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Outcomes of transplant recipients on ECMO for COVID-19 respiratory failure: an ELSO registry study

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Abstract

Background ECMO outcomes in COVID-19-related respiratory failure among solid organ transplant (SOT) and hematopoietic stem-cell transplant recipients (HSCT) are poorly described. We investigated: (1) whether transplant patients (SOT/HSCT) with COVID-19 have worse outcomes than non-immunocompromised (IC) COVID-19 patients, and (2) whether among transplant recipients (SOT/HSCT), those with COVID-19 have worse outcomes than those with non-COVID-19-related respiratory failure. Additionally, we aimed to identify factors independently associated with mortality among COVID-19 transplants.

Methods Retrospective analyses of the Extracorporeal Life Support Organization Registry from 1/1/2017 to 31/07/2023. Two comparisons were made: (1) transplant COVID-19 versus non-IC COVID-19, and (2) transplant COVID-19 versus transplant non-COVID-19 patients. Outcomes were analyzed using propensity score (PS)-adjusted, multivariable, and PS-matched analyses, adjusting for a priori identified confounders. Primary outcome was in-hospital mortality.

Results Among 38,270 runs, 146 transplant COVID-19, 12,552 non-IC-COVID-19 and 886 transplant non-COVID-19 runs were identified. In-hospital mortality in transplant COVID-19 patients was 75.3% and the risk was invariably increased compared to non-IC-COVID-19 (PS-adjusted OR: 2.36 [95%CI:1.61–3.46], $p < 0.001$, multivariable OR:2.35 [95%CI:1.59–3.49], $p < 0.001$, and PS-matched analysis OR: 1.89 [95%CI:1.21–2.95], $p < 0.005$) and transplant non-COVID-19 patients (PS-adjusted OR: 4.20 [95%CI:2.74–6.44], $p < 0.001$, multivariable OR: 3.79 [95%CI:2.51–5.74], $p < 0.001$, and PS-matched analyses OR: 3.17 [95%CI:1.90–5.28], $p < 0.001$). Mortality difference remained stable over time. Older age independently associated with higher mortality. This was accompanied by higher need for renal replacement therapy compared to non-IC-COVID-19 patients. Compared to transplant non-COVID-19 patients, ECMO runs and time-to-live discharge were invariably prolonged. Hemorrhagic, metabolic, pulmonary and infectious complications consistently occurred more frequently.

Conclusions Mortality was high in COVID-19 transplant ECMO patients, warranting cautious use of ECMO in this population.

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Keywords Extracorporeal membrane oxygenation, Respiratory failure, COVID-19, Transplant

Background

The COVID-19 pandemic posed significant challenges for immunocompromised (IC) patients, particularly those with solid organ transplantation (SOT) or hematopoietic stem-cell transplantation (HSCT) [1–5]. Short-lived protective immunity and poor vaccine responses render these patients vulnerable to life-threatening COVID-19 infections [3, 4, 6, 7]. During the pandemic, cases with intractable respiratory failure overwhelmed ICUs worldwide. Before the pandemic, extracorporeal membrane oxygenation (ECMO) was well-established as the standard treatment for refractory respiratory failure [8]. Early pandemic experience with ECMO seemed quite comparable to other conditions [9, 10], leading to application of general respiratory ECMO guidelines to COVID-19 cases as well [11–13]. However, being immunocompromised increases mortality in patients undergoing respiratory ECMO, both in general [14–17] and in COVID-19 populations [9, 18, 19]. Pre-COVID-19 data, though, suggest that among this heterogeneous population of immunocompromised ECMO patients, those with SOT or HSCT in the late post-transplant period may have better prognosis than other IC patients [20–22]. Data on COVID-19-related ECMO outcomes in SOT and HSCT patients are very scarce, with only one case series involving five kidney transplants patients, raising concerns about the appropriateness of ECMO in this context [23].

This study aimed to determine suitability of ECMO for these vulnerable groups. Specifically, we aimed to investigate: (1) whether transplant recipients (SOT/HSCT) with COVID-19 have worse outcomes than non-IC-COVID-19 patients receiving ECMO for respiratory failure, and (2) whether among transplant recipients (SOT/HSCT), those with COVID-19 have worse outcomes than those with other causes of respiratory failure. Additionally, we explored factors associated with mortality among COVID-19 transplant recipients.

Methods

Data source

We queried the international Extracorporeal Life Support Organisation (ELSO) registry and identified solid organ, bone marrow or stem cell transplant recipients through the International Classification of Diseases 10th version (ICD-10) and Current Procedural Terminology (CPT) codes (Table S1, Additional file 1). Patient characteristics, including COVID-19 status, treatments and outcomes were collected in accordance with ELSO definitions [24]. The study was approved by the Institutional Ethical Committee.

Patients

Adults (age ≥ 18years) receiving ECMO for respiratory failure between January 1, 2017 and July 31, 2023 were eligible for inclusion. We first excluded: (1) other than first runs, (2) patients with a pre-ECLS decision to bridge-to-transplant, (3) peri-transplant runs, identified on either: (a) transplant-related CPT-codes and procedure timing marked as 'on-ECMO' or 'post-ECMO' (within 30 days after stopping ECMO), (b) lung transplant-related CPT-codes with procedure timing marked 'pre-ECMO' (within 30 days prior to ECMO run), (c) ECMO discontinuation reason marked as transplantation, (4) unknown COVID-19 status in runs from 2020 onwards, (5) suspected but untested COVID-19 cases from 2020 onwards. For confirmed COVID-19 cases, we further excluded immunocompromised patients other than transplants, identified through ICD-10 codes (Table S2, Additional file 1) or COVID-19 comorbidity fields 'immunocompromised' or 'cancer'. For non-COVID-19 patients, non-transplant recipients were excluded. This stepwise process resulted in three patient groups: transplant (Tx)-COVID-19, non-immunocompromised (non-IC)-COVID-19 and Tx-non-COVID-19 patients.

Outcomes

Primary outcome was in-hospital mortality. Secondary outcomes included time-on-ECMO, registry-defined complications (cardiovascular, hemorrhagic, mechanical, metabolic, neurological, pulmonary, renal, infectious, limb complications, need for repair), hospital length-of-stay, and discharge location.

Confounders

In line with current recommendations for explanatory modeling [25], analyses were adjusted for confounders pre-identified from respiratory ECMO and COVID-19-specific ECMO literature. For the Tx COVID-19 versus non-IC COVID-19 comparison, these included: age, sex, BMI, chronic respiratory and heart disease, chronic renal insufficiency, diabetes, co-infection, septic shock, pneumothorax, acute renal failure, pO_2/FiO_2, PIP, PEEP, pH, pCO_2, pre-ECMO lactate, pre-ECMO arrest, intubation-to-time on ECMO, pre-ECMO prone positioning, NMBA use and vasopressors/inotropes, CRP, corticosteroids, cannulation mode, transport on ECMO, and center experience. For the Tx COVID-19 vs. Tx non-COVID-19 comparison, confounders included: age, sex, BMI, chronic respiratory and heart disease, respiratory rate, pO_2/FiO_2, PIP, PEEP, pH, pCO_2, HCO_3^-, pre-ECMO lactate, mean arterial pressure, pre-ECMO arrest, intubation-to-time on ECMO, pre-ECMO renal replacement

therapy, inhaled NO, prone positioning, NMBA use, vasopressors/inotropes, IV bicarbonate, cannulation mode, transport on ECMO, and center experience. Septic shock and acute renal failure, identified as relevant confounders, were not available in the data structure. Vasopressors/inotropes were taken as a proxy for septic shock, while pre-ECMO RRT was considered a proxy for severe acute kidney injury. (see Additional File 1, Table S3 and S4).

Statistics

Continuous variables are summarized as median and interquartile range, categorical variables as frequencies and proportions. Data were analysed with SAS, version 9.4, SAS Institute Inc (2002). Statistical tests were 2-sided and considered significant at $p \leq 0.05$. No adjustments were made for multiple testing as our aim was not confirmatory testing but to generate clinically relevant insights to guide future research and care. Data were assumed to be missing at random (MAR) and multiple imputations (100 datasets, fully conditional specification) were performed [26, 27]. Results were pooled with Rubin's rule.

Two comparisons were made: (1) Tx-COVID-19 versus non-IC-COVID-19, (2) Tx-COVID-19 versus Tx-non-COVID-19. Baseline characteristics were compared with Wilcoxon test for continuous and chi-squared or Fisher's exact for categorical variables. For outcomes, several confounder-adjusted analyses were performed for each comparison, including propensity-score (PS)-adjusted, multivariable and PS-matched analyses (details in Additional file 1).

Sensitivity analyses

Patients without clinical suspicion of COVID-19 and without testing were retained in the main analysis, as the database explicitly distinguished unknown cases and cases without clinical suspicion and without testing. We considered that high clinical suspicion combined with low testing thresholds made undiagnosed COVID-19 unlikely. Recognizing some residual uncertainty, we performed sensitivity analyses excluding this group from the Tx-non-COVID-19 cohort.

Exploratory analyses

To identify potential drivers of differences in complication rates, the incidence of registry-defined subcategories of each complication was compared. Significant effects in the Tx-COVID-19 versus Tx-non-COVID-19 comparison were further examined across transplant subgroups. These subgroups included heart, lung, kidney, liver and other transplants, with the latter category grouping those with fewer than 10 cases. This analysis aimed to identify any differential patterns of effect across various transplant groups. Multivariable logistic regression was performed to assess factors associated with mortality in Tx-COVID-19 patients.

Results

Patients and characteristics

The registry contained 38,270 ECMO runs for respiratory failure between January 1st, 2017 and July 31st 2023. After excluding 5,027 non-first runs, bridge-to-transplant, peri-transplant runs, and those with unknown or unconfirmed COVID-19 status, 13,161 COVID-19-related and 20,082 non-COVID-19-related runs remained. Among COVID-19-related runs, 146 were Tx-COVID-19 and 12,552 non-IC-COVID-19 patients. For non-COVID-19-related runs, 886 were Tx-non-COVID-19 patients (Fig. 1). SOT accounted for 94.5% of all transplants, as the number of hematological transplants was very low.

Median ages were 55(48–61), 48(38–56) and 58(45–65) years in Tx-COVID-19, non-IC-COVID-19 and Tx-non-COVID-19 patients (Table 1). Most patients were male (70%, 70%, 58% respectively). Median ECMO run duration was 520 h (329–845), 467 h (237–839), and 141 h (65–313), in Tx-COVID-19, non-IC-COVID-19 and Tx-non-COVID-19 patients (Table S5). Compared to non-IC-COVID-19 patients, Tx-COVID-19 patients were older, had lower BMI and more frequently had comorbidities such as chronic respiratory, heart or renal disease and diabetes. Septic shock and acute renal failure were present more often than in the non-IC-COVID-19 patients. Respiratory failure was less severe, as indicated by pre-ECMO PO_2/FIO_2 and pCO_2, consistent with lower PEEP, less frequent use of prone ventilation and neuromuscular blocking agents (NMBAs), possibly reflecting initiation of ECMO at a slightly earlier stage of respiratory failure in this vulnerable population with reduced physiological reserve. Expectedly, Tx-COVID-19 patients more frequently received corticosteroids and were treated in experienced centers, while being less often transported on ECMO. Likewise, COVID-19 vaccination was more common in this group (41% vs. 4.8%, Table S6).

Tx-COVID-19, compared to Tx-non-COVID-19 patients, more frequently were male, had higher BMI and less often had chronic respiratory disease. Prior to ECMO, Tx-COVID-19 patients had higher respiratory rates, peak pressures, and PEEP levels, indicating more severe respiratory disease, consistent with the increased use of proning and NMBAs. They had longer times from intubation to ECMO initiation, were more often placed on VV-ECMO and transported on ECMO than Tx-non-COVID-19 patients. However, mean blood pressure was higher, lactate levels were lower and pre-ECMO arrest occurred less frequently.

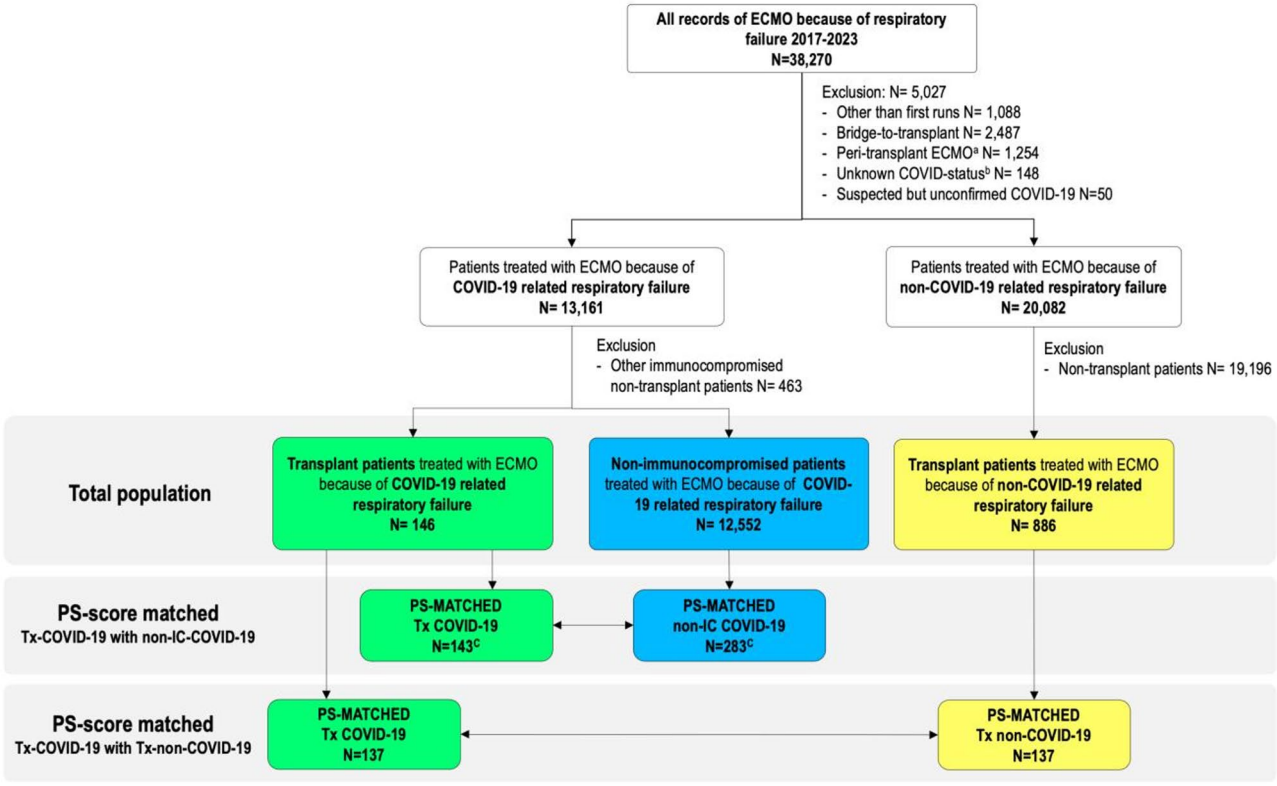

Fig. 1 Patient flow chart.[a] Peri-transplant ECMO was defined as either (1) transplant-related CPT code and procedure timing marked as 'on ECMO' or 'post ECMO' (within 30 days of stop ECMO), (2) lung transplant-related CPT code and procedure timing marked as 'pre-ECMO' (within 30 days prior to ECMO run), (3) reason for discontinuation of ECLS labeled as transplantation; [b] All ECMO runs before 2020 were considered non-COVID-19; [c] 1–2 PS matching except for 3 patients for whom no second match could be established due to the predefined caliper. *ECMO*: extracorporeal membrane oxygenation; *PS*: propensity score; *Tx*: transplant; *IC*: immunocompromised

PS-matching

One-to-two PS-matching between Tx-COVID-19 and non-IC-COVID-19 yielded 143 and 283 patients (no second match for 3 patients). One-to-one PS-matching between Tx-COVID-19 and Tx-non-COVID-19 resulted in 137 patients per group. C-statistic for both comparisons were 0.855 and 0.849, indicating strong discrimination. PS distribution after matching was similar in both comparisons (Figure S1, Additional file 1), although some residual confounder imbalance (standardized mean difference > 0.1) remained (Table 1 and Figure S2, Additional file 1).

Comparison between Tx-COVID-19 and non-IC-COVID-19 patients

Hospital mortality was higher in Tx-COVID-19 compared to non-IC-COVID-19 (75.3% vs. 49.8%,$p < 0.001$) (Fig. 2). Figure S3 shows patient disposition following ECMO initiation, with outcomes including alive, on ECMO, discharged on ECMO or deceased. PS-adjusted [OR:2.36(95%CI:1.61–3.46),$p < 0.001$], multivariable [OR:2.35(95%CI:1.59–3.49),$p < 0.001$] and PS-matched analyses [OR:1.89(95%CI:1.21–2.95),$p = 0.005$] were consistent with these findings, with no significant changes over time, with time serving as a surrogate for evolving factors such as viral strains, vaccination and treatments (Table S7 and Figure S4, Additional file 1). Crude incidence of hemorrhagic complications (24.0% versus 16.7%,$p = 0.020$), metabolic complications (17.8% versus 10.2%,$p = 0.003$) and need for renal replacement therapy (RRT)(57.5% versus 32.1%,$p < 0.001$) were higher in Tx-COVID-19 compared to non-IC-COVID-19 (Fig. 3, Figure S5, Additional file 1). In the unadjusted analysis of the total population, the probability of earlier successful decannulation [HR:0.53(95%CI:0.39–0.71),$p < 0.001$] and live hospital discharge [HR:0.51(95%CI:0.29–0.90),$p = 0.019$] was lower for Tx-COVID-19 compared to non-IC-COVID-19 (Figure S6, Additional file 1). All other complications and discharge destination were not different. Incidence of limb complications was extremely low and not analyzed. In all adjusted analyses, need for RRT was consistently higher in Tx-COVID-19 compared to non-IC-COVID-19 (Fig. 3, Figure S5 in Additional file 1). All point estimates for metabolic complications and time-to-successful decannulation suggest worse outcomes in Tx-COVID-19 patients. These differences were statistically significant in both the multivariable and PS-adjusted models, but not in the PS-matched analysis

Table 1 Demographic, clinical, pre-ECMO and cannulation characteristics

	Total population					Matched population					
	Tx COVID-19 *N*=146	**Non-IC COVID-19** *N*=12,552	**Tx non-COVID-19** *N*=886	**p-value**[4]	**p-value**[5]	**Tx COVID-19** *N*=143	**Non-IC COVID-19** *N*=283	**SMD (95%CI)**	**Tx COVID-19** *N*=137	**Tx non-COVID-19** *N*=137	**SMD (95%CI)**
Demographics											
Age	55 (48-61)	48 (38-56)	58 (45-65)	<0.001	0.127	55 (48-61)	56 (47-63)	−0.07 (−0.09,−0.05)	55 (48-61)	53 (46-60)	0.07 (0.05, 0.10)
Sex, female	44 (30)	3,760 (30)	368 (42)	1.000	0.010	42 (29)	88 (31)	−0.04 (−0.06, −0.02)	44 (32)	40 (29)	0.06 (0.03, 0.09)
BMI (kg/m^2)	29 (26-33)	32 (28-38)	26 (23-30)	<0.001	<0.001	29 (26-33)	29 (26-32)	−0.04 (−0.06, −0.02)	29 (26-33)	29 (24-33)	0.12 (0.09, 0.15)
Comorbidities and associated conditions											
Chronic respiratory disease[1]	18 (12)[2]	350 (3)	235 (27)	<0.001	0.003	16 (11)	31 (11)	0.01 (−0.01,0.03)	22 (16)	25 (18)	−0.06 (−0.09, −0.03)
Chronic heart disease[1]	22 (15)[2]	387 (3)	105 (12)	<0.001	0.221	20 (14)	12 (4)	0.34 (0.32-0.36)	19 (14)	15 (11)	0.09 (0.06, 0.12)
Chronic renal insufficiency[2]	55 (38)	247 (2)	NA	<0.001	-	55 (38)	10 (4)	0.95 (0.93, 0.97)	NA	NA	-
Diabetes[2]	58 (40)	2,996 (24)	NA	<0.001	-	56 (39)	114 (40)	−0.02 (−0.04, 0.00)	NA	NA	-
Co-infection[2]	83 (57)	6,458 (51)	NA	0.212	-	80 (56)	157 (55)	0.01 (−0.01, 0.03)	NA	NA	-
Septic shock[2]	48 (33)	3,107 (25)	NA*	0.027	-	46 (32)	82 (29)	0.07 (0.05, 0.09)	NA*	NA*	-
Pneumothorax[2]	22 (15)	2,028 (16)	NA	0.821	-	22 (15)	46 (16)	−0.02 (−0.04, 0.00)	NA	NA	-
Acute renal failure[2]	63 (43)	3,212 (26)	NA*	<0.001	-	60 (42)	127 (45)	−0.06 (−0.08, −0.04)	NA*	NA*	-
Pre-ECMO variables and treatments											
RR (/min)	28 (24-32)	NA	22 (18-28)	-	<0.001	NA	NA	-	28 (24-32)	28 (24-32)	−0.02 (−0.06, 0.01)
pO_2/FIO_2	79 (60-98)	70 (57-89)	77 (59-132)	0.003	0.436	79 (60-97)	77 (58-97)	0.03 (0.01, 0.06)	80 (61-102)	75 (59-95)	0.02 (−0.02, 0.06)
PIP (cmH_2O)	34 (30-39)	34 (30-38)	31 (26-37)	0.391	<0.001	34 (30-40)	34 (30-38)	0.06 (0.03, 0.09)	34 (30-40)	35 (29-40)	−0.02 (−0.05, 0.02)
PEEP (cmH_2O)	12 (10-14)	14 (10-16)	10 (8-12)	<0.001	<0.001	12 (10-14)	12 (10-14)	−0.10 (−0.12, −0.07)	12 (10-14)	12 (8-14)	0.06 (0.02, 0.09)
pH	7.28 (7.22-7.36)	7.30 (7.21-7.37)	7.28 (7.19-7.36)	0.892	0.179	7.27 (7.21-7.36)	7.29 (7.22-7.37)	−0.05 (−0.08, −0.03)	7.28 (7.21-7.37)	7.27 (7.21-7.35)	0.17 (0.13, 0.20)
pCO_2 (cmH_2O)	56 (46-66)	61 (51-75)	51 (41-65)	<0.001	0.069	57 (46-66)	55 (45-66)	0.00 (−0.03, 0.02)	56 (45-66)	61 (49-70)	−0.21 (−0.25,−0.18)
HCO_3 (mmol/l)	25.0 (22.9-29.0)	NA	24.0 (20.4-27.0)	-	<0.001	NA	NA	-	25.0 (22.6-28.5)	26.0 (22.2-30.0)	−0.07 (−0.10, −0.03)
Lactate (mmol/l)	1.40 (1.00-2.20)	1.60 (1.10-2.20)	2.30 (1.20-4.60)	0.087	<0.001	1.40 (1.00-2.20)	1.70 (1.30-2.15)	−0.10 (−0.14, −0.07)	1.40 (1.00-2.20)	1.50 (1.00-2.30)	−0.17 (−0.22, −0.11)

Table 1 (continued)

	Total population					Matched population					
Mean BP (mmHg)	78 (69-86)	NA	71 (63-82)	-	<0.001	NA	NA	-	78 (69-86)	78 (69-87)	0.11 (0.07, 0.15)
pre-ECMO arrest	4 (3)	399 (3)	48 (5)	0.413	0.014	4 (3)	5 (2)	0.04 (0.02, 0.06)	3 (2)	3 (2)	0.07 (0.04, 0.10)
Intubation-to-time to ECMO (hours)	59 (18-136)	75 (24-145)	11 (5-57)	0.168	<0.001	59 (18-136)	59 (16-132)	0.02 (0.00, 0.05)	59 (18-129)	43 (8-126)	−0.18 (−0.21, −0.15)
pre-ECMO RRT	22 (15)	NA	113 (13)	-	0.429	NA	NA	-	20 (15)	20 (15)	0.00 (−0.03, 0.03)
pre-ECMO NO	37 (25)	NA	165 (19)	-	0.071	NA	NA	-	34 (25)	27 (20)	0.12 (0.09, 0.15)
pre-ECMO prone	65 (45)	7,135 (57)	38 (4)	0.003	<0.001	65 (45)	121 (43)	0.05 (0.03, 0.08)	59 (43)	12 (9)	0.85 (0.82, 0.88)
pre-ECMO NMBA	92 (63)	8,943 (71)	384 (43)	0.034	<0.001	90 (63)	187 (66)	−0.07 (−0.09,−0.05)	84 (61)	87 (64)	−0.05 (−0.07, −0.02)
pre-ECMO vasopressors/inotropes	88 (60)	6,911 (55)	570 (64)	0.211	0.354	85 (59)	166 (59)	0.02 (0.00, 0.04)	86 (63)	93 (68)	−0.11 (−0.14, −0.08)
pre-ECMO IV bicarbonate	15 (10)	NA	130 (15)	-	0.198	NA	NA	-	14 (10)	13 (10)	0.02 (0.00, 0.05)
CRP-level pre-ECMO[2]	116 (34-159)	115 (29-234)	NA	0.387	-	116 (34-159)	117 (15-206)	−0.12 (−0.18,−0.06)	NA	NA	-
Corticosteroid therapy[2]	125 (86)	9,882 (79)	NA	0.042	-	122 (85)	247 (87)	−0.06 (−0.08,−0.04)	NA	NA	-
ECMO											
Cannulation, VV	142 (97)	12,280 (98)	793 (90)	0.562	0.002	139 (97)	280 (99)	−0.13 (−0.15,−0.11)	133 (97)	135 (99)	−0.10 (−0.13, −0.07)
Transported on ECMO	14 (10)	3,698 (30)	19 (2)	<0.001	<0.001	14 (10)	24 (9)	0.04 (0.01, 0.06)	12 (9)	11 (9)	0.01 (−0.02, 0.03)
Center, experienced[3]	122 (84)	8,790 (70)	785 (89)	<0.001	0.099	119 (83)	241 (85)	−0.05 (−0.07,−0.03)	116 (85)	118 (86)	−0.04 (−0.07, −0.01)

Continuous variables are presented as median (interquartile range); categorical variables are presented as number (proportions).

[1] For Tx COVID-19 vs. non-IC COVID-19 comparison, data were obtained from the COVID-19 specific addendum of the registry, for Tx COVID-19 vs. Tx non-COVID-19 comparison, data were obtained from the ICD-10 codes; [2] data obtained from the COVID-19 -specific addendum of the registry; [3] center experience was defined as 'experienced' based on the presence of at least 12 respiratory ECMO runs per year in the registry; [4] p-value Tx COVID-19 vs. non-IC COVID-19; [5] p-value Tx COVID-19 vs. Tx non-COVID-19 *BMI*: body mass index; *ECMO*: extracorporeal membrane oxygenation; *PIP*: peak inspiratory pressure, *PEEP*: positive end-expiratory pressure; *BP*: blood pressure; *RRT*: renal replacement therapy; *NO*: nitric oxide; *NMBA*: neuromuscular blocking agent; *RR*: respiratory rate; *VV*: veno-venous; *IV*: intra-venous; *CRP*: C-reactive protein; *SMD*: standardized mean difference; *NA*: not applicable; the variable was not identified as a confounder for the specific comparison; *NA**: not applicable; the variable was not available in the data structure

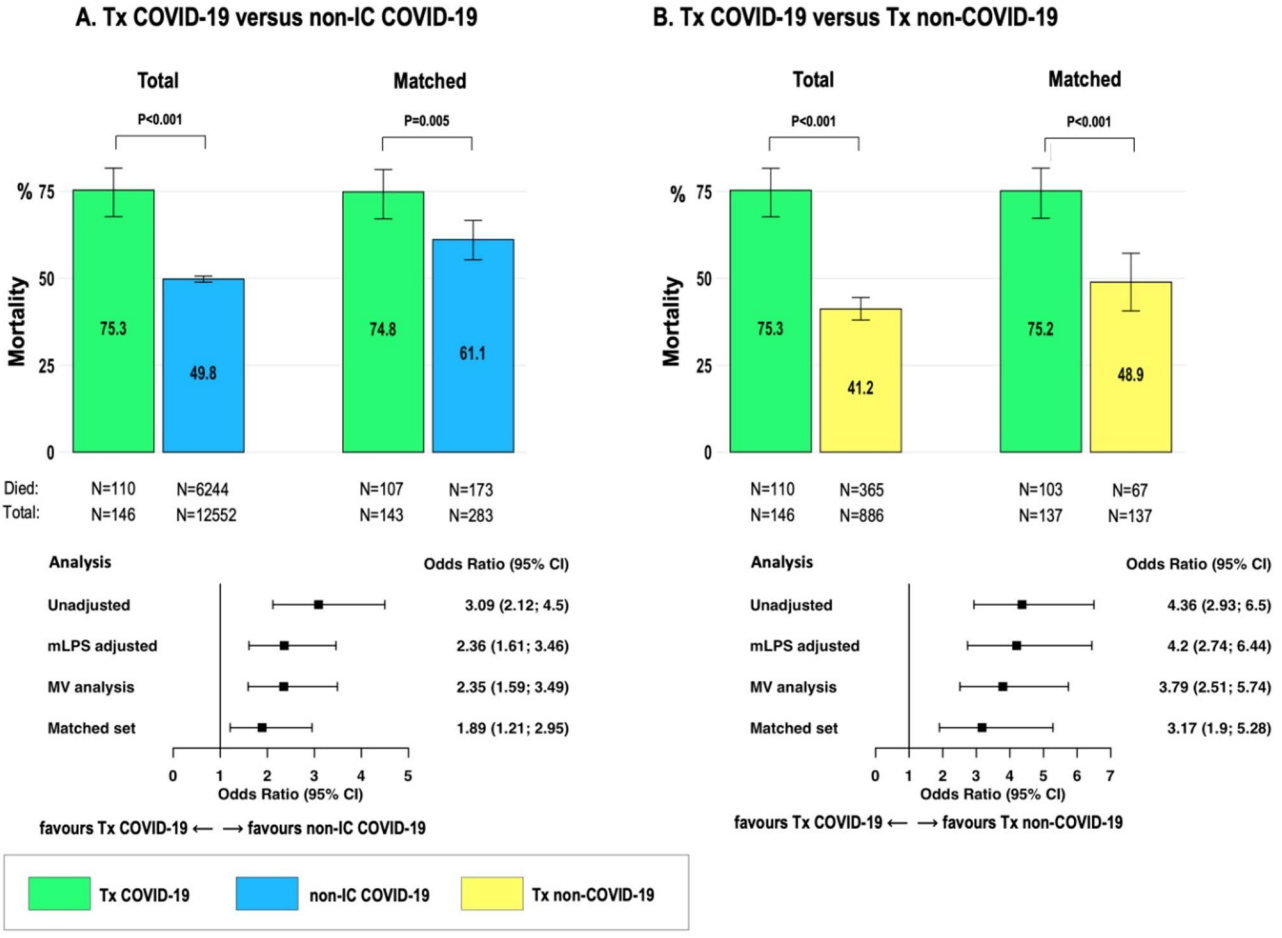

Fig. 2 Hospital mortality for total and matched population in **(A)** Tx-COVID-19 versus non-IC-COVID-19 patients; **(B)** Tx-COVID-19 versus Tx-non-COVID-19 patients. Bar charts report incidences with 95% confidence intervals. Odds ratios are provided for Tx-COVID-19 patients, using as a reference: **(A)** non-IC-COVID-19 patients; **(B)** Tx-non-COVID-19 patients. *Tx*: transplant; *IC*: immunocompromised

($p = 0.187$ and 0.115, respectively), possibly due to limited power or effect heterogeneity in the smaller matched subgroups. Findings for hemorrhagic complications and time-to-live discharge were not statistically significant across analyses, indicating that any apparent differences in unadjusted analyses were likely due to baseline confounding.

Comparison between Tx- COVID-19 and Tx-non-COVID-19 patients

Hospital mortality was higher in Tx-COVID-19 compared to Tx-non-COVID-19 patients (75.3% versus 41.2%,$p < 0.001$) (Fig. 2). PS-adjusted [OR:4.20(95%CI:2.74–6.44),$p < 0.001$], multivariable [OR:3.79(95%CI:2.51–5.74),$p < 0.001$] and PS-matched analyses [OR:3.17(95%CI:1.90–5.28),$p < 0.001$] were consistent with these findings. Patient disposition over time is shown in Figure S3, Additional file 1. The mortality difference remained stable over time (Table S7, Figure S4, Additional file 1). Incidence of hemorrhagic (24.0% versus 15.6%,$p = 0.013$), mechanical (30.1% versus 12.3%,$p < 0.001$; metabolic (17.8% versus 7.9%,$p < 0.001$), neurological (10.3% versus 4.5%,$p = 0.005$), pulmonary (16.4% versus 6.0%,$p < 0.001$), renal complications (48.6% versus 36.1%,$p = 0.004$), and infection (68.5% versus 32.2%,$p < 0.001$) were higher in Tx-COVID-19 patients (Fig. 4, Figure S7, Additional file 1). The probability of earlier successful decannulation [HR:0.29(95%CI:0.22–0.38),$p < 0.001$] and live hospital discharge [HR:0.24(95%CI:0.13–0.42),$p < 0.001$] was significantly lower for Tx-COVID-19 compared to Tx-non-COVID-19 (Figure S8, Additional file 1). Cardiovascular complications, repair and discharge destination were not different. Limb complications were rare. Findings were consistent across all adjusted analyses for hemorrhagic, metabolic, pulmonary complications and infection. The probability of earlier successful decannulation and live hospital discharge was significantly lower for Tx-COVID-19 compared to Tx-non-COVID-19 across all adjusted analyses. All point estimates for renal and mechanical complications suggest worse outcomes in Tx-COVID-19 patients, though these were not significant in

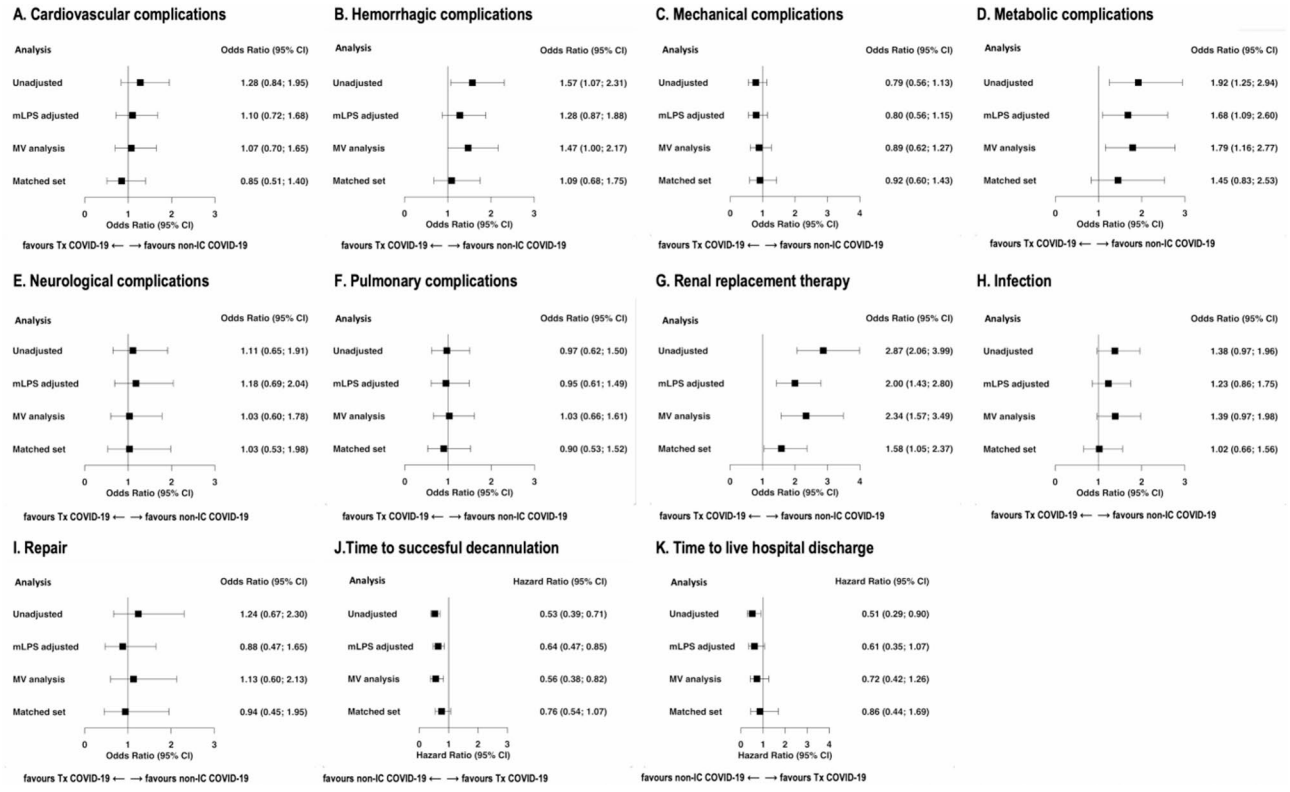

Fig. 3 Secondary outcomes in Tx-COVID-19 versus non-IC-COVID-19 patients. Odds ratios and hazard ratios are provided for *Tx-COVID-19* as compared to *non-IC-COVID-19* patients, for unadjusted, mLPS-adjusted, multivariable and PS-matched analyses. *Tx*: transplant; *IC*: immunocompromised; *mLPS*: mean logarithm of the propensity score; *MV*: multivariable; *PS*: propensity score; RRT: renal replacement therapy

the PS-matched analyses. Findings for neurological complications were not consistently significantly different.

Exploratory analyses indicates that differences in hemorrhagic complications were mainly driven by peripheral cannulation site bleeding and gastro-intestinal hemorrhage (Table S8, Additional file 1). Among metabolic complications, moderate, but not severe, hemolysis and hyperbilirubinemia more frequently occurred in Tx-COVID-19 patients. Among mechanical complications, oxygenator failure, pump failure, circuit change and cannula problems were more frequent. The difference in pulmonary complications was primarily due to pneumothorax requiring treatment. Finally, Tx-COVID-19 patient showed markedly increased rates of fungal, gram-positive, gram-negative and viral/prion infections, with more frequent positive results from urinary, respiratory and blood cultures.

Sensitivity analysis

The sensitivity analysis removed 118 untested patients without clinical suspicion of COVID-19, from the Tx-non-COVID-19 group. Another 1-to1 PS-matched subgroup was generated with $N = 135$ in both groups. All significant differences in the main analyses (mortality, hemorrhagic, metabolic, pulmonary complications, infections, time-to-successful decannulation, time-to-life discharge) were confirmed in all adjusted analyses (Table S9, Additional file 1).

Potential impact of residual confounding in the PS-score matched analyses

Exploratory analyses revealed that the increased mortality in Tx-COVID-19 compared to non-IC-COVID-19 patients was not explained by residual confounding between matched populations, whereas the difference in RRT was likely explained by residual imbalance in chronic renal insufficiency (Table S10, Additional file 1). Likewise, residual imbalance after matching in the Tx-COVID-19 versus Tx-non-COVID-19 matched population did not explain the difference in mortality, metabolic, pulmonary complications, infection, time-to-successful decannulation and time-to-life discharge. However, residual imbalance likely explained at least part of the difference in hemorrhagic complications.

Outcomes according to transplant subtypes

The Tx-COVID-19 group consisted of more heart (18.5% versus 10.8%,$p = 0.012$) and kidney transplants (43.2% versus 8.9%,$p < 0.001$), but less lung transplants (22.6% versus 67.2%, $p < 0.001$) than the Tx-non-COVID-19

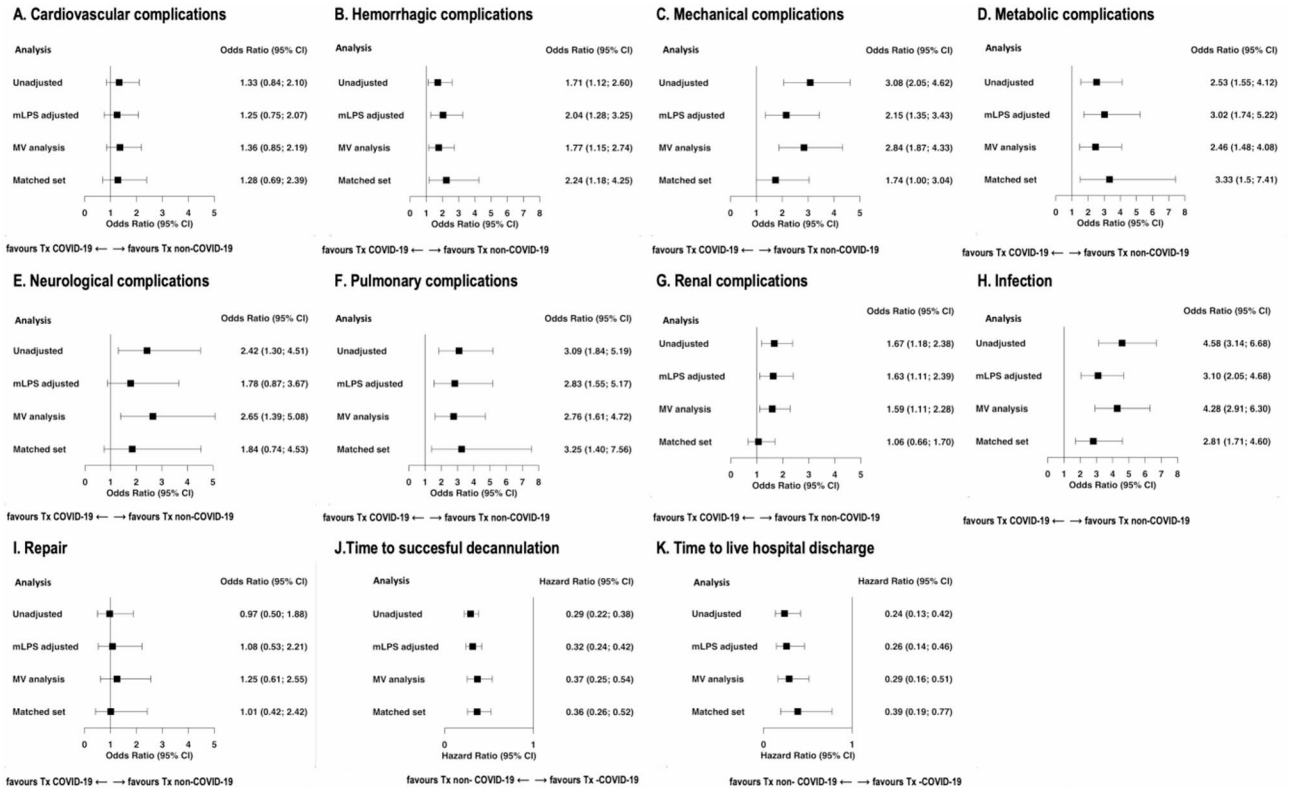

Fig. 4 Secondary outcomes in Tx-COVID-19 versus Tx-non-COVID-19. Odds ratios and hazard ratios are provided for *transplant COVID-19* as compared to *transpant-non-COVID-19* patients. *Tx*: transplant; *mLPS*: mean logarithm of the propensity score; *MV*: multivariable; *PS*: propensity score

group. Liver (11.0% versus 10.0%,$p = 0.735$) and other transplants (12.3% versus 9.5%,$p = 0.285$) were similarly represented. Mortality rates in all transplant subtypes were numerically higher in COVID-19 than non-COVID-19 matched patients (heart:70.4% versus 54.2%, lung:81.8% versus 33.9%, kidney:71.1% versus 57.0%, liver:75% versus 47.2%, other:88.9% versus 66.7%) (Table S11 and Figure S9, Additional file 1). Thus, differences in transplant subtype distribution do not seem to explain the mortality difference in the main analysis. Similarly, no opposing effects were found in secondary outcomes for different transplant subgroups.

Factors associated with mortality in transplant COVID-19 patients

Factors associated with mortality in Tx-COVID-19 patients are shown in Table S12, Additional file 1. Multivariable analysis showed that only higher age independently associated with mortality.

Discussion

In this international ELSO-registry study, in-hospital mortality was 75.3% among 146 transplant recipients supported with ECMO for COVID-19-related respiratory failure. This was significantly higher than the 49.8% in non-immunocompromised COVID-19 patients and 41.2% in transplant recipients, receiving ECMO for non-COVID-19-related respiratory failure. These findings were consistent across all confounder-adjusted analyses and over time, which served as a surrogate for evolving strains, vaccination and treatments. Higher age was the only independent risk factor for mortality among Tx-COVID-19 ECMO patients.

The high mortality rate in Tx-COVID-19 patients undergoing respiratory ECMO compared to non-IC-COVID-19 patients aligns with pre-COVID-19 ECMO studies, where immunocompromised patients experienced high hospital and 6-month mortality rates of 66% and 70–75% [21, 28], respectively. In HSCT patients, mortality rates of 81–93% were reported [15, 20, 21, 29]. However, within this heterogeneous population, SOT recipients and late post-transplant HSCT patients showed better outcomes [20–22, 28], supporting judicious ECMO use in these populations pre-COVID-19 [22, 30]. Nevertheless, we found significantly higher mortality in Tx-COVID-19 compared to non-IC-COVID-19 ECMO patients. This corroborates that transplant recipients in general, face a higher risk of severe COVID-19 and associated mortality, likely due to poor vaccine response, immunosuppressive drugs, and comorbidities [1, 2, 31–33]. Tx-COVID-19 patients in our study were older, had more comorbidities and more frequently presented with

acute kidney injury. Yet, these factors did not explain the excess mortality, which may instead reflect worse disease trajectory possibly driven by delayed viral clearance in this immunocompromised population [34]. Regarding complications, only need for RRT was consistently more frequent in Tx-COVID-19 patients, compared to non-IC-COVID-19 patients. This is not surprising, as transplant recipients are more prone to acute and chronic kidney injury due to comorbidities and immunosuppressive treatments [3, 35, 36]. In the matched set, this difference was possibly explained by residual imbalance, particularly the higher incidence of chronic kidney disease in the transplant group.

Mortality in Tx-COVID-19 patients was also markedly higher than in Tx-non-COVID-19 patients, consistent across all transplant subgroups. This difference was most pronounced in lung transplant recipients, a finding that-while exploratory and based on unmatched subgroups-warrants further investigation. This pattern aligns with higher mortality reported in general COVID-19 patients on respiratory ECMO, compared to those on ECMO for non-COVID-19-related respiratory failure [37, 38], particularly from other viral infections [39]. Delayed ECMO initiation, possibly due to more extensive use of prone and NMBA, was proposed to explain higher mortality in COVID-19 versus non-COVID-19 ECMO [39]. Alternatively, some residual baseline imbalances may suggest differing disease phenotypes between groups. However, further analyses showed that increased mortality was not explained by these or other baseline differences. Also, higher pathogenicity [40] with protracted disease course may lead to prolonged ECMO support and increased complications [10, 37–40]. Our study corroborates this hypothesis, as Tx-COVID-19 patients had longer ECMO runs and complications rates than Tx-non-COVID-19 patients. Hemorrhagic, metabolic, pulmonary and infectious complications were more frequent and consistent across all confounder-adjusted analyses. Beyond prolonged ECMO exposure, COVID-19 associated coagulation activation is well-recognized for increasing the risk of thromboembolic events and bleeding [41]. The bleeding rate of 24% in Tx-COVID-19 patients aligns with the 21–47% rates reported in other COVID-19 ECMO populations [10, 18, 37, 39, 42]. Coagulation activation likely also contributed to increased metabolic complications, primarily driven by a higher incidence of moderate hemolysis and hyperbilirubinemia. Others signs hereof, such as oxygenator failure, circuit change, pump failure and cannula problems, occurred more frequently, but the difference in mechanical complications was marginally non-significant in the PS-matched analysis. The higher incidence of pulmonary complications, predominantly due to pneumothorax requiring treatment, corroborates with the reported 18.4% pneumothorax rate in ventilated COVID-19 patients [43]. While pathophysiology remains unclear, severe viral/inflammatory alveolar damage, possibly predisposing to self-inflicted lung injury and ventilator-induced lung injury, were proposed. The higher incidence of infectious complications in our Tx-COVID-19 patients, compared to Tx-non-COVID-19 patients, mirrors the increased infection rates reported in critically ill COVID-19 patients in general [44] and ECMO patients in particular [37], compared to non-COVID-19 patients. Our overall infection rate (68%) in the Tx-COVID-19 cohort was somewhat higher than the 36% reported in general COVID-19 ECMO patients [45]. Respiratory infections (55.5%) and bacteremia (38.4%) were similar to reported rates of 38–87% for VAP and 25–44% for bacteremia in ECMO-treated COVID-19 patients [10, 18, 37, 42]. However, viral-induced impairment in antifungal immunity combined with chronic immunosuppression raised fungal infection rates (27.4%) compared to the 10–20% in general critically ill COVID-19 patients [46].

Of note, in 886 Tx-non-COVID-19 ECMO patients -the largest cohort of its kind and excluding bridge-to-transplant and peri-transplant runs- we observed a surprisingly low mortality rate of 41.2% compared to previous studies. In contrast, Schmidt reported 6-month mortality of 59% in 27 SOT recipients and 93% in 14 allo-HSCT patients, within a cohort of 203 immunocompromised patients [21]. Similarly, Na reported a 57.1% hospital mortality in 42 SOT patients [28]. Our encouraging survival rate may be attributed to our case mix, with two-thirds being lung transplants, who had the lowest mortality (33.9%). This is a novel and promising finding for Tx-non-COVID-19 patients, which warrants further investigation.

This study has several strengths. This is the first comprehensive international report on transplant recipients receiving ECMO for COVID-19-related respiratory failure. Unlike the heterogeneous population of immunocompromised patients with COVID-19-related respiratory failure requiring ECMO, who are known to have a poor prognosis, transplant recipients constitute a distinct subgroup with unique characteristics and challenges. This study fills a critical gap in the literature for this population, where data are virtually absent. Despite the relatively small sample size of COVID-19 Tx patients ($n = 146$), it represents the largest international cohort to date, offering valuable insights that are directly relevant to clinicians at the bedside. Data were consistent across multiple confounder-adjusted analyses and reflect daily care management. Limitations included registry-based constraints, including limited data granularity, with certain key variables available only in the COVID-19 addendum, risk of underreporting -including for neurological complications, as noted in prior ELSO studies

[47, 48]- and potential bias from favoring ECMO-focused centers. Also, the registry lacked data on other key factors informing ECMO candidacy, such as functional status and resource availability. We cannot exclude residual bias from unmeasured factors, such as changes in transplant allocation policies over time or clinical variables not captured in the core dataset such as septic shock (only available in the COVID-19 addendum). Post-discharge survival, neurological function and quality of life data were also unavailable, though important for contextualizing outcomes. Given that SOT recipients comprised 94.5% of the cohort, the findings predominantly reflect this group. We acknowledge that HSCT recipients have distinct risk profiles, but their low numbers precluded separate analysis. Poor outcomes were observed despite the likely presence of selection bias, as the decision to offer ECMO to transplant patients may have been more carefully scrutinized. Notably, available literature indicates that mortality among transplant recipients with severe COVID-19 ARDS requiring mechanical ventilation is already very high (≈50–70%) [2, 49–52], which provides important context for interpreting our findings. Despite some residual confounder imbalance in the matched sets, exploratory analyses indicated this did not explain differences in mortality and most complication rates, with findings consistent across all other adjusted analyses. Nevertheless, unmeasured confounding cannot be excluded. In particular, factors such as the time from transplant to ECMO initiation, immunosuppressive regimens, and information on viral strains, were not captured in the registry. Discrepancies between MV and PS-matched analyses not necessarily indicate inconclusive results. They may reflect limited power or distinct effects in these small subgroups of matched patients. Finally, given the evolving dynamics of COVID-19 variants, future relevance of these findings may be unclear. While we did not observe significant changes in mortality risks over time, we acknowledge that the declining virulence of recent variants and changes in population immunity may limit direct extrapolation of our results to future COVID-19 strains or other viral pandemics. Nonetheless, excess break-through infections and mortality persists in SOT patients [31, 32, 53] and we did not observe significant changes of mortality risks over time. Additionally, the proportion of immunocompromised patients among ICU COVID-19 admissions is rising [54], underscoring the continued need for vigilance and ongoing evaluation of outcomes in this high-risk group [32, 53–55].

Conclusion

We observed high mortality rates in transplant recipients treated with ECMO for COVID-19-related respiratory failure. These findings predominantly reflect outcomes in SOT recipients, as HSCT numbers were low. ECMO use in this population should remain cautious and selective, recognizing that future applicability may depend on evolving viral dynamics.

Abbreviations

BM	Bone marrow
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CPT	Current procedural terminology
CRP	C-reactive protein
ECMO	Extracorporeal membrane oxygenation
ELSO	Extracorporeal Life Support Organization
HIV	Human immunodeficiency virus
HR	Hazard ratio
HSCT	Hematopoietic stem-cell transplant
IC	Immunocompromised
ICD-10	10th revision of the International Classification of Diseases
iNO	Inhaled nitric oxide
IV	Intra-venous
mLPS	mean logarithm of the propensity score
MV	Multivariable
NA	Not applicable
NMBA	Neuromuscular blocking agent
NO	Nitric oxide
OR	Odds ratio
PEEP	Positive end-expiratory pressure
PIP	Peak inspiratory pressure
PS	Propensity score
RR	Respiratory rate
RRT	Renal replacement therapy
SC	Stem cell
SMD	Standardized mean difference
SOT	Solid organ transplant
Tx	Transplant
VV	Veno-venous

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Author contributions

GH conceived the study; GH, AB and AB conceived the analysis plan; GH, MP, TM, AV, AC designed the study; AB and AB led the data analyses, supported by GH; GH, MP, AB drafted the initial manuscript. All authors revised and approved the manuscript for submission. GH and AB have directly accessed and verified the underlying data reported in the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Data availability

The data supporting this study's findings were obtained under license from the ELSO registry for use in the current study only. While not publicly available,

these data can be accessed by member centers upon approval from the ELSO Scientific Oversight Committee.

Declarations

Ethics approval and consent to participate
The study was approved by the UZLeuven Ethical Committee (S67501).

Consent for publication
Not applicable.

Competing interests
TM is a member of the Board of ELSO. The other authors have no conflict of interest.

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