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ORIGINAL ARTICLE

Sex and organ-specific risk of major adverse renal or cardiac events in solid organ transplant recipients with COVID-19

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While older males are at the highest risk for poor coronavirus disease 2019 (COVID-19) outcomes, it is not known if this applies to the immunosuppressed recipient of a solid organ transplant (SOT), nor how the type of allograft transplanted may impact outcomes. In a cohort study of adult (>18 years) patients testing positive for COVID-19 (January 1, 2020-June 21, 2021) from 56 sites across the United States identified using the National COVID Cohort Collaborative (N3C) Enclave, we used multivariable Cox proportional hazards models to assess time to MARCE after COVID-19 diagnosis in those with and without SOT. We examined the exposure of age-stratified recipient sex overall and separately in kidney, liver, lung, and heart transplant recipients. 3996 (36.4%) SOT and 91 646 (4.8%) non-SOT patients developed MARCE. Risk of post-COVID outcomes differed by transplant allograft type with heart and kidney recipients at highest risk. Males with SOT were at increased risk of MARCE, but to a lesser degree than the non-SOT cohort (HR 0.89, 95% CI 0.81–0.98 for SOT and HR 0.61, 95% CI 0.60–0.62 for non-SOT [females vs. males]). This represents the largest COVID-19 SOT cohort to date and the first-time sex-age–stratified and allograft-specific COVID-19 outcomes have been explored in those with SOT.

KEYWORDS
age, allograft type, cardiac, COVID-19, gender, heart, infection, kidney, liver, lung, MACE, MARCE, mortality, outcome, SARS-CoV-2, sex, solid organ transplantation

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; HR, hazard ratio; MACE, major adverse cardiac event; MARCE, major adverse renal or cardiac event; N3C, National COVID Cohort Collaborative; NCATS, National Center for Advancing Translational Sciences; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SOT, solid organ transplant.

Authorship was determined using ICMJE recommendations.

Members of the National COVID Cohort Collaborative (N3C) Consortium are listed in the Appendix.

1 | INTRODUCTION

The critical manifestations of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection have been attributed to catastrophic immune dysregulation and a pathologic cytokine release syndrome resulting in many downstream complications, including acute kidney injury (AKI), major adverse cardiovascular events (MACE), acute respiratory distress syndrome (ARDS), and death.[1–3] The most important predictor of poor outcomes is older age.[4] In the general population, male sex has been strongly associated with COVID-19 attributable mortality; with a 1.4–2-fold higher case-fatality rate in males compared with females.[5,6]

Solid organ transplant (SOT) patients with COVID-19 appear to be at an even higher risk than the general population based on their exposure to chronic maintenance immunosuppression and underlying comorbidities.[7–9] In this population, older individuals with COVID-19 have a 28-day case fatality rate of ~20%[9,10] compared to a 0.8%–2% risk in the general population.[11] Likewise, the risk of AKI in SOT patients with COVID-19 is increased at ~50%,[12] with one study demonstrating a need for renal replacement therapy in 23% and graft loss in 6.3% of kidney transplant recipients.[13]

While several studies have examined outcomes in SOT recipients who develop COVID-19, most have been small scale and many are single-center analyses.[7,8,14–17] Both organ transplantation and COVID-19 have been shown to independently increase the risk of cardiovascular disease, but the risk of MACE or major adverse renal or cardiac events (MARCE) in transplant patients who have COVID-19 has not been previously explored, nor the impact of specific allograft type on this outcome. Additionally, older age is clearly associated with poor outcomes in SOT patients with COVID-19,[13,18] however, male SOT patients with COVID-19 do not appear to be at increased risk.[7,10,13,16,18–20] In the largest study of SOT patients with COVID-19 to date (a meta-analysis of 74 studies including 5559 kidney transplant recipients from March 2020–January 2021) sex was not associated with an increased risk of death or AKI.[21] Whether this reflects the size of the individual SOT studies reported, or a true mitigation of the sex-specific difference in COVID-19 disease observed in the general, non-immunosuppressed population, is an important question that remains to be seen. A better understanding of potential sex-based differences in COVID-19 risk may guide insights into mechanisms of SARS-CoV-2 pathology and result in more specific interventions and management of COVID-19 in both sexes. Likewise, the relative risk of organ transplant type with adverse outcomes after COVID-19 diagnosis has been underappreciated.

With these questions in mind, we investigated potential predictors of MARCE in SOT recipients with COVID-19 disease using the largest COVID-19 database in the United States, the National COVID Cohort Collaborative (N3C).[22] N3C represents a large, national repository of 56 academic medical centers contributing data on more than 1.9 million adult patients with COVID-19 and more than 4 million COVID-19–negative controls. This centralized, harmonized, and highly granular repository of electronic health record (EHR) data represents the most representative and substantive resource for studying the U.S. COVID-19 population.[23] Capitalizing on this large database, we aimed to explore if COVID-19 risk in SOT recipients is effected by allograft type, and if male sex remains associated with worse outcomes in the SOT population. This is the largest study of SOT recipients with COVID-19 to date.

2 | METHODS

N3C includes a broad category of patients with limited inclusion criteria for incoming data; specifically COVID-19 positivity or suspected positivity by lab testing or diagnostic codes for both inpatient and outpatient encounters.[24] The incoming data comes from four primary data models—OMOP, PCORnet, TriNetX, and ACT—harmonized into the OMOP 5.3.1 data model and made available within a secure enclave for analysis at the patient- and encounter-level (Figure S1).[22] A heat map of the geographical distribution of all patients contributing data to N3C is shown in Figure S2.

2.1 | Design

We conducted a retrospective cohort study to examine adult SOT patients (>18 years of age) in the United States with at least one positive test for COVID-19 between January 1, 2020 and June 21, 2021. SOT patients were defined as having kidney, liver, lung or heart organ transplantation. The N3C Enclave was developed to facilitate analysis of patient-level data across the United States for multiple conditions, consisting of regular refresh cycles with data contributing organizations providing updated electronic medical records (EMRs) into a centralized, federally secured platform.[21] Our data were extracted from release 34 (June 21, 2021). As a comparator group, we examined all adult non-SOT patients captured in N3C with a positive test for COVID-19 over the same period.

2.2 | Exposure

The primary exposure was sex-age strata (female vs. male for each of age 18–45, 46–65, and >65 years, for a total of six sex-age categories). Males 18–45 years were considered the reference group. The exposure for a secondary analysis was transplant allograft type (kidney, liver, lung, or heart). We excluded patients with multiple allograft types from this secondary analysis.

2.3 | Outcomes

The primary outcome was MARCE in the 90 days post COVID-19 diagnosis, defined as a composite of AKI with or without dialysis, acute myocardial infarction, angina, stent occlusion/thrombosis, stroke, transient ischemic attack, congestive heart failure or death from

any cause. As secondary outcomes we examined components of MARCE including (i) MACE, (ii) AKI, and (iii) death from any cause in the 90 days post-COVID-19 diagnosis, as well as (iv) COVID-19 disease severity (requiring hospitalization for or death from COVID-19) as defined by the WHO Ordinal Scale for Clinical Improvement.[23] Finally, in an organ-specific analysis we included the outcome of allograft rejection.

2.4 | Data collection

In addition to the primary exposure, a computable phenotype was created to include known predictors of MARCE including race, time since transplant, type of organ transplant (kidney, liver, heart, lung), comorbidities (chronic kidney disease [CKD], hypertension, diabetes, chronic obstructive pulmonary disease [COPD]/asthma, cancer, coronary artery disease, congestive heart failure, peripheral vascular disease, liver disease, and obesity [body mass index, BMI ≥30 kg/m^2]). Concept sets defining all standardized vocabulary used for medications, labs, procedures, and outcomes, are available on the project Github repository.[25] For the primary analysis, a complete case analysis was performed. Given large amounts of missingness for BMI (>40%), an indicator was created for missing BMI and included as an adjustment variable in multivariate analyses. CKD staging was missing in 51% of patients, thus CKD status was included as a binary outcome for presence or absence (not stage).

2.5 | Analysis

Descriptive statistics were used to report baseline characteristics for all SOT and non-SOT patients included in the study, stratified by whether they experienced MARCE.

2.6 | Primary analysis

Separately for SOT and non-SOT patients, the association between each sex-age strata (relative to males 18–45 years) and MARCE was evaluated using a multivariable Cox proportional hazards model adjusting for the covariates indicated above (with time since transplant and organ type in the SOT group). For those with SOT, time to MARCE within 90 days after COVID-19 diagnosis was displayed graphically using Kaplan Meier survival curves for each sex-age strata.

2.7 | Secondary analyses

1. Using multivariable Cox proportional hazards models adjusting for the above covariates, we examined the adjusted hazard ratio for each sex-age strata separately on MACE, AKI, organ rejection and mortality. To determine the association between sex-age strata and COVID-19 severity as a binary outcome (severity ≥ moderate [hospitalized], severe [hospitalized and ventilated] or death with COVID-19),[23] we used multivariable logistic regression, again adjusting for the covariates listed above. Again, these analyses were repeated for non-SOT patients as a comparator group (except for the outcome of organ rejection).
2. An overall analysis of the entire cohort (SOT and non-SOT) with SOT status included in the regression was performed to determine the independent association of SOT status with (i) MARCE, (ii) MACE, (iii) AKI, (iv) death from any cause, and (v) COVID-19 disease severity.
3. The primary analysis described above was repeated using organ-specific cohorts ([i] kidney, [ii] liver, [iii] lung, and [iv] heart transplant recipients separately) instead of all SOT. For the secondary analysis, patients with combined transplants were excluded from the organ-specific cohorts.
4. We meta-analyzed the relative risk of each primary (MARCE) and secondary outcome ([i] MACE, [ii] AKI, [iii] death from any cause, [iv] COVID-19 disease severity [requiring hospitalization for or death from COVID-19] and [v] organ rejection) in the 90 days following COVID-19 diagnosis, by allograft type relative to (i) those without SOT and (ii) those with a kidney transplant (to allow for comparison of rejection risk). Finally, we explored potential sex-based differences in each primary and secondary outcome, stratified by allograft type, to determine if allograft type modified the association of recipient sex on post-COVID outcomes. We used random-effects meta-regression using aggregate-level data for each organ type. Heterogeneity in outcome between transplant allograft types was evaluated by Higgins I^2 and the chi-square test of heterogeneity.

All statistical analyses were performed using R built in the N3C Enclave.

3 | RESULTS

Over the study period, we identified 10 987 SOT patients and 1 890 246 non-SOT patients with COVID-19 (Figure 1), of whom 3996 (36.4%) and 91 646 (4.8%) developed MARCE in the 90 days post COVID diagnosis, respectively ($p < .0001$). There was an ongoing, progressive increase in the number of patients diagnosed with COVID-19 over the study period, in keeping with the natural history of the pandemic. Baseline characteristics for SOT and non-SOT patients are shown in Table 1. Notably, the proportion with MARCE in both the SOT and non-SOT cohorts increased with increasing age and more male patients experienced MARCE overall (38.0% of COVID-19 positive males vs. 34.0% of COVID-19 positive females with SOT; 6.2% of COVID-19 positive males vs. 3.7% of COVID-19 females in non-SOT; age-sex stratified results are shown in Figure S3).

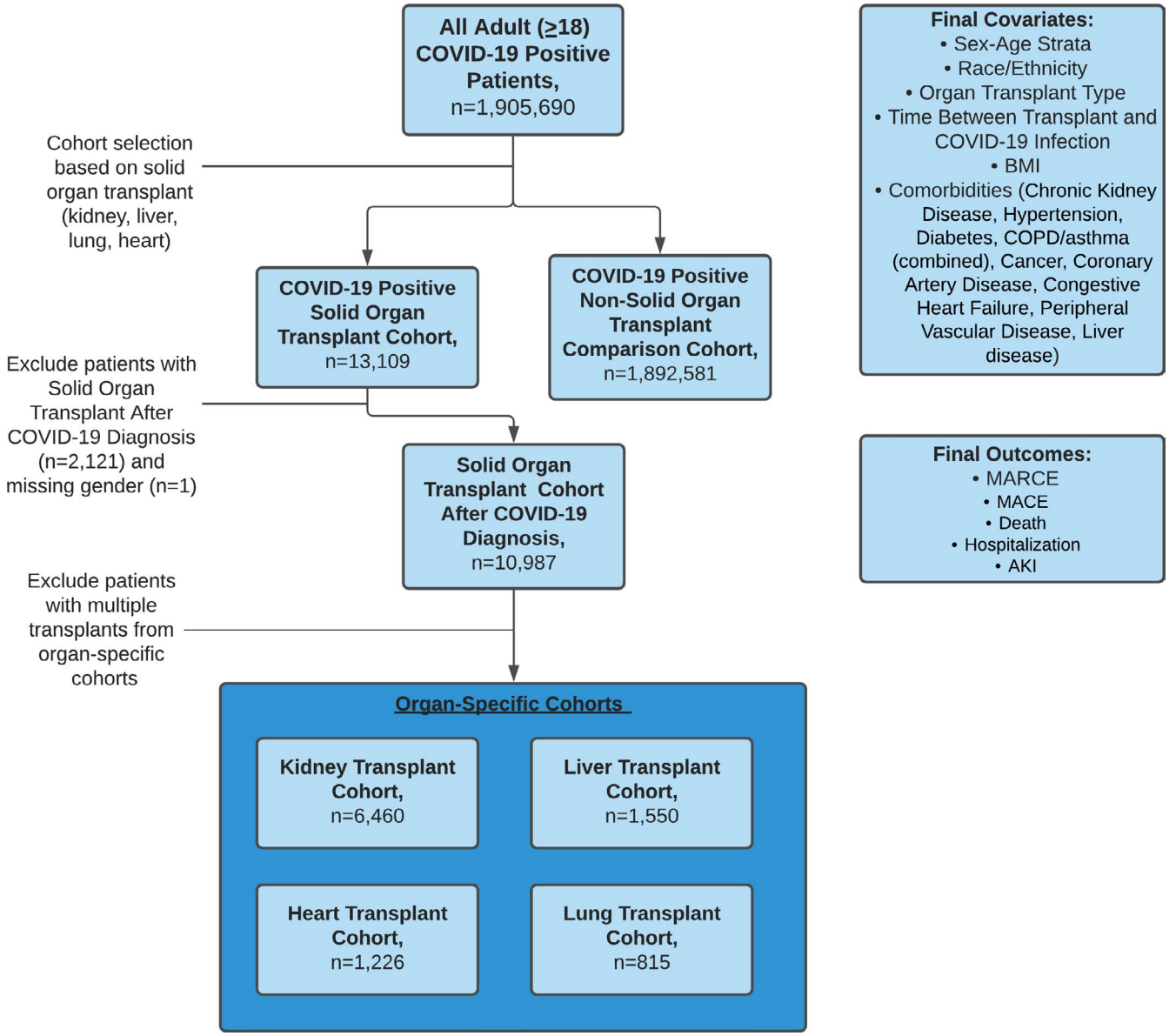

FIGURE 1 Consort diagram of solid organ transplant (SOT) and non-SOT patients in the N3C collaborative [Color figure can be viewed at wileyonlinelibrary.com]

3.1 | MARCE risk is less impacted by sex in COVID-19 positive transplant recipients

As expected, there was an increased risk of MARCE in both SOT and non-SOT populations with advancing age (HR 1.55, 95% CI 1.35–1.78 for SOT >65 relative to 18–45 years and HR 10.08, 95% CI 9.71–10.45 for non-SOT >65 relative to 18–45 years). Females overall had a lower risk of MARCE compared with males (HR 0.89, 95% CI 0.81–0.98 for SOT and 0.61, 95% CI 0.60–0.62 for non-SOT). Predictors of MARCE in the SOT and non-SOT cohorts are demonstrated in Table 2 and the adjusted hazard ratios for MARCE with female versus male sex within each age strata (18–45, 46–65, and >65 years) in those with and without SOT is demonstrated in Figure 2A. The standardized 90-day MARCE rates among the four different groups defined by sex and transplant status were 0.112 for female SOT, 0.152 for male SOT, 0.0347 for female non-SOT, and 0.0559 for male non-SOT. Overall risk reduction for MARCE in female versus male patients was mitigated in those with SOT (Table S1). Kaplan–Meier curves examining time to MARCE in SOT recipients are shown in Figure 2B.

The risk for MARCE was highest within the first 6 months after transplantation. The association between age-sex strata and MARCE was relatively preserved in those with a diagnosis of COVID-19 in the first 24 months posttransplant and in those diagnosed with COVID-19 >24 months posttransplant. Irrespective of the timing posttransplant, the relative risk of age-sex strata with MARCE in SOT recipients differed from that in the non-SOT population (Table S2).

TABLE 1 Baseline characteristics for COVID-19 positive solid organ transplant recipients and non-solid organ transplant recipients with and without a major adverse renal or cardiac event

	SOT with COVID N = 10 987			Non-SOT with COVID N = 1 890 246		
Exposure variable	N (%) with MARCE N = 3996 (36.4)	N (%) without MARCE N = 6991 (63.1)	p-value	N (%) with MARCE N = 91 646 (4.8)	N (%) without MARCE N = 798 600 (95.2)	p-value
Sex-age strata						
Male 18–45 (reference)	392 (9.8)	946 (13.5)	<.001	5073 (5.5)	397 239 (22.1)	<.001
Female 18–45	337 (8.4)	917 (13.1)	<.001	3131 (3.4)	528 609 (29.4)	<.001
Male 46–65	1219 (30.5)	2078 (29.7)	.402	18 525 (20.2)	277 141 (15.4)	<.001
Female 46–65	685 (17.1)	1387 (19.8)	.001	11 458 (12.5)	324 837 (18.1)	<.001
Male >65	855 (21.4)	1003 (14.3)	<.001	29 543 (26.1)	123 835 (6.9)	<.001
Female >65	508 (12.7)	660 (9.4)	<.001	23 916 (26.1)	146 939 (8.2)	<.001
Sex						
Male (reference)	2466 (61.7)	4027 (57.6)	<.001	53 141 (58.0)	798 215 (44.4)	<.001
Female	1530 (34.0)	2964 (42.4)	<.001	38 505 (42.0)	1000,385 (55.6)	<.001
Age						
18–45 (reference)	729 (18.2)	1863 (26.6)	<.001	8204 (9.0)	925 848 (51.5)	<.001
46–65	1904 (47.6)	3465 (49.6)	<.001	29 983 (58.3)	601 978 (15.1)	<.001
>65	1363 (34.1)	1663 (23.8)	.056	53 459 (32.7)	270 774 (33.5)	<.001
Race/Ethnicity						
White (reference)	1766 (44.2)	3623 (51.8)	<.001	46 642 (50.9)	883 668 (49.1)	<.001
Black	1191 (29.8)	1440 (20.6)	<.001	22 452 (24.5)	206 392 (11.5)	<.001
Hispanic	580 (14.5)	1045 (14.9)	.557	10 254 (11.2)	224 186 (12.5)	<.001
Other	459 (11.5)	883 (12.6)	.083	12 298 (13.4)	484 354 (26.9)	<.001
Organ transplant						
Kidney	2799 (70.0)	4463 (63.8)	<.001			
Liver	631 (15.8)	1509 (21.6)	<.001			
Lung	395 (9.9)	663 (9.5)	.514			
Heart	580 (14.5)	937 (13.4)	.110			
Time between transplant and COVID infection						
>24 months (reference)	2048 (51.3)	3438 (49.2)	.038			
6–24 months	1047 (26.2)	2228 (31.9)	<.001			
<6 months	901 (22.5)	1325 (19.0)	<.001			
Comorbidities						
Chronic kidney disease	3263 (81.7)	4364 (62.4)	<.001	29 212 (31.9)	44792 (2.5)	<.001
Hypertension	3672 (91.9)	5611 (80.3)	<.001	61 764 (67.4)	334331 (18.6)	<.001
Diabetes	2695 (67.4)	3579 (51.2)	<.001	42 226 (46.1)	185054 (10.3)	<.001
COPD/asthma (combined)	881 (22.0)	1123 (16.1)	<.001	21 640 (23.6)	134540 (7.5)	<.001
Cancer	667 (16.7)	1047 (15.0)	.018	12 729 (13.9)	64218 (3.6)	<.001
Coronary artery disease	1480 (37.0)	1614 (23.1)	<.001	23 914 (26.1)	57454 (3.2)	<.001
Congestive heart failure	1678 (42.0)	1567 (22.4)	<.001	30 357 (33.1)	37836 (2.1)	<.001
Peripheral vascular disease	1131 (28.3)	1278 (18.3)	<.001	15 893 (17.3)	49064 (2.7)	<.001
Liver disease	637 (15.9)	1147 (16.4)	.542	4877 (5.3)	15294 (0.9)	<.001
Obesity (BMI≥30)	980 (24.5)	1628 (23.3)	.078	22 101 (24.1)	216007 (12.0)	<.001
Obesity missing	1543 (38.6)	2678 (38.3)	.766	45 361 (49.5)	1303152 (72.5)	<.001

TABLE 2 Adjusted hazard ratios for the outcome of major adverse renal or cardiac events in COVID-19 positive patients with and without solid organ transplant

	SOT with COVID			Non-SOT with COVID		
Exposure variable	HR for MARCE	95% CI for MARCE	*p*-value	HR for MARCE	95% CI for MARCE	*p*-value
Sex-age strata						
Female 18–45	0.84	0.68–1.05	.120	0.40	0.37–0.42	<.001
Male 18–45 (reference)	Ref	—	—	Ref	—	
Female 46–65	0.96	0.80–1.15	.632	1.74	1.65–1.83	<.001
Male 46–65	1.01	0.95–1.20	.898	3.34	3.18–3.50	<.001
Female >65	1.31	1.07–1.59	.008	5.45	5.20–5.72	<.001
Male >65	1.54	1.28–1.84	<.001	7.72	7.36–8.09	<.001
Race/Ethnicity						
White (reference)	Ref	—	—	Ref	—	
Black	1.25	1.12–1.41	<.001	1.67	1.63–1.71	<.001
Hispanic	1.02	0.88–1.19	.749	1.23	1.19–1.27	<.001
Other	1.09	0.94–1.27	.272	1.17	1.13–1.20	<.001
Organ transplant						
Kidney	1.21	1.03–1.43	.023			
Liver	1.01	0.85–1.20	.909			
Lung	1.41	1.17–1.71	<.001			
Heart	0.94	0.78–1.14	.553			
Time between transplant and COVID infection						
>24 months (reference)	0.79	0.70–0.89	<.001			
6–24 months	0.67	0.59–0.76	<.001			
<6 months	Ref	—	—			
Comorbidities						
Chronic kidney disease	1.53	1.35–1.72	<.001	2.08	2.03–2.13	<.001
Hypertension	1.33	1.13–1.58	.001	1.16	1.13–1.19	<.001
Diabetes	1.22	1.10–1.36	<.001	1.30	1.27–1.33	<.001
COPD/asthma (combined)	1.15	1.03–1.30	.017	1.15	1.12–1.18	<.001
Cancer	1.08	0.96–1.22	.212	1.15	1.12–1.18	<.001
Coronary artery disease	1.10	0.99 –1.23	.073	1.19	1.16–1.22	<.001
Congestive heart failure	1.50	1.34–1.67	<.001	2.22	2.16–2.27	<.001
Peripheral vascular disease	1.16	1.04–1.29	.009	1.15	1.12–1.18	<.001
Liver disease	0.97	0.83–1.13	.676	1.46	1.40–1.53	<.001
Obesity (BMI≥30)	1.05	0.93–1.19	.427	1.00	0.97–1.02	.750
Obesity missing	1.18	1.06–1.32	.003	0.82	0.81–0.84	<.001

Pre-existing CKD, hypertension, diabetes, COPD/asthma, congestive heart failure and peripheral vascular disease were all associated with an increased risk of MARCE in the SOT cohort (Table 2). All comorbidities examined except obesity were associated with MARCE after COVID-19 diagnosis in the non-SOT cohort. Those of black race were more likely to experience MARCE in both the SOT and non-SOT cohort compared with white race (HR 1.25, 95% CI 1.12–1.41 and HR 1.67, 95% CI 1.63–1.71, respectively).

3.2 | Secondary analyses

3.2.1 | COVID-19 risk is independently associated with SOT status

In the combined SOT and non-SOT cohorts, SOT was independently associated with the risk of MARCE (HR 1.56, 95% CI 1.48–1.64). SOT was also associated with an increased risk of AKI (HR 1.73, 95% CI 1.64–1.82), mortality (HR 1.15, 95% CI 1.07–1.24), and slightly

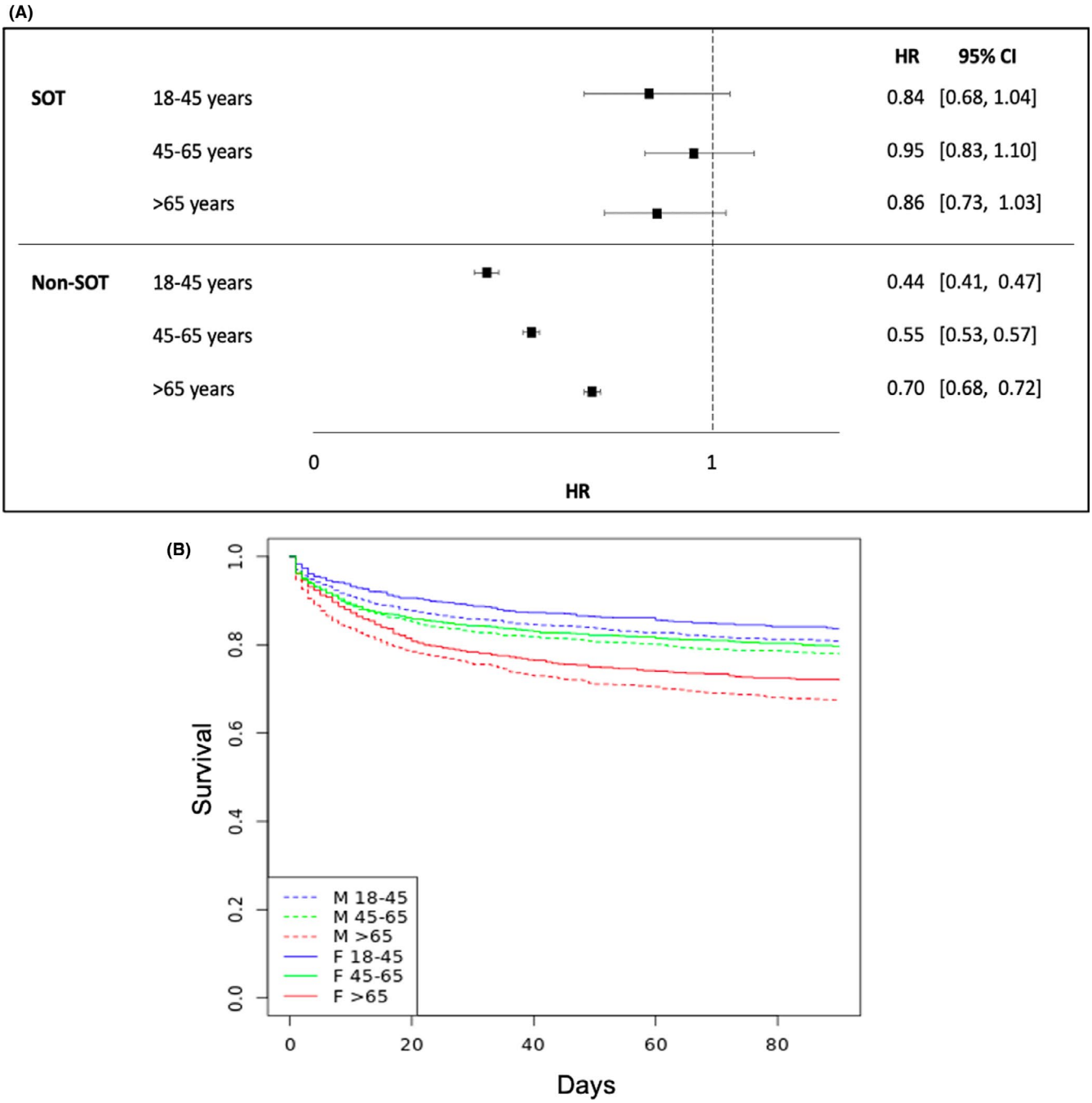

FIGURE 2 (A) Hazard ratios for major adverse renal or cardiac events (MARCE) in COVID-19 positive patients, comparing female to male patients with and without solid organ transplants, stratified by age. Analysis is adjusted for race, organ transplant type, time since transplant, comorbidities (chronic kidney disease, hypertension, diabetes, COPD/asthma, cancer, coronary artery disease, congestive heart failure, peripheral vascular disease, liver disease, obesity). (B) Kaplan–Meier curves for the time to MARCE events in SOT recipients, stratified by sex and age

worse COVID-19 severity (need for hospitalization) (OR 1.03, 95% CI 1.02–1.03); median time from COVID-19 diagnosis to hospitalization was 1 day (IQR 0–8) and 1 day (0–5) in SOT and non-SOT patients, respectively. SOT status was not associated with MACE (HR 1.03, 95% CI 0.95–1.12) when accounting for the effects of pre-existing CHF and CKD, however, when not adjusting for these factors, the association of SOT with MACE after COVID-19 diagnosis was significant (HR 1.52, 95% CI 1.40–1.65) (Table S3).

3.2.2 | Individual MARCE endpoints are differentially affected by sex in SOT and non-SOT

The adjusted hazard ratios for individual endpoints (MARCE, mortality, MACE, AKI, and severe COVID-19) for female versus male sex in SOT and non-SOT cohorts are shown in Figure 3. Overall, female SOT patients had a small reduction in risk of MARCE and mortality (but not MACE, AKI, or COVID-19 severity) compared

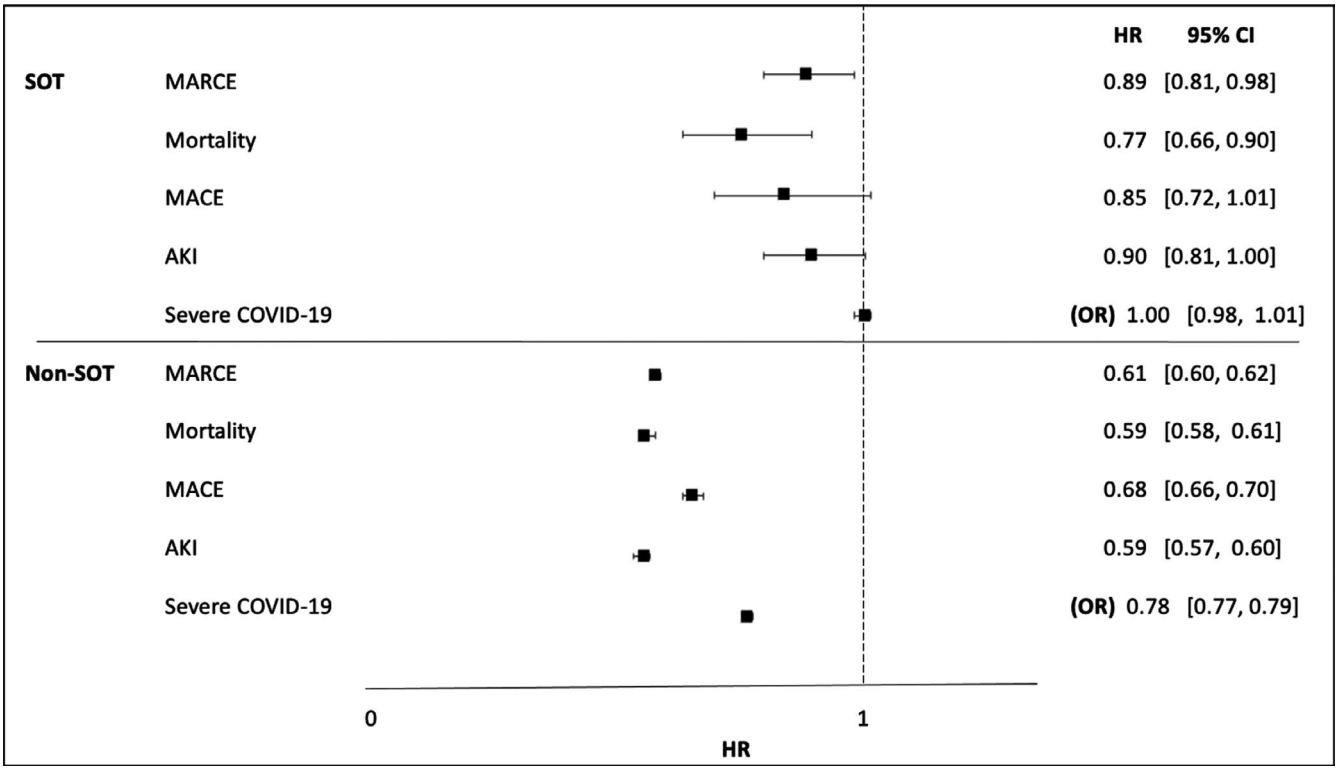

FIGURE 3 Hazard ratios for individual outcomes (MARCE, mortality, MACE, AKI) and odds ratio for hospitalization in COVID-19 positive patients comparing females to males with and without SOT. Analysis was adjusted for age group, race, organ transplant type, time since transplant, comorbidities (chronic kidney disease, hypertension, diabetes, COPD/asthma, cancer, coronary artery disease, congestive heart failure, peripheral vascular disease, liver disease, obesity)

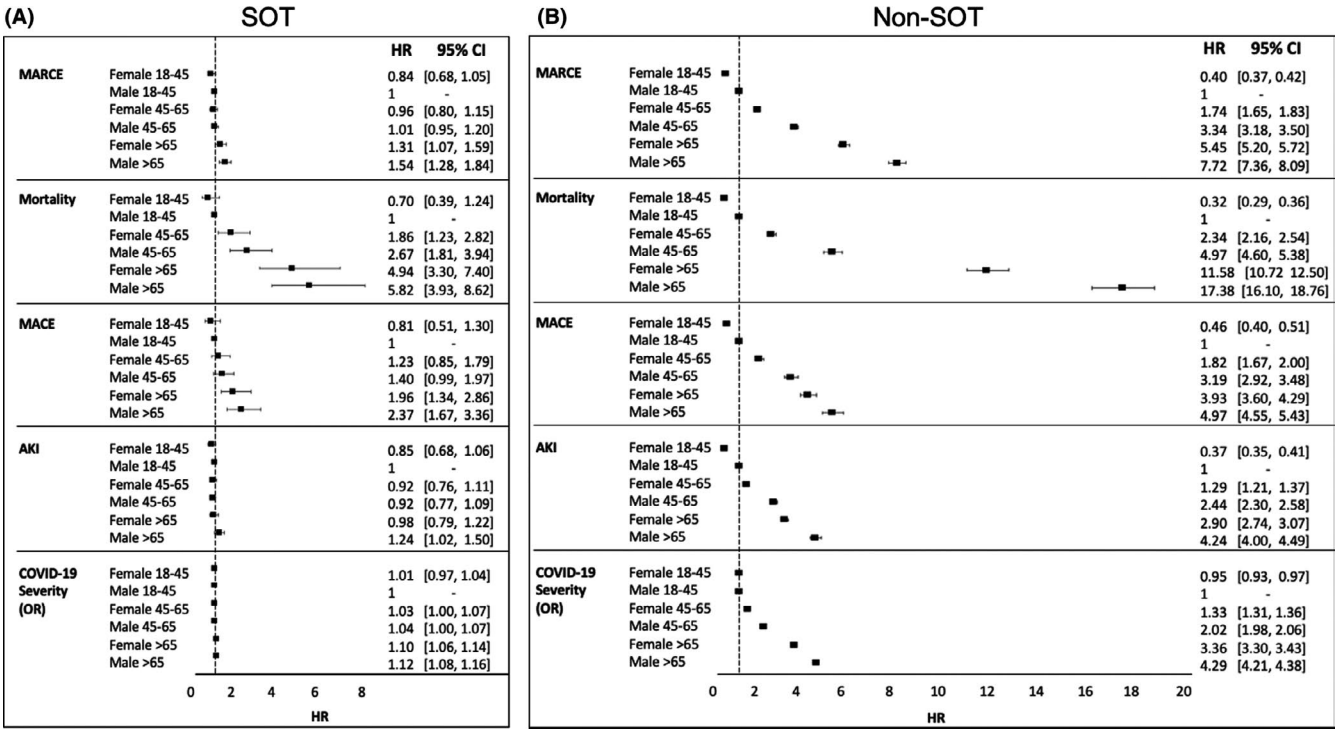

FIGURE 4 Adjusted hazard ratios for the 90-day outcomes of MARCE, death, MACE, and AKI and the adjusted odds ratio for hospitalization in COVID-19 positive patients (A) with solid organ transplants and (B) without solid organ transplant, based on sex-age stratification. Adjusted for race, organ transplant type, time since transplant, comorbidities (chronic kidney disease, hypertension, diabetes, COPD/asthma, cancer, coronary artery disease, congestive heart failure, peripheral vascular disease, liver disease, obesity)

with male SOT patients, whereas females without SOT were significantly lower risk for all endpoints compared with males. When we evaluated the adjusted impact of sex and age on each endpoint, SOT males and females had similar age-stratified risk profiles with overlapping confidence intervals in most cases for each of the five endpoints (Figure 4A). Conversely, in the non-SOT cohort, within each age strata, female sex was protective against all outcomes (Figure 4B).

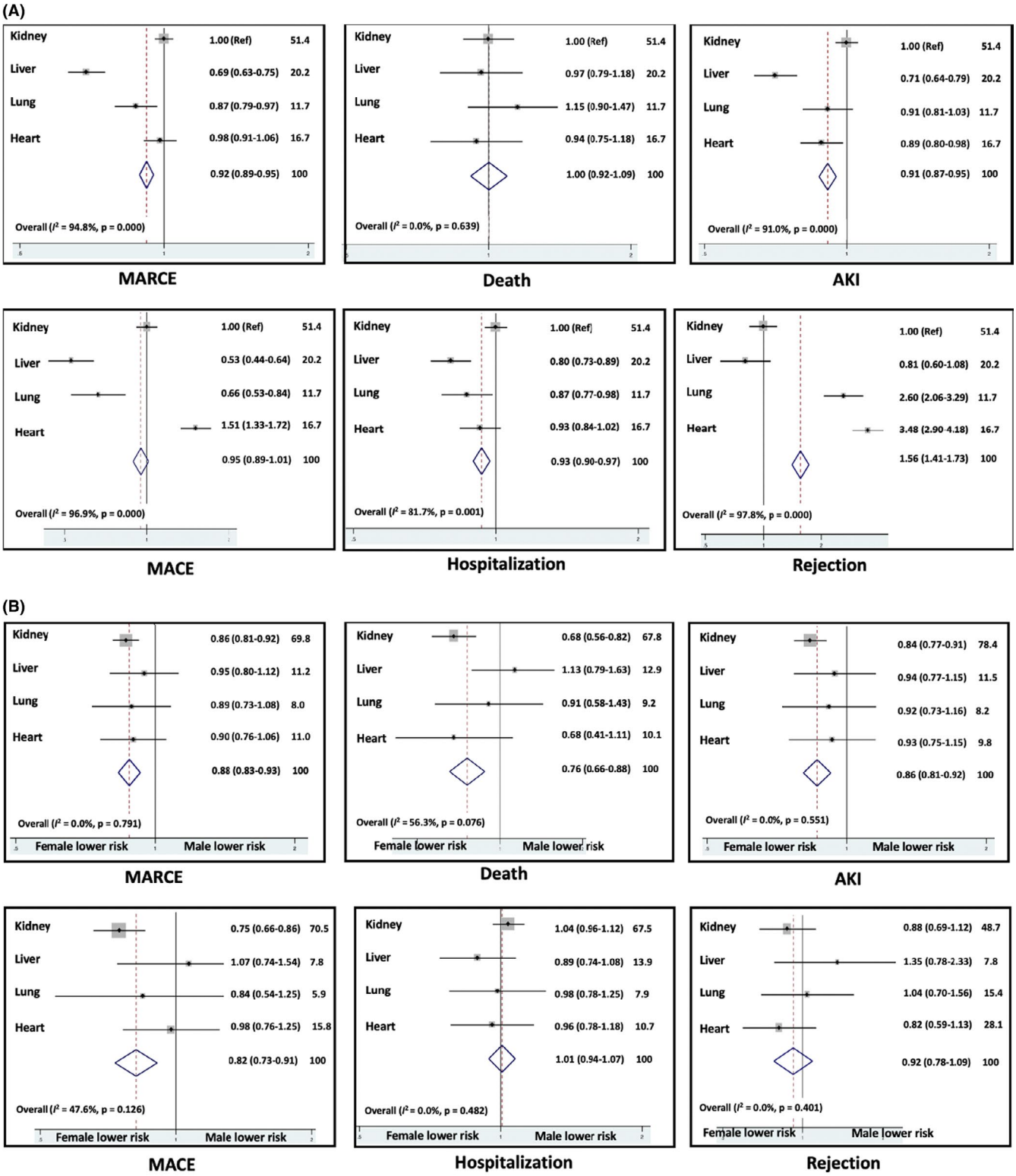

FIGURE 5 Meta-analysis of relative risk (95% CI) for the outcomes of MARCE, MACE, death, hospitalization, AKI, and rejection after COVID-19 diagnosis by (A) transplant organ type relative to kidney transplant (B) female versus male sex stratified by organ type [Color figure can be viewed at wileyonlinelibrary.com]

3.2.3 | Organ-specific analyses

We examined the risk of each primary and secondary outcome stratified by organ type relative to those without SOT (Figure S4), and relative to those with a kidney transplant only (Figure 5A). Kidney transplant recipients (n = 6460) accounted for the largest population in the SOT cohort, followed by liver (n = 1550), lung (n = 815), and heart (n = 1226). Each organ-specific transplant population had a significantly higher risk of MARCE (RR 5.44–7.87), MACE (RR 3.69–10.53), death (RR 4.69–5.73), hospitalization (RR 2.61–3.25), and AKI (RR 7.38–10.43) with COVID-19 compared to those without a transplant (Figure S4). Heterogeneity between organ types was high for all outcomes except death (I^2 > 80%). In most cases, kidney transplant patients were at the highest relative risk; however, there were no organ-specific differences in death risk, and heart transplant recipients experienced significantly more MACE (Figure 5A). Importantly, organ rejection was significantly higher in those with a lung (RR 2.60, 95% CI 2.06–3.29) and heart (RR 3.48, 95% CI 2.90–4.18) transplant compared to those with a kidney transplant.

Finally, we assessed the potential impact of the specific type of organ transplanted for the association of age and sex with MARCE (Tables S4A–D), examining the overall risk in females versus males for each primary and secondary outcome (including organ rejection) by organ type (Figure 5B). Females with a kidney transplant were at lower risk than males for all outcomes except hospitalization and rejection. There were no sex-based differences noted in any of the other organ systems and no sex-based heterogeneity for any outcome (p-value >.05 for all analyses). When stratifying by age, there were no significant age-sex associations with MARCE in any of the individual organ types (Table S5).

4 | DISCUSSION

Our analysis of COVID-19 in SOT patients is the largest to date, including nearly 11 000 SOT recipients and over 1.8 million non-SOT patients. Our study demonstrates an increased risk of MARCE, MACE, AKI, COVID-19 severity, and all-cause mortality in SOT patients with COVID-19 compared with the general population. Being the largest and most granular database of SOT COVID-19 patients thus far, our work examined two novel questions; (i) the COVID-19 risk associated with specific transplant allograft type (i.e., kidney, liver, lung, and heart), and (ii) the role of SOT recipient sex in predicting COVID-19 outcomes.

Earlier studies have shown kidney,[7,10,21] lung,[26,27] and heart[28] transplant recipients to be at high COVID-19 risk compared to non-SOT patients, and liver transplant recipients to be at the same or lower risk than the general non-SOT population for reasons unknown.[29,30] However, this is the first large-scale analysis to compare COVID-19 outcomes directly between different allograft types. A recent meta-analysis of 2772 unique SOT recipients with COVID-19 included kidney, liver, lung, and heart transplant recipients, but did not compare results by organ type.[31] A much smaller cohort study of Spanish SOT recipients failed to demonstrate any organ-specific differences in COVID-19 outcomes; however, included less than 100 liver, lung, and heart recipients combined and was thus underpowered for this comparison.[32]

In the absence of SARS-CoV-2 infection, lung transplant recipients have the highest posttransplant mortality rate, followed by heart, liver, and kidney recipients.[17] However, the cumulative probability of cardiovascular disease has been shown to be significantly higher in heart and kidney transplant recipients (excess absolute risk [EAR] 458.3/10 000 person-years for heart recipients and 86.2/10 000 person-years for kidney recipients), compared to 26.6/10 000 person-years in liver transplant recipients.[17] This may explain the higher risk of MARCE, MACE and hospitalization we demonstrate in kidney and heart transplant recipients compared to liver and lung recipients, especially given the known compound effects of COVID-19 on the cardiovascular system.[33] However, we show that all organ transplant types (including liver) have worse COVID-19 outcomes than the non-SOT comparator population, contrary to earlier studies demonstrating liver transplant to be protective.[29,30] Finally, in our study, lung and heart transplant recipients were at highest risk for organ rejection in the 90 days after COVID-19 diagnosis. This may relate to systemic differences in immunosuppression and immunogenicity between organ types; lung and heart allografts evoke a stronger immune response than kidney, and especially, liver allografts.[34]

Interestingly, females were at lower risk than males for MARCE, MACE, death and AKI if they had a kidney transplant; however, there were no sex-based differences for any other organ type. Furthermore, in the 90 days after COVID diagnosis, there was no sex bias in hospitalization or rejection rates for any transplant type, despite females without COVID-19 being higher risk for SOT rejection.[35]

Our study investigates the impact of sex and age in a complex patient population at high risk for infections and resulting infectious complications.[36-39] In the general population, males have a significantly higher COVID-19-related mortality than females do.[3,5] Estradiol is generally immune enhancing and testosterone immune suppressing[40] thus in the immunocompetent state, females have a more robust anti-viral immune response than males.[41] As endogenous steroids decrease with advancing age (rapidly in post-menopausal females and more gradually in males) there is a parallel functional decline in the immune system,[42] which may explain the attenuated benefit we demonstrate for the first time in aging non-SOT females versus males in response to COVID-19 (Figure 2). "Inflam-aging" refers to a decline in adaptive immunity and a dysregulated activation of the innate immune system with advancing age.[43] This is more prominent in older males than females (though effects both sexes) and is associated with an increased risk of cytokine storm following SARS-CoV-2 infection and thereby, COVID-19 related death.[5] Hyperinflammation following SARS-CoV-2 infection has also been proposed to contribute to vascular inflammation and plaque instability, with resulting myocardial infarction, cardiomyopathy and heart

failure[44,45]; further contributing to the increased risk of COVID-19 related cardiovascular morbidity in older immunocompetent males compared with females.

These sex disparate outcomes have not been previously observed in the SOT population.[7,10,13,16,18-20]

In our study, we demonstrate for the first time that SOT males with COVID-19 also have an increased risk of MARCE compared with females, albeit to a lesser degree than in the general population (11% vs. 39% reduction in the hazard of MARCE with female vs. male sex in SOT and non-SOT cohorts, respectively). In SOT recipients, maintenance immunosuppression may have a differential impact on COVID-19 risk in males and females. While maintenance immunosuppression is a risk for infection in all SOT patients, it may disproportionately impact females, mitigating their relative benefit versus males when infected with SARS-CoV-2. Additionally, there may in fact be a paradoxical benefit with immunosuppression reducing the exaggerated and often fatal immune reaction to COVID-19 that disproportionately impacts older males. In keeping with this hypothesis, it is interesting to note that critically ill male patients with COVID-19 appeared to benefit most from dexamethasone immunosuppressive therapy in the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial.[46,47] Likewise, in hypoxic hospitalized patients with COVID-19, the RECOVERY Collaborative group demonstrated reduced mortality with the interleukin (IL)-6 inhibitor, Tocilizumab[48]; this result was again only significant in male patients.

In the non-SOT population, differences by sex were most pronounced in the youngest (reproductive) age strata, followed by mid-age (peri-menopause/andropause), and finally by the oldest group (post-menopause/andropause). On the contrary, age did not impact observed sex differences in those with SOT. These findings are important as they provide a better understanding of the pathophysiology driving COVID-19 risk (indicating a potential role of sex hormones in the COVID-19 response). Furthermore, it risk stratifies individuals with COVID-19 disease; highlighting the critical importance of considering sex (and age)-stratified analyses when examining outcomes related to COVID-19. As demonstrated here, differences in males and females may result in a sex-based risk profile that varies by age in immunocompetent, but not immunosuppressed populations.

A strength of this study is that it includes both inpatient and outpatient SOT recipients with a positive COVID-19 test, unlike most other studies of COVID-19 in SOT where the cohort is incepted at the time of hospitalization.[14,15,49] These reports provide a false impression of disease severity as the population included is biased towards those sick enough to require admission. Earlier studies of hospitalized SOT and non-SOT patients have shown similar outcomes after adjusting for comorbidity burden, however as we show, SOT is associated with a higher likelihood of hospitalization (although this may reflect a lower threshold to hospitalize less sick SOT recipients). For the first time, we compare outcomes in SOT patients to the general non-SOT population to determine if there are predictors of MARCE that differ between these two groups. Finally, we directly examine and meta-analyze organ-specific COVID-19 risk; a novel comparison.

This study has limitations, however. Given the retrospective nature of our analysis, it is subject to bias related to miscoding and misclassification of patient covariates or outcomes. Patients with missing records for comorbidities may have been misclassified as not having them which might attenuate the true signal; however, collection data was complete for those with mandatory inputs (i.e., age, sex, race, etc.) and thus we expect missingness of comorbidity data to be small and randomly distributed. Furthermore, although we had comprehensive encounter information from contributing data partners, primarily representing tertiary care centers, we did not have access to community-based health records. This data set is unable to provide consistent access to biomarker testing, such as IL-6 and TNFα levels, which varied from center to center and over time of the pandemic. Likewise, we did not have access to measured sex hormones. Finally, there is considerable heterogeneity across studies in the definition for MARCE, including the criteria used to identify cardiovascular and renal events. Lacking granular eGFR data, we did not include this in our criteria for MARCE. Some studies restrict cardiac events to only those experiencing ischemic endpoints, whereas like our present study, others include non-ischemic cardiovascular events such as arrhythmia, heart failure and stroke as outcomes. This heterogeneity may lead to a lack of generalizability between studies, but our definition for MARCE is consistent with earlier literature.

In conclusion, SOT patients with COVID-19 are at an increased risk of MARCE (and other adverse outcomes) relative to their non-SOT counterparts. Similar to the general population, the risk of MARCE was increased with male sex, albeit to a lesser degree than in the immunocompetent non-SOT cohort. Finally, we demonstrate significant heterogeneity in the risk of adverse outcomes post COVID-19 diagnosis by transplant allograft type, with the greatest risk in heart and kidney recipients. This is the largest COVID-19 SOT cohort to date and the first-time sex-age–stratified COVID-19 outcomes have been explored in those with (and without) SOT. Finally, we provide a novel analysis of differential COVID-19 outcomes in SOT recipients by allograft type.

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DATA AVAILABILITY STATEMENT

All diagnostic, medication, procedure, and laboratory concepts and raw code (R, Python, SQL) used in this study are available in a GitHub repository. N3C is a public resource maintained by NCATS to support COVID-19 research. Investigators can request access to the Enclave here.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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APPENDIX

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