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ORIGINAL ARTICLE

Incidence and outcome of SARS-CoV-2 infection on solid organ transplantation recipients: A nationwide population-based study

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Abstract

Since February 21 2020, when the Italian National Institute of Health (Istituto Superiore di Sanità–ISS) reported the first autochthonous case of infection, a dedicated surveillance system for SARS-CoV-2-positive (COVID+) cases has been created in Italy. These data were cross-referenced with those inside the Information Transplant System in order to assess the cumulative incidence (CI) and the outcome of SARS-COV-2 infection in solid organ transplant recipients (SOTRs) who are assumed to be most at risk. We compared our results with those of COVID+ nontransplanted patients (Non-SOTRs) with follow-up through September 30, 2020. The CI of SARS-CoV-2 infection in SOTRs was 1.02%, higher than in COVID+ Non-SOTRs (0.4%, $p < .05$) with a greater risk in the Lombardy region (2.89%). The CI by type of organ transplant was higher for heart (CI 1.57%, incidence rate ratio [IRR] 1.36) and lower for liver (CI 0.63%, IRR 0.54). The 60-day CI of mortality was 30.6%, twice as much that of COVID+ Non-SOTRs (15.4%) with a 60-day gender and age adjusted odds ratio (adjusted-OR) of 3.83 for COVID+ SOTRs (95% confidence interval [3.03–4.85]). The lowest 60-day adjusted-OR was observed in liver SOTRs (OR 0.46, 95% confidence interval [0.25–0.86]). More detailed studies on disease management and evolution will be necessary in these patients at greater risk of COVID-19.

Abbreviations: CFR, case fatality rate; CI, cumulative incidence; CNT, Italian National Transplantation Centre; COVID, SARS-CoV-2 not positive; COVID+, SARS-CoV-2 positive; COVID-19, Coronavirus Disease 2019; ECDC, European Center for Disease Prevention and Control; ICU, intensive care unit; ISS, Italian National Health Institute; MERS-CoV, Middle East respiratory syndrome; Non-SOT, not solid organ transplant; Non-SOTRs, Not Solid Organ Transplant Recipients; PA, autonomous provinces; SARS-CoV, severe acute respiratory syndrome virus; SARS-CoV-2, Severe Acute Respiratory Syndrome Virus - 2; SOT, solid organ transplant; SOTRs, solid organ transplant recipients; SOTs, solid organ transplants; WHO, World Health Organization; YRS, years.

*The Italian Network of Regional Transplant Coordinating Centers Collaborating group are listed in Appendix 1.

KEYWORDS
clinical research/practice, epidemiology, health services and outcomes research, infection and infectious agents, infectious disease, organ transplantation in general, patient survival

1 | INTRODUCTION

Italy has faced a real health emergency in the past months. The Coronavirus Disease 2019 (COVID-19) pandemic has spread rapidly in the initial months of 2020, leading to the saturation of Intensive Care Unit (ICU) beds and channeling of all of the efforts of healthcare workers towards COVID-19 management and containment. Due to the upward daily trend of positive cases, the Italian government set the so-called national lock-down period from March 9 to May 18 2020, during which increasingly strict measures were introduced for the entire population, in order to curb contagion. The maximum number of positive cases was reached in April (108 237 confirmed positive cases as of April 20), then a steady decrease was recorded during the months of May, June and July (12 230 confirmed cases as of 30 July).[1] On June 3, the government ordered the reopening of the interregional borders. To date, with 542 789 cumulative cases confirmed as of October 27, 2020, Italy is among the most affected countries by the pandemic, after the Russian Federation (1 547 774 confirmed cases), France (1 134 296 confirmed cases), Spain (1 046 132 confirmed cases) and the United Kingdom (894 694 confirmed cases) in Europe, that is after the United States (8 548 111 confirmed cases) and South-East Asia (8 969 707 confirmed cases) globally.[2]

During the initial months of the COVID-19 outbreak, all the efforts of the Italian National Transplant Center (CNT), the competent authority in the donation and transplantation field, were focused on the preservation of donation and transplantation activities, as urgent and life-saving procedures calling for continuity. Regulatory measures were issued to safely continue this activity in Italy, by routinely testing donors and recipients on the waiting list for SARS-CoV-2 and creating COVID-free pathways inside the transplant centers. The collaboration between transplant centers in the regions most affected by COVID-19 with those of less involved areas was fostered.[3-5] Adopted measures allowed the balanced performance of transplantation activity in Italy in the first 4 weeks of the COVID-19 epidemic compared to the same period of previous years, despite a reduction of 30% in the deceased donor rate being observed in the Northern regions, where 70% of all Italian deceased donors are procured.[6]

As of October 31, 2020 a minimal reduction in donation and transplantation activities in Italy (−10% and −6.6% compared to the same period of 2019, respectively) is confirmed.[7] Another end-point for the Italian Competent Authorities was the surveillance of the solid organ transplant recipients (SOTRs) in relation to the ongoing pandemic.

COVID-19 has proven to be more severe and lethal in subjects of older age and with various preexisting comorbidities.[8-11] Therefore, due to the need for chronic immunosuppressive therapy and to more or less prolonged end-stage organ disease, it is conceivable that SOTRs might present a less favorable outcome of the disease.[12] In the first month of epidemic in Italy, the Bergamo experience showed that, among patients followed-up for cirrhosis, transplantation, autoimmune disease, or chemotherapy for hepatoblastoma, none developed a clinical pulmonary disease, despite some testing positive for SARS-CoV-2 (both children and adults).[13] Conflicting opinions about this are currently being expressed and so far there are no conclusive data in the literature allowing us to say a final word.

For these reasons, this study aims at evaluating whether SOTRs were at increased risk of SARS-CoV-2 infection and mortality in the early peak period of the pandemic, by assessing the cumulative incidence (CI) of infection and analyzing mortality and the role of solid organ transplantation (SOT) as mortality risk factor in SOTRs compared to the global infected population.

2 | METHODS

2.1 | The Italian integrated COVID-19 surveillance system

After the Italian National Institute of Health (Istituto Superiore di Sanità – ISS) reported the first autochthonous case of COVID-19 disease on February 22 2020, the ISS was appointed as the coordinator of the COVID-19 surveillance system with the task of gathering microbiological and epidemiological data provided daily by the Italian Regions and Autonomous Provinces (Regions).[14] Data on all laboratory-confirmed COVID+ cases per definitions published and regularly updated by the European Centre for Disease Prevention and Control (ECDC) were collected in the system.[15] The data collected were in a continuous consolidation phase, as foreseeable in an emergency situation.[14]

2.2 | Patients undergoing Solid Organ Transplantation

All of the data on SOTRs were collected prospectively from January 1 2002, and analyzed retrospectively up to June 22 2020, through the Information Transplant System (SIT) which is managed by CNT, established by Law 91/99 as the national competent Authority for organ donation and transplantation activities.[7,16]

2.3 | Data collection

National SARS-CoV-2-positive (COVID+) case data entered into the surveillance system from February 21 to June 22 2020 (239 409 patients) were cross-referenced with SOTRs data from January 1 2002 to June 22 2020, as recorded in the SIT (58 067).

The surveillance data were limited to the first 4 months of the COVID-19 epidemic and analyzed on September 30 2020, in order to allow the consolidation of data sent by the Italian regional authorities and to use a cohort with a follow-up of at least 90 days.

The record linkage between the two databases was implemented through deterministic technique, thanks to the presence of personal data for all patients (first name, family surname, date of birth and the national unique identification code for each person), identifying the unique correspondence between patients from the two databases. SOTRs with nonfunctional grafts were excluded from the study (Figure 1). The COVID+ SOTR cohort was analyzed by comparing it both with COVID+ nontransplanted patients (COVID+ Non-SOTRs) and with the total transplanted patients (all Italian SOTRs). The information about the patient and graft status is based on patient follow-up recorded in the SIT until September 30 2020.

2.4 | Statistical analysis

As a preliminary analysis, demographic and geographical data were evaluated: categorical variables are shown as frequencies and percentages and continuous variables as the mean and standard deviation, median and IQR; the χ^2 test, adjusted for unequal variance, independent sample *t* test and Kruskal-Wallis rank test were performed, as appropriate.

The cumulative incidence (CI) with 95% confidence interval of the SARS-CoV-2 infection in the Italian transplant population was performed with reference both to the studied cohort of 238 895 COVID+ Non-SOTRs and to the 43 983 SOTRs. Specific CIs were calculated for Italian Regions, age groups (<18, 18–39, 40–49, 50–59, 60–69, 70–79, >80 years), sex and transplanted organ (heart, kidney, lung, liver and pancreas) in the SOTRs; specific for these categories Incidence Rate Ratios (IRR) by Poisson regression were provided. An indirect standardization to estimate an adjusted CI for COVID+ SOTRs was performed accounting for the estimate of sex and age groups rates in the Italian population (2019 Italian population distribution was available from the Italian National Institute of Statistics (Istituto Nazionale di Statistica – ISTAT). Accounting for more than 90 days of delay and assuming the absence/limited of outcome (death) under-reporting, we provided the Case Fatality Rates (CFR).[17]

Thirty- and sixty-day cumulative incidence of mortality were obtained by Kaplan-Meier estimation and incidence rate ratio in the comparison group along with the log-rank test, as appropriate.

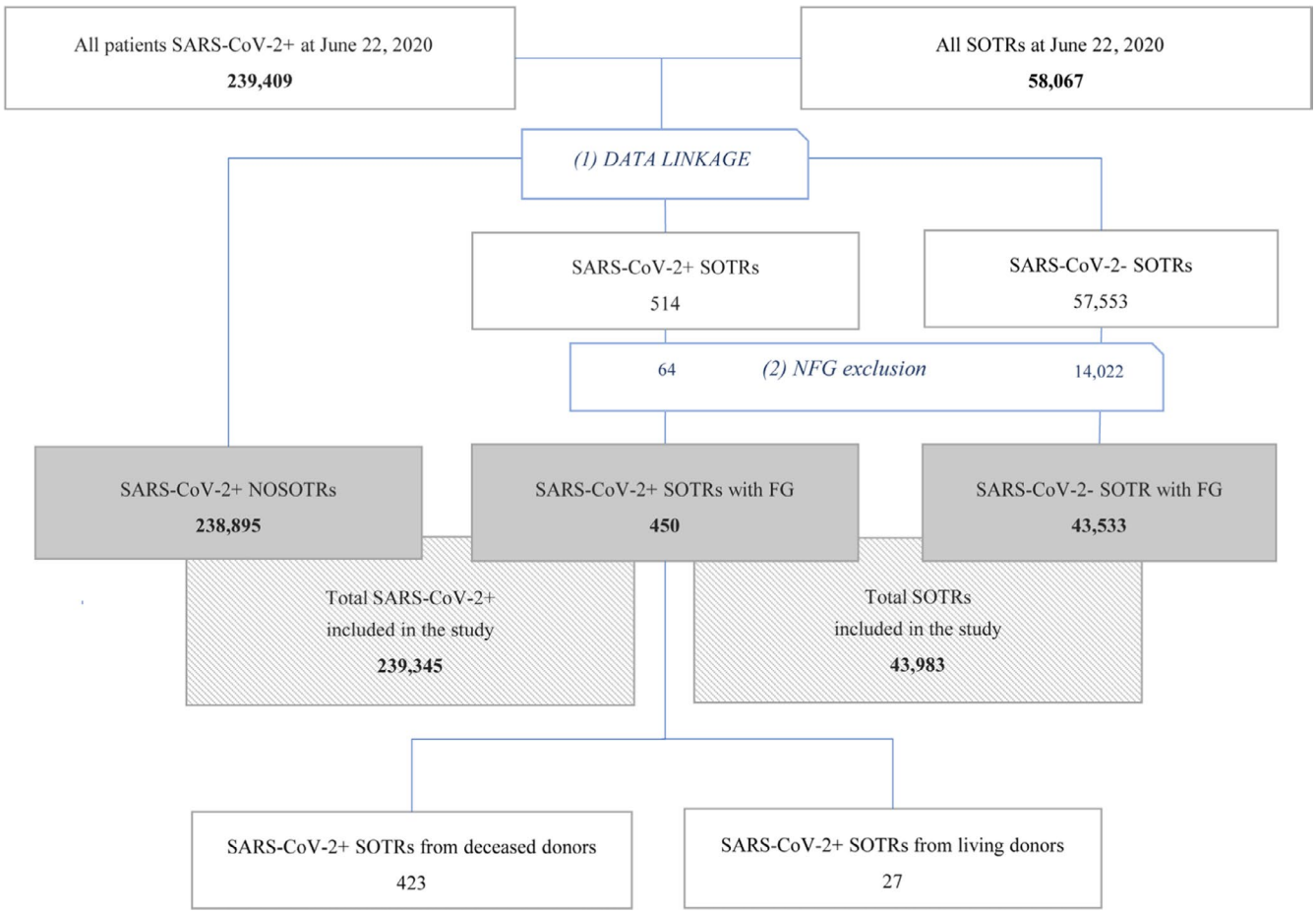

FIGURE 1 Data flow chart: (1) *Data linkage* - personal data of all patients entered in the COVID-19 surveillance system from February 21 to June 22, 2020 were cross-referenced with all SOTRs recorded in the SIT from January 1, 2002 to June 22, 2020; (2) *NGF exclusion* – all SOTRs, both SARS-CoV-2-positive and-negative, who had a graft failure were excluded from the study [Color figure can be viewed at wileyonlinelibrary.com]

Multivariable logistic regression analyses were performed in order to evaluate the 30-day and 60-day odds ratios (30-day OR, 60-day OR, respectively) of likelihood of death adjusting for age groups and sex in the COVID+ cohort, and stratifying by Lombardy and the other Regions- all together, as well as to assess the adjusted ORs of the different transplanted organs and the time elapsed from transplantation on the likelihood of death among the 450 COVID+ SOTRs. In order to assess the hypothesis of the equality of the coefficients (rate or OR) by group, Wald test for comparisons (testparm function by Stata) has been run. We used Akaike's information-criterion (AIC) to distinguish between full (including all indicated variables) models and those resulting from carrying out stepwise selection ($p > .2$ significance level for removal, $p \leq .1$, significance level for addition variables); for the sake of simplicity, only ORs resulting in the final (more parsimonious) models are presented.

In an attempt to supply the estimation of expected mortality in the Italian SOTRs, mortality rates were calculated on SOTRs identified as alive, with a functioning organ and showing a minimum follow-up time as long as the median one observed in the dead COVID+ SOTRs. These specific organ mortality rates were estimated at 0–6 months, 6 months–1 year, and more than 1 year (Table S2).

The 95% confidence intervals are reported along with the point estimations.

All statistical analyses were performed using Stata Software, Release 13.0 (StataCorp LP).

3 | RESULTS

3.1 | SARS-CoV-2 infection in SOTRs in Italy

Out of the 60 317 000 inhabitants in Italy (ISTAT data as of January 1 2020), 239 409 COVID+ patients were reported to the COVID-19 surveillance system until June 22 2020. Out of these, 239 345 were enrolled in the study, including 450 (0.19%) COVID+ patients with a functional graft. In particular, 423 patients (94%) were SOTRs from deceased donors and 27 (6%) from living donors (Figure 1). The cumulative incidence of infection among COVID+ SOTRs was 1.02% [95% confidence interval 0.93–1.12], higher than in COVID+ NOSOTR (0.40%, $p < .05$) and adjusting for the age-gender group rates of the Italian population, the indirectly standardized CI resulted to be almost three times higher than the rate in Italy (290%). Table 1 shows the COVID+ cases according to their regional residence. Lombardy is the most affected region, accounting for 39% of total cases, and for half of infected SOTRs (51.8%) with a percentage of 0.25% of COVID+ SOTRs over the total cases, which is higher than in the remaining Regions altogether (0.15%, $p < .0001$). Lombardy is confirmed to be the region with greater infection risk, with a cumulative incidence of COVID+ cases in the regional resident transplanted population of 2.89% [95% confidence interval 2.54–3.30], thus having the highest value in Italy.

Table 2 shows the demographic characteristics of COVID+ SOTRs compared to COVID+ Non-SOTRs and COVID− SOTRs. The median age at diagnosis of infected SOTR was 61 years, equal to COVID+ Non-SOTRs population and older than COVID− SOTRs (59, $p < .0001$). Looking at the distribution of positive cases by age groups, it may be inferred that the infection affects older age groups, over 80 years for COVID+ NON-SOTRS (25.3%) and 60–69 years for COVID+ SOTRs (38%), consistent with the characteristics of the transplanted population. Females are more affected than males among COVID+ Non-SOTRs (54.3%), while in COVID+ SOTRs males are more affected than females (75.6%) with a CI of infection of 1.145 and a RR of 1.503 ($p < .001$) (Table 2). SOTRs frequently presented two or three comorbidities more than COVID+ Non-SOTRs (37.7% vs. 23.6%; $p = .06$). We observed the same results by stratifying the comorbidity by transplanted organ (data not shown).

3.2 | Cumulative incidence of SARS-CoV-2 infection according to type of transplantation

Out of the 450 SOTRs analyzed, 285 (63.3%) were kidney transplants, 89 (19.8%) were liver transplants (including one liver-kidney), 53 (11.8%) were heart transplants (including one heart-kidney), 15 (3.3%) were lung transplants and eight (1.8%) were pancreas transplants (including six kidney-pancreas). Twenty-six kidney transplants and one liver transplant were from living donors.

With reference to the Italian SOTRs, the cumulative incidence of SARS-CoV-2 infection was shown to be higher in heart recipients (1.57% [95% confidence interval 1.2–2.1]; IRR 1.36 compared to kidney) and lower in liver recipients (0.63% [95% confidence interval 0.5–0.8]; IRR 0.54 compared to kidney) (Table 3). Detailing demographic characteristics by organ, in COVID+ SOTRs the mean age was higher in heart (59.8 ± 13.1 vs. 55.6 ± 18.0, $p = .0219$) and lung recipients (59.9 ± 8.5 vs. 51.2 ± 15.3, $p = .0016$) compared to COVID− SOTRs. A lower mean age was instead observed in kidney (59.2 ± 11.9 vs. 61.0 ± 95.0, $p = .0520$), liver (59.2 ± 14.1 vs. 62.7 ± 95.0, $p = .0407$) and pancreas recipients (48.9 ± 7.3 vs. 51.7 ± 9.4, $p = .3165$).

Fifty (11.1%) SOTs (10 heart, 27 kidney, 11 livers, and two lungs) were performed less than 122 days before the diagnosis of infection, 31 (6.9%) between 123 and 364 days and 369 (82%) more than 1 year before. In particular, 225 (50%) were performed more than 5 years before. Furthermore, 16 (3.5%) SOTs (10 kidneys, five livers, and one lung) were performed during the study period.

The median time from organ transplantation was globally 6 years, 5 years or more for each organ (Table 3) slightly different to the COVID− SOTRs (7 years, $p = .001$).

3.3 | Outcome of COVID+ SOTRs

We were able to verify that COVID+ SOTRs were more often hospitalized (72.2% vs 39.6%, $p < .0001$; OR 3.9 [95% confidence interval 3.2–4.9]) and in a severe clinical status (54.9% vs 32.36%, $p < .0001$;

TABLE 1 Italian regional distribution of COVID+ cases and Italian SOTR population. Study period 21 February–22 June 2020

	All COVID+	COVID+ SOTRs		COVID+ SOTRs CI × 100 in the SOTRs[a]
Regions	***N* (%)**	***N* (%)**	**All Italian SOTRs**	**95% confidence interval**
Italy	239 345 (100.0)	450 (100.0)	43 983	1.02 (0.93–1.12)
Piemonte	31 437 (13.1)	68 (15.1)	3684	1.79 (1.41–2.28)
Valle d'Aosta	1189 (0.5)	3 (0.7)	135	2.22 (0.72–6.89)
Lombardy	93 239 (39.0)	233 (51.8)	7810	2.89 (2.54–3.30)
PA BZ	2617 (1.1)	1 (0.2)	77	1.30 (0.18–9.22)
PA TN	4851 (2.0)	5 (1.1)	335	1.49 (0.62–3.59)
Veneto	19 261 (8.0)	30 (6.7)	3583	0.81 (0.56–1.16)
Friuli Venezia G.	3338 (1.4)	0 (0.0)	990	–
Liguria	10 010 (4.2)	15 (3.3)	1239	1.29 (0.79–2.11)
Emilia Romagna	28 315 (11.8)	36 (8.0)	3124	1.06 (0.75–1.49)
Toscana	9984 (4.2)	11 (2.4)	2684	0.48 (0.28–0.83)
Umbria	1439 (0.6)	3 (0.7)	539	0.37 (0.09–1.48)
Marche	6771 (2.8)	12 (2.7)	1011	1.19 (0.67–2.09)
Lazio	8095 (3.4)	8 (1.8)	3881	0.23 (0.12–0.45)
Abruzzo	3284 (1.4)	3 (0.7)	826	0.36 (0.12–1.13)
Molise	444 (0.2)	0 (0.0)	228	0.44 (0.06–3.11)
Campania	4628 (1.9)	8 (1.8)	4571	0.26 (0.15–0.46)
Puglia	4525 (1.9)	6 (1.3)	2824	0.28 (0.14–0.57)
Basilicata	364 (0.2)	0 (0.0)	338	–
Calabria	1165 (0.5)	0 (0.0)	1260	0.08 (0.01–0.56)
Sicilia	3029 (1.3)	4 (0.9)	3271	0.18 (0.08–0.41)
Sardegna	1360 (0.6)	4 (0.9)	1272	0.31 (0.12–0.84)
Foreign State			302	
	$p < .0001$			

	All COVID+	COVID+ SOTRs	%
Italy	239 345	450	0.19
Lombardy	93 239	233	0.25
Other regions	146 106	217	0.15
		$p < .0001$	

Abbreviations: COVID−, SARS-CoV-2 not positive; COVID+, SARS-CoV-2 positive; SOTRs, solid transplant recipients.

[a]CI, cumulative incidence, of SOTR SARS-CoV-2 with reference to all Italian SOTRs.

OR 2.6 [95% confidence interval 2.1–3.1]) than non-SOTRs and also more often admitted in ICU (17.3% vs 7.3%, %, $p < .0001$; OR 2.6 [95% confidence interval 2.1–3.4]) (Table S1) and intubated (2% vs 0.5%, $p < .0001$). Consistently with these data, two or three comorbidities were more frequently associated in critical/severe SOTRs than in non-SOTRs. Detailing the analysis among SOTRs, even though kidney and heart recipients were more often hospitalized and admitted to ICU than liver recipients, no significant difference was found by transplanted organ type (Table S1).

Out of the 450 COVID+ SOTRs, 123 died within our follow-up date (September 30 2020) so we registered a crude case fatality rate x 100 (CFR) of 27.3% higher than in COVID+ Non-SOTRs (14.2% $p < .001$). Consistently, also the 30–60-day CI of mortality was higher in the COVID+ SOTRs compared to COVID+ Non-SOTRs (30-day CI 43.1% vs 21.9%; IRR 1.90 [95% confidence interval 1.60–2.30]; 60-day CI 30.6% vs 15.4%; IRR 1.99 [95% confidence interval 1.66–2.38], respectively). The same analysis conducted according to the type of transplantation revealed a different survival trend between the SOTs evaluated ($p = .011$) (Figure 2a,b). In particular, both at 30 and 60 days the highest mortality was observed in heart recipients (30-day CI 57.6% [95% confidence interval 36.7–90.3] and 60-day CI 43.2% [95% confidence interval 27.5–67.7]) and the lowest in liver recipients (30-day CI 26.4% [95% confidence interval 15.6–44.6] and 60-day CI 17.5% [95% confidence interval 10.4–29.5]). Lung and pancreas recipients concur only with a few cases, therefore having no significance (Table 4).

Most of deceased COVID+ (49.1%) and COVID+ SOTRs (49.1% and 56.1%, respectively) were resident in the Lombardy region, and

TABLE 2 Characteristics of COVID+ cases and Italian SOTR population

Age, years Median [IQR] Min–max Mean ± SD	COVID+ Non-SOTRs 61 [47–80] 0–109 61.4 ± 21.11 *n* (%)	COVID− SOTRs 59 [49–68] 1–89 56.7 ± 15.4 p^a < .0001 *n* (%)	COVID+ SOTRs 61 [53–67] 5–84 59.09 ± 12.4 *n* (%)	CI COVID+ SOTRs[b] CI × 100	95% confidence interval	IRR[c] IRR × 100	95% confidence interval	*p*-value[d]
Age group								
<18	4910 (2.1)	1254 (2.9)	5 (1.1)	0.397	0.165–0.954	1		
18–39	33 845 (14.2)	4253 (9.8)	25 (5.6)	0.584	0.395–0.865	1.476	0.565–3.854	.427
40–49	31 214 (13.1)	5558 (12.8)	50 (11.1)	0.892	0.676–1.176	2.251	0.898–5.645	.084
50–59	42 743 (17.9)	10807 (24.8)	115 (25.6)	1.053	0.877–1.264	2.661	1.087–6.515	.032
60–69	31 760 (13.3)	12972 (29.8)	171 (38.0)	1.301	1.120–1.511	3.291	1.353–8.008	.009
70–79	33 963 (14.2)	7854 (18.0)	78 (17.3)	0.983	0.788–1.228	2.491	1.009–6.153	.048
80+	60 440 (25.3)	835 (1.9)	6 (1.3)	0.713	0.321–1.588	1.809	0.548–5.886	.328
Total[e]	238 875 (100.0)	43 533 (100.0)	450 (100.0)	1.02	0.933–1.122			
Female	129 615 (54.3)	14 271 (32.8)	110 (24.4)	0.761	0.631–0.918	1		
Male	109 261 (45.7)	29 262 (67.2)	340 (75.6)	1.145	1.029–1.273	1.503	1.213–1.865	<.001
Total[f]	238 876 (100.0)	43 533 (100.0)	450 (100.0)					

Abbreviations: CI, cumulative incidence; COVID−, SARS-CoV-2 not positive; COVID+, SARS-CoV-2 positive; IQR, interquartile range; SOTRs, solid organ transplant recipients.

[a]one-tailed t test of mean age difference in COVID+ SOTRs vs. COVID− SOTRs.

[b]CI of COVID+ SOTRs calculated with reference of the Italian SOTR population; 95% confidence interval calculated by the quadratic approximation to the Poisson log likelihood.

[c]Incidence-rate ratios by Poisson regression.

[d]Wald test *p*-value of the result by testing the null hypothesis that the IRR of different organs are equal.

[e]20 (0.008%) missing data.

[f]19 (0.008%) missing data.

TABLE 3 Solid organ transplant characteristics according to kind of organ

	Total	Kidney[a]	Heart[b]	Liver[c]	Lung	Pancreas[d]
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
	450 (100.0)	285 (63.3)	53 (11.8)	89 (19.8)	15 (3.3)	8 (1.8)
CI × 100[e]	1.02	1.15	1.57	0.63	1.39	0.98
95% confidence interval	(0.93–1.12)	(1.03–1.30)	(1.20–2.05)	(0.51–0.77)	(0.84–2.3)	(0.49–1.95)
IRR[f]	$p < .001$[g]	1	1.36	0.54	1.21	0.85
95% confidence interval			(1.02–1.82)	(0.43–0.69)	(0.72–2.03)	(0.42–1.71)
			$p = .038$	$p < .0001$	$p = .7$	$p = .4$
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Lombardy	233 (51.8)	134 (47.0)	33 (62.3)	51 (57.3)	11 (73.3)	4 (50.0)
Other regions	217 (48.2)	151 (53.0)	20 (37.7)	38 (42.7)	4 (26.7)	4 (50.0)
Years from transplant						
Mean (SD)	6.9 (5.4)	7.0 (5.5)	6.9 (5.5)	6.9 (5.7)	4.9 (3.3)	7.3 (3.7)
Median	6.0	6.1	6.1	6.1	5.1	7.6
IQR	1.8–11.3	1.8–11.6	1.0–11.5	1.5–11.3	2.6–8.4	4.5–9.9
<122 days (*n* pts)	50 (11.1)	27 (9.5)	10 (18.9)	11 (12.4)	2 (13.3)	0 (–)
123–364 days (*n* pts)	31 (6.9)	22 (7.7)	3 (5.7)	5 (5.6)	1 (6.7)	0 (–)
1–2 years (*n* pts)	64 (14.2)	40 (14.0)	5 (9.4)	16 (18.0)	1 (6.7)	2 (25.0)
3–5 years (*n* pts)	80 (17.8)	53 (18.6)	8 (15.1)	12 (13.5)	7 (46.7)	0 (–)
6–10 years (*n* pts)	85 (18.9)	53 (18.6)	7 (13.2)	18 (20.2)	3 (20.0)	4 (50.0)
>10 years (*n* pts)	140 (31.1)	90 (31.6)	20 (37.7)	27 (30.3)	1 (6.7)	2 (20.0)

Abbreviations: CI, cumulative incidence; COVID−, SARS-CoV-2 not positive; COVID+, SARS-CoV-2 positive; IQR, interquartile range; RR, risk ratio; SOTRs, solid organ transplant recipients.

[a]26 kidney transplant recipients from living donors.

[b]1 heart – kidney included.

[c]1 liver transplant recipient from living donor; 1 liver – kidney included.

[d]6 kidney-pancreas included.

[e]CI of COVID-19 SOTRs calculated with reference of the Italian SOTR population.

[f]Incidence-rate ratios by Poisson regression.

[g]Wald test *p*-value of the result by testing the null hypothesis that the IRR of different organs are equal.

this figure is also confirmed by the stratification by type of SOT (Table 4). However, comparing the 30- and 60-day CI of mortality of the Lombardy region to the other regions combined, despite the great disparity, we did not detect a statistically significant difference (47.8 vs 38.2% and 32.5% vs 28.6%; $p = .24$). The mortality rates of the overall transplanted population, selected by kind of organ and alive with functional graft up to the median time from transplantation observed in the COVID+ SOTRs, show that heart recipients would have experienced a 6-month mortality rate of 4%, liver recipients 2%, lung recipients 6.6% and kidney recipients 2.2% (Table S2). All deceased recipients were older than patients surviving COVID+ (65.4 ± 9.1 vs. 56.7.1 ± 12.7 respectively, $p < .001$) similar to Non-SOTRs (80.2 ± 10.6 vs. 58.2 ± 20.8 respectively, $p < .001$). Deceased SOTRs were significantly younger than deceased Non-SOTRs (65.4 ± 9.1 vs. 80.2 ± 10.6, $p < .001$) and had two or three associated comorbidities different to COVID+ Non-SOTRs (45% vs. 34.8%, $p = .03$). Out of 123 (92.4%) deceased SOTRs, 104 (84.6%) had been transplanted for over a year and 78 out of these (63.4%) for over 5 years. The median time from organ transplantation was 7.4 years, higher than those alive (5.3 years, $p = .008$). Out of fifty recipients transplanted during the 122 days preceding the infection diagnosis, 12 (24%, two hearts, eight kidneys, and two livers) died at the date of our follow-up (30-day OR 0.6, $p = .2$; 60-day OR 0.3, $p = .6$). Out of the 16 SOTRs transplanted during the study period, three (18.8%, all kidneys) died within 30 days from the transplant and three (18.8%, all kidneys) within 60 days, showing a higher mortality compared to the other SOTRs (37.5% vs. 27%) but no significance was observed ($p = .35$).

The multivariable logistic regression analysis on 30–60-day CI of mortality conducted on all COVID+ patients revealed that only organ transplantation was independently associated with mortality (adjusted-OR: 3.84 [3.02–4.87] and 3.83 [3.03–4.85] respectively, $p < .0001$ for all). The same results were also confirmed by stratifying according to geographical areas (Lombardy region vs other regions) (Table 5). If we only consider the COVID+ SOTRs cohort, the multivariable logistic regression analysis revealed that liver

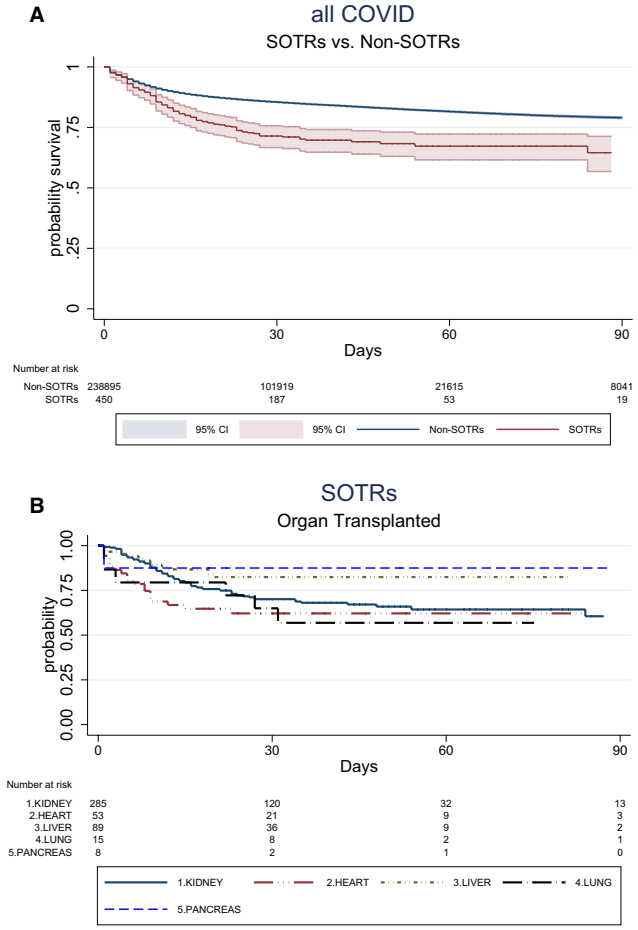

FIGURE 2 Kaplan-Meier cumulative incidence curves for mortality. (A) Time to death in COVID+ patients: SOTRS and Non-SOTRs. (B) Time to death in COVID+ SOTRs: kidney, liver, heart, lung, and pancreas recipients

transplantation had a 60-day CI of mortality lower compared to kidney (Adjusted-OR 0.41 [0.17–0.98], p = .045) (Table 6).

4 | DISCUSSION

The risk factors for SARS-CoV-2 infection and the categories of patients at a greater risk of more intense and prolonged disease manifestation, as well as worse outcome, are currently of great interest. Presently, the virus is only known to present varying degrees of severity, from flu-like symptoms to death.[9,18] SOTRs are on chronic immunosuppressive therapy and are more likely to experience respiratory virus infections, with faster disease progression, and bacterial or fungal super-infection. COVID-19 appears to progress more rapidly in such patients, increasing the rates of ICU admission and death.[19] Literature data are still quite fragmented, either presented as clinical cases or limited to a single type of organ transplant. Even the largest cases concerning all solid organ transplants still have limited numbers and in any case most refer to the first months of the pandemic. Our study analyzed 450 SOTRs and provides a broader overview, by outlining the characteristics of this population and their most significant involvement in SARS-CoV-2 infection. The cumulative incidence of SARS-CoV-2 infection in SOTRs turns out to be three times higher than that estimated for the Italian population, highlighting that SOTRs were more at risk of infection than Non-SOTRs. The predominant role of the Lombardy region, which acted as the gateway of infection in Italy, cannot be ignored, since it had to face a sudden and very rapidly spreading epidemic,[20-22] representing 39% of the total COVID+ cases and for half of infected SOTRs. However, the significant number of transplant patients residing in the region should be also considered (17.8%). Older COVID+ SOTRs, predominantly males, were more often in a critical/severe state and hospitalized compared to Non-SOTRs.

Unfortunately, the underreported data (over 50% of missing data) do not allow us to provide more detailed information about comorbidities and we are able to confirm only that SARS-CoV-2 infection occurs more frequently when two or three comorbidities are associated. By detailing by type of organ transplant, heart recipients appear to be at greatest risk of infection, while liver recipients appear to have the lowest risk. In a recent national cohort study conducted in England, Ravanan et al reported similar incidence data both overall and by type of organ.[23]

The most remarkable finding of our analysis is also that the 30- and 60-day CI of mortality of COVID+ SOTRs was twice higher when compared to Non-SOTRs. The Italian mortality rate is already reported as being higher than in other countries: the WHO data released at the time of our analysis (June 22, 2020) reported a case fatality rate of 5.3% globally, 5.3% in the USA and 7.6% in European Regions. Among these, Italy was reported to be the second, after France (19.1%), for mortality rate (14.5%).[1,24] This higher CFR in Italy could be partly explained by the demographic structure of the Italian population and by testing policies applied in most of the regions in the initial months of pandemic, targeting only symptomatic cases resulting in underestimated incidence rates of infection and consequently overestimated CFR, in relation to infected cases. From 4 May 2020, when Italy entered the transition phase and a test-track-trace strategy was adopted, testing policy was broadened to asymptomatic close contacts and to various screening programmes (e.g., ahead of hospital admission of other causes).[25] Therefore, as no specific recommendations regarding SOTR testing have been issued nationwide, the data reported in our study are well representative of ongoing infection transmission and its evolution. Certainly, a factor that may have influenced a higher CI of mortality rate is the choice to define associated deaths in a very inclusive manner.[26,27] Finally, most of the COVID+ SOTRs (51.8%) and most of registered deaths (56.1%) have been reported in Lombardy region, a circumstance which has probably affected the mortality data reported in our study.

In the specific case of the transplanted population, similar mortality rate was reported in several case series, such as a Spanish study which reported a 28% lethality rate and two American studies, conducted on kidney transplants, which reported a 30% lethality rate.[28-30] More recently, the UK cohort study described an overall

TABLE 4 Cumulative incidence of mortality in COVID+ population: Non-SOTRs and SOTRs

	Total COVID+ Non-SOTRs		Total COVID+ SOTRs		Kidney		Heart		Liver		Lung			Pancreas
	Total	Deaths	Total	Deaths	Total	Deaths	Total	Deaths	Total	Deaths	Total	Deaths	Total	Deaths
	n	*n* (%)	*n*	*n* (%)	*n*	*n* (%)	*n*	*n* (%)	*n*	*n* (%)	*n*	*n* (%)	*n*	*n* (%)
Italy	238 895	33 972 (14.2)	450	123 (27.3)	285	83[a] (29.1)	53	19 (35.8)	89	14 (15.7)	15	6 (40.0)	8	1 (12.5)
% 30-day cum. incid. of mortality (95% confidence interval)	21.9 (21.7–22.2)		43.1 (35.9–51.7)		45.2 (36.1–56.6)		57.6 (36.7–90.3)		26.4 (15.6–44.6)		71.4 (29.7–171.6)			16.7 (2.3–118.3)
IRR	1.9 (95% confidence interval 1.6–2.3)				Log-rank test: $^2(4)$, $p = .011$									
% 60-day cum. incid. of mortality (95% confidence interval)	15.4 (15.2–15.5)		30.6 (25.7–36.6)		32.3 (26.0–40.1)		43.2 (27.5–67.7)		17.5 (10.4–29.5)		46.2 (20.7–102.7)			14.3 (2.0–101.4)
IRR	2.00 (95% confidence interval 1.66–2.38)				Log-rank test: $^2(4)$, $p = .015$									
Lombardy	93 006	16 676 (17.9)	233	69 (29.6)	134	38 (28.4)	33	16 (48.5)	51	10 (19.6)	11	4 (36.4)	4	1 (84.6)
% 30-day cum. incid. of mortality (95% confidence interval)	27.3 (26.8–27.7)		47.8 (37.5–60.9)											
IRR	1.75 (95% confidence interval 1.4–2.2)													
% 60-day cum. incid. of mortality (95% confidence interval)	19.7 (19.4–20.0)		32.5 (25.6–41.3)											
IRR	1.65 (95% confidence interval 1.3–2.1)													
Other regions	145 889	17 296 (11.9)	217	54 (24.9)	151	45 (29.8)	20	3 (15.0)	38	4 (10.5)	4	2 (50.0)	4	0 (0.0)
% 30-day cum. incid. of mortality (95% confidence interval)	18.4 (18.1–18.6)		38.2 (28.9–50.4)											
IRR	2.3 (95% confidence interval 1.7–2.9)													
% 60-day cum. incid. of mortality (95% confidence interval)	12.7 (12.5–12.9)		28.6 (21.9–37.3)											
IRR	1.99 (95% confidence interval 1.7–2.4)													

Abbreviations: COVID–, SARS-CoV-2 not positive; COVID+, SARS-CoV-2 positive; SOTRs, solid organ transplant recipients.

[a]6 kidney transplant recipients from living donors.

Incidence-rate ratios by Poisson regression.

TABLE 5 Outcome (death) analysis in COVID+ cases: univariate and multivariable logistic regression analysis in all COVID+ population

	Univariate logistic regression analysis		Multivariable logistic regression analysis					
	Italy		Italy		Lombardy		Other regions	
	30 days	60 days	30 days	60 days	30 days	60 days	30 days	60 days
	OR (95% confidence interval)	OR (95% confidence interval)	OR* (95% confidence interval)	OR* (95% confidence interval)	OR* (95% confidence interval)	OR* (95% confidence interval)	OR* (95% confidence interval)	OR* (95% confidence interval)
SOTR vs. Non-SOTR	2.29 (1.85–2.83)	2.27 (1.85–2.80)	3.86 (3.02–4.87)	3.83 (3.03–4.85)	3.33 (2.42–4.57)	3.27 (2.39–4.48)	4.05 (2.82–5.81)	4.13 (2.90–5.87)
Age								
51–70 vs. ≤ 50 (Ref.)	12.51 (11.28–13.89)	12.22 (11.09–13.48)	11.67 (10.52–12.96)	11.44 (10.37–12.61)	10.89 (9.39–12.63)	10.56 (9.21–12.18)	11.56 (9.99–13.38)	11.43 (9.96–13.12)
>70 vs. ≤ 50 (Ref.)	76.13 (68.86–84.18)	73.92 (67.26–81.24)	81.71 (73.88–90.36)	79.33 (72.17–87.20)	66.83 (57.88–77.18)	64.19 (56.07–73.49)	91.67 (79.61–105.57)	89.92 (78.76–102.67)
M vs. F (Ref.)	1.81 (1.7–1.8)	1.76 (1.72–1.80)	2.30 (2.24–2.36)	2.24 (2.19–2.31)	2.47 (2.38–2.57)	2.41 (2.32–2.50)	2.14 (2.07–2.22)	2.10 (2.03–2.18)

mortality rate of 25.8% and detailed by organ type rates similar to ours.[23] In our study, we reported the increasing age and the organ transplantation as risk factor of death. Moreover, among SOTRs we did not observe any additional risk neither for the more recent SOTs (performed less than 122 days from infection diagnosis) nor for the SOTs performed during the study period and no additional risk was observed for heart recipients too, despite of the worse outcome.

From the literature, we learn of an epidemiological association between history of cardiac disease and worsened outcome during COVID-19. SARS-CoV-2 seems to cause direct damage to the myocardium, leading to increased mortality,[31] but no specific risk to heart transplant recipients is known. The lung also has high mortality rates but we have too few cases to draw conclusions. On the contrary, liver was confirmed to have a protective effect against the infection and a lower mortality rate (CFR 15.7%) and IRR versus the other organs. Also when observing hospitalization data, liver recipients are those hospitalized less often. Both an European Liver and Intestine Transplantation Association (ELITA)/European Liver Transplant Registry (ELTR) study and an International European Liver Transplant cohort reported for the liver CFRs between 12 and 17%, similar to ours.[32,33] The same UK study by Ravanan et al described a lower CFR in the liver than in other organs.[23] The most plausible hypothesis to explain these results could be represented by the different immunosuppressive regimen featuring liver transplant compared to other organ transplants. The liver recipient is subject to milder immunosuppressive therapy and presents a greater immunological tolerance compared to other SOTRs.[34] Our analysis was unfortunately limited by the lack of further information on site of hospitalization and on the management of the immunosuppression (IS) therapy. In Italy all transplant specialists agreed to not interrupt immunosuppressive therapy but only to modulate it, on the basis of disease severity.[35-37] The criticality could be that SOTRs have not always been admitted to a transplant center, but to general hospitals lacking specific expertise, where a proper management of immunosuppressive therapy cannot be guaranteed. Furthermore, the lack of information about the comorbidities, the transplanted organ status, the disease course, and the final cause of death keeps our analysis from being a break-through.

In conclusion, SOTRs category resulted to be more at risk of infection, of hospitalization and admission in ICU and of mortality compared to Non-SOTRs, during the first peak period of epidemic in Italy. Probably, their weaker immune system seems to be predisposed to a more serious disease as proven by a higher mortality. We did not observe any difference in mortality risk between recent and long-standing transplants, a very important piece of information for directing local health policies. However, further studies are certainly needed to draw definitive conclusions on this interesting topic.

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TABLE 6 Outcome (death) analysis in COVID+ cases: univariate and multivariable logistic regression analysis in COVID+ SOTRs

	Univariate logistic regression analysis			Multivariable logistic regression analysis			Univariate logistic regression analysis			Multivariable logistic regression analysis		
	30 days			30 days			60 days			60 days		
	OR[b]	95% confidence interval	*p*-value	OR[b]	95% confidence interval	*p*-value	OR[b]	95% confidence interval	*p*-value	OR[b]	95% confidence interval	*p*-value
Kidney (Ref.)	1						1					
Heart	1.54	(0.83–2.86)	.174				1.38	(0.75–2.56)	.303			
Liver	0.51	(0.27–0.96)	.037				0.46	(0.25–0.86)	.016	0.41	(0.17–0.98)	.001
Lung	1.38	(0.46–4.16)	.572				1.65	(0.57–4.78)	.356			
Pancreas	0.39	(0.05–3.25)	.386				0.35	(0.04–2.92)	.335			
Age												
51–70 vs. ≤50 (Ref)	3.66	(1.62–8.29)	.002	3.47	(1.18–10.16)	.024	4.00	(1.77–9.05)	.001	4.22	(1.44–12.38)	.009
>70 vs. ≤50 (Ref)	11.95	(4.84–29.51)	.001	7.03	(1.98–24.96)	.003	13.40	(5.42–33.12)	.001	9.17	(2.59–32.76)	.045
M vs. F (Ref)	1.40	(0.84–2.36)	.200				1.36	(0.82–2.25)	.235			
Time from transplant to infection												
>122 vs. ≤122 days (Ref)	0.61	(0.31–1.32)	.198		–		0.83	0.42–1.73)	.6		–	

Abbreviations: COVID−, SARS-CoV-2 not positive; COVID+, SARS-CoV-2 positive. Ref: reference group; SOTRs, solid organ transplant recipient.

[a]For all variables $p < .0001$.

[b]OR was reported only for significant effects of the best-fit model; (1) 1 heart-kidney included; *p* value obtanei by Wald test.

and transplanted patients, as well as those that made organ donation possible, even during this difficult COVID-19 pandemic period. Finally, yet importantly, our deepest gratitude is for the donor families, whose generosity makes, each day, transplantation accessible for many patients. The authors thank Paola Di Ciaccio and Valentina Caramia for the paper linguistic review. No funding sources were employed.

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 from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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

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APPENDIX 1

Italian Network of Regional Transplant Coordinating Centers Collaborating group

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