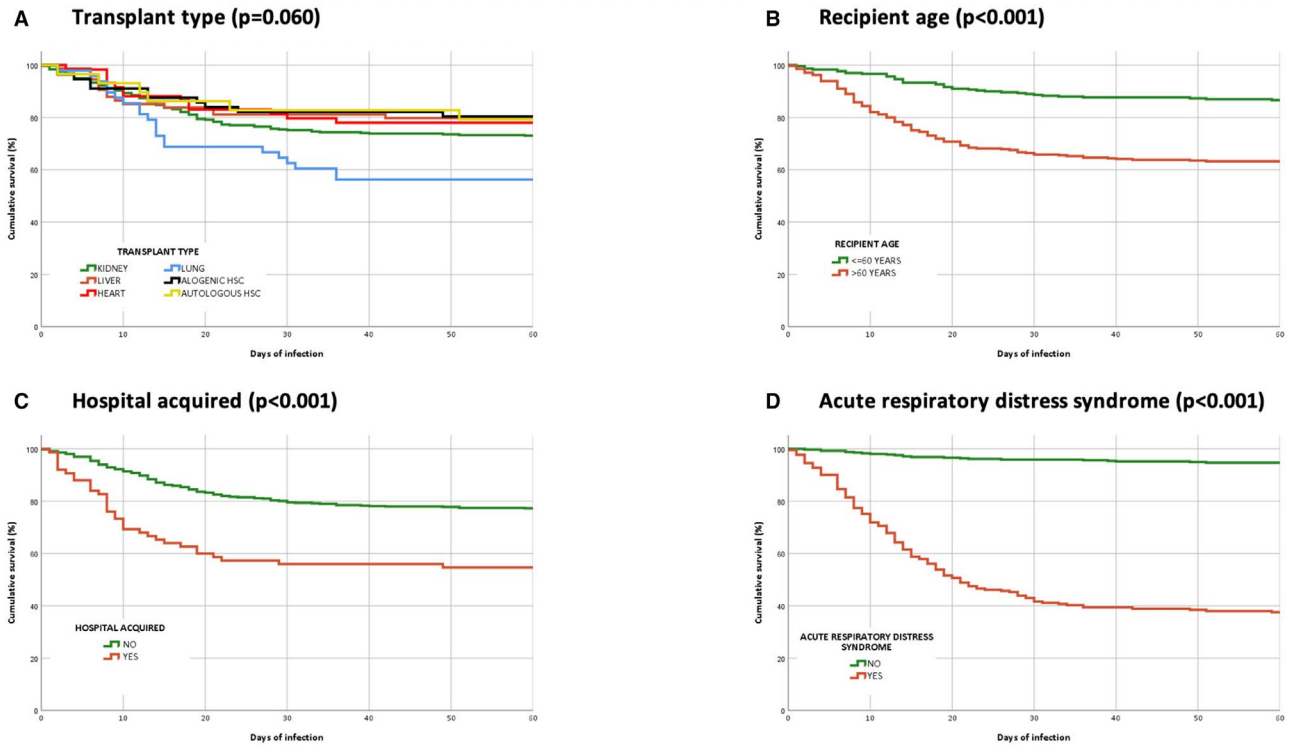

FIGURE 3 Kaplan-Meier survival curves in solid organ and hematopoietic stem cell transplant recipients with COVID-19: according to the transplant type (a), recipient age (b), hospital-acquired SARS-CoV-2 infection (c),and development of acute respiratory distress syndrome (d) (log-rank test for comparisons) [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Mortality of solid organ and hematopoietic stem cell transplant recipients with COVID-19 according to therapeutic approaches, overall and by the development of ARDS

	Overall			With ARDS			Without ARDS		
	N	Deaths, n (%)	*p*-value	N	Deaths, n (%)	*p*-value	N	Deaths, n (%)	*p*-value
Antiviral therapy			<.001			.003			.758
None	74	17 (23)		13	12 (92)		61	5 (8)	
HCQ alone or with AZT	307	55 (18)		86	44 (51)		221	11 (5)	
Protease inhibitor[a]	239	85 (36)		117	79 (68)		122	6 (5)	
Other	16	6 (38)		5	5 (100)		11	1 (9)	
Immunomodulatory therapy			.001			.384			.148
None	327	63 (19)		70	48 (69)		257	15 (6)	
Corticosteroids alone[b]	171	46 (27)		56	38 (68)		115	8 (7)	
Tocilizumab	125	49 (39)		86	49 (57)		39	0 (0)	
Anakinra	13	5 (39)		9	5 (56)		4	0 (0)	

Abbreviations: ARDS, acute respiratory distress syndrome; AZT, azithromycin; HCQ, hydroxychloroquine.

[a]Protease inhibitors in any combination.

[b]Defined as the administration of bolus of corticosteroids, initiation of corticosteroids, or increase of baseline doses.

SARS-CoV-2-triggered cytokine storm seem to have been rapidly extrapolated in clinical practice to the transplant setting, despite the paucity of data for this specific population. Indeed, corticosteroids (either as boluses or by increasing baseline doses) and tocilizumab were administered in 41% and 21% of patients, respectively. Overall, the therapeutic strategies described in our cohort, as well as the management of immunosuppression, were similar to those reported in other series of transplant patients with COVID-19.[13,14,16–19,22]

It has been suggested that long-term immunosuppression could potentially protect SOT recipients from developing the exacerbated

TABLE 5 Mortality of solid organ and hematopoietic stem cell transplant recipients with COVID-19 according to the management of immunosuppression, overall and by development of ARDS

	Overall			With ARDS			Without ARDS		
	N	Deaths, n (%)	*p*-value	N	Deaths, n (%)	*p*-value	N	Deaths, n (%)	*p*-value
Adjustment of calcineurin inhibitors			<.001			.109			.124
No adjustment	174	33 (19)		33	22 (67)		141	11 (8)	
Dose reduction	135	20 (15)		38	18 (47)		97	2 (2)	
Withdrawal	183	73 (40)		100	66 (66)		83	7 (8)	
Adjustment of antimetabolites			.171			.033			.381
No adjustment	89	23 (26)		23	19 (83)		66	4 (6)	
Dose reduction	21	9 (43)		8	7 (88)		13	2 (15)	
Withdrawal	268	65 (24)		98	57 (58)		170	8 (5)	
Adjustment of mTOR inhibitors			.092			.485			.624
No adjustment	49	8 (16)		13	7 (54)		36	1 (3)	
Dose reduction	13	1 (8)		1	1 (100)		12	0 (0)	
Withdrawal	69	22 (32)		33	22 (67)		36	0 (0)	

Abbreviations: ARDS, acute respiratory distress syndrome; mTOR, mammalian target of rapamycin.

inflammatory response triggered by SARS-CoV-2.[15,48,49] However, our experience suggests a particularly severe course in transplant patients with respect to the overall nontransplant population.[3,50] The 27% mortality rate in this cohort is similar to that reported in the largest COVID-19 transplant series published so far.[17,19,20,22,23] The more aggressive course of infection after transplantation may be due to the effects of chronic immunosuppression, but also to demographics and baseline comorbidities (eg, cardiovascular risk factors) of this group of patients compared to the general population. In fact, when we adjusted the COVID-19 case-fatality rate after transplantation to match the age and gender of the Spanish general population, it decreased to 15.8% (data not shown). Therefore, such a high crude mortality rate seems to be mainly influenced by the demographic profile—and comorbidity burden—of transplant recipients rather than by the direct impact of transplantation or associated immunosuppression. One important aspect of our experience is that, despite the severe course of the infection (as reflected by the frequent development of ARDS), only a limited number of patients were subject to ICU admission (13%) and IMV (10%), accounting for rates substantially lower than those reported from the US and Italy.[17,19,20] Similar inter-regional differences in the access to intensive care have been reported for cancer patients with COVID-19.[51] Although therapeutic approaches could largely differ across participating centers according to locally available resources at the different stages of the pandemic, this finding would suggest that decisions of limiting life-sustaining therapies were common among transplant patients perceived to have a poor baseline prognosis and a reduced likelihood of survival. However, it is unlikely that the mortality rate would have been lower should more patients had been subject to critical care. Indeed, 58% of COVID-19 transplant patients admitted to the ICU eventually died, in line with previous studies.[17,19]

The course of the infection, in terms of development of ARDS and death, was more aggressive in lung transplant recipients, and less severe in liver transplant patients. The poorer outcomes observed in the lung transplant group may be related to a lower respiratory reserve and the use of more potent immunosuppression. Other authors have described a relatively benign evolution for liver recipients with COVID-19, with age- and gender-adjusted mortality rates even lower than in the general population.[23] As reported in nontransplant patients,[52,53] the risk of death increased with recipient age, but we did not find any apparent impact of gender. Recipients reported to have acquired SARS-CoV-2 infection during hospitalization for different causes were found to experience worse outcomes than outpatients; it may be hypothesized that this subgroup was more likely to have higher comorbidity burden and poorer graft function at the time of infection. Of note, the proportion of patients receiving mTOR inhibitors (21%) was relatively high as compared to US series,[17,19] although no outcome differences were found according to the type of baseline immunosuppression. Finally, the analysis of mortality rates according to antiviral and immunomodulatory agents administered and the management of baseline immunosuppression should be considered as merely exploratory, due to potential confounding by indication and the lack of adjustment for clinical covariates.

Despite its strengths in terms of large sample size and comprehensiveness, which provide a nationwide picture of the incidence, clinical management and natural history of posttransplant COVID-19 in Spain, this study has a number of limitations. First, it is likely that hospitalized patients with severe clinical pictures have been reported more frequently than patients with less severe symptoms. The granularity of available data was limited, since no information on underlying comorbidities (eg, diabetes or hypertension), clinical and radiological presentation, severity indexes, laboratory parameters or timing of treatments administered was collected. This prevented us from testing the prognostic factors identified at the multivariate level. Finally, differences in clinical practices across participating

centers might have led to some heterogeneity in the reporting of major complications or the management of immunosuppression.

The scientific community is immersed in a rapidly evolving research on COVID-19. The healthcare effects of this pandemic, with no recent precedent, makes the knowledge on the course of the disease and clinical and therapeutic determinants of outcome imperative, particularly for immunocompromised hosts such as SOT and HSCT recipients. The value of this study lies is the large volume of cases captured that allows to provide valuable information on general aspects of the disease in the transplant setting. Therefore, this experience may serve as a reference to better understand the natural history of SARS-CoV-2 infection in transplant patients and to support further research in the field.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Mario Fernández-Ruiz https://orcid.org/0000-0002-0315-8001
Marta Crespo https://orcid.org/0000-0001-6992-6379
Francesc Moreso https://orcid.org/0000-0002-7267-3963
María O. López-Oliva https://orcid.org/0000-0003-3503-3518
Edoardo Melilli https://orcid.org/0000-0001-6965-3745
Laura Lladó https://orcid.org/0000-0002-3717-3306
Carmelo Loinaz https://orcid.org/0000-0002-1873-0568
Domingo Hernández https://orcid.org/0000-0001-5469-2119
Beatriz Domínguez-Gil https://orcid.org/0000-0002-5695-8993

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX 1

SPANISH GROUP FOR THE STUDY OF COVID-19 IN TRANSPLANT RECIPIENTS

Victoria Oviedo (C. A. Palencia); Pilar Fraile, Manuel Heras, Laura Prieto, Guadalupe Tabernero (C. A. Salamanca); María J. Fernández-Reyes (C. A. Segovia); Ana I. Díaz-Mareque, María T. García-Falcón, Santiago Tomé (C. H. A Coruña); Ernesto J. Fernández-Tagarro, Antonio González-Rodríguez, María L. Pérez-Tamajón, Ana Ramírez-Puga, Orlando Siverio (C. H. Canarias); Joaquín Manrique, Maite Zudaire (C. H. Navarra); Luz M. Cuiña, Enrique Peláez (C. H. Pontevedra); Marisa Crespo-Leiro, Isabel Otero (C. H. Santiago de Compostela); Carlos J. Cabezas, Miguel A. Muñoz-Cepeda (C. H. Toledo); Jesús Grande (C. H. Zamora); José I. Herrero, Paloma Martín-Moreno, Gregorio Rábago (C. U. Navarra); Elena Calvo (Clínica Girona); Cristina Canal (F. Puigvert); Nuria Garra (Fundación Althaia); Rodrigo Alonso, Amado Andrés, Ana Hernández-Vicente, María L. Paciello, Carlos A. Quezada, Ángel M. Sevillano, Hernando Trujillo (H. 12 de Octubre); Lourdes De la Vara, Carmen Gómez-Roldán, Francisco Llamas (H. Albacete); Lucas Lage (H. Álvaro Cunqueiro); Ainara Lozano (H. Basurto); Carme Baliellas, Alba Cachero, José González-Costello, Nicolás Manito (H. Bellvitge); María L. González-Diéguez, José L. Lambert, María Pérez-Fernández, María L. Suárez (H. Central de Asturias); Miquel Blasco, María A. Castel, Armando Coca, Montserrat Rovira (H. Clinic Barcelona); Secundino Cigarran (H. da Mariña); José I. Aranzábal Pérez, Mikel Gastaca, Juan J. Mateos, Sofía Zárraga (H. de Cruces); María P. Pérez del Barrio (H. de Jaén); Martín Giorgi (H. de la Princesa); Vicente Paraíso (H. del Henares); Anna Buxeda, María D. Redondo (H. del Mar); Raquel Santana (H. Doctor Negrín); Julia Kanter (H. Doctor Peset); María T. Rodrigo, Juan C. Vallejo (H. Donosti); Emma Montenegro (H. Duran i Reynals); Fernando Simal (H. El Bierzo); Amir Shabaka (H. Fundación Alcorcón); Javier Cornago (H. Fundación Jiménez Díaz); Ainhoa Hernando (H. Galdakao Usansolo); Antonio Franco, Raquel López-Vilella, Carlos Santiago (H. General de Alicante); María E. Moral (H. General de Ciudad Real); Leónicas Cruzado (H. General de Elche); Joaquín De Juan (H. General de Elda); Javier Juega, Andrés Villegas (H. Germans Trial i Pujol); Inés Aragoncillo, Cristina Beléndez, Zorba Blázquez, Mi Kwon, Carlos Ortiz, María M. Salcedo, Luis A. Sánchez-Cámara (H. Gregorio Marañón); Concepción Álamo, María D. Morales (H. Guadalajara); Begoña Navas (H. HLA Moncloa); Gerardo Blanco, Román Hernández-Gallego (H. Infanta Cristina); Raquel Díaz (H. Infanta Sofía); Fernando Fernández-Girón, Raquel Saldaña (H. Jerez de la Frontera); Isabel Beneyto, José L. Piñana, David Ramos, Gabriel Sales, Carmen Vinaixa (H. La Fe); Alida Alcolea, Laura Espinosa, María E. González-García, Loreto Hierro, Carlos Jiménez-Martín, Luisa Sisinni (H. La Paz); Diego Pastor (H. Lucus Augusti); Manuel Cobo, Emilio Fábrega, Víctor M. Mora, Juan C. Ruiz San Millán (H. Marqués de Valdecilla); María J. Aladrén, María T. Blasco, Alex Gutiérrez-Dalmau, Javier Paul (H. Miguel Servet); Inmaculada Heras (H. Morales Meseguer); Marta González-Vicent (H. Niño Jesús); Antonio Gascón (H. Obispo Polanco); Juan C. Martínez-Ocaña (H. Parc Taulí); Myriam Aguilar, Ana Arias, Gracia Bravo (H. Puerta de Hierro); Auxiliadora Mazuecos (H. Puerta del Mar); María T. García-Álvarez, María G. Sánchez-Márquez (H. Puerto Real); Pilar Herrera (H. Ramón y Cajal); Ana I. Gallardo, Rocío González-Grande, Verónica López-Jiménez, Francisco A. Nieto (H. Regional de Málaga); Carmen Martín-Calvo, José L. Montero, Alberto Rodríguez-Benot (H. Reina Sofía); Yurena Montoro (H. Requena); Belén Gómez-Giralda, Milagros Méndez-Pascual (H. Río Hortega); Marta Artamendi, Fernando Gil (H. San Pedro); Jaime Pérez de Oteyza (H. Sanchinarro); Vicens Brossa, Sonia Mirabet (H. Sant Pau); Aniana Oliet, Pedro Sánchez-Godoy (H. Severo Ochoa); Sheila Cabello (H. Son Espases); Gema Ariceta, Joana Sellares, Lluis Castells, Teresa Pont (H. Vall d'Hebrón); Pablo Ramírez-Romero, Isabel M. Saura (H. Virgen de la Arrixaca); María A. Rodríguez-Pérez (H. Virgen de la Macarena); Manuel Jurado, María F. Nogueras, María C. Ruiz Fuentes (H. Virgen de las Nieves); José M. Álamo, Gabriel Bernal, Juan A. Martín-González, José M. Sobrino (H. Virgen del Rocío); Pablo Castro (CATA, Andalucía); Manel Vázquez (OCATT, Cataluña).