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Perioperative cardiovascular and cerebrovascular outcomes in recipients of ECMO bridge to lung transplant

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MACCE;
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BACKGROUND: The use of extracorporeal membrane oxygenation (ECMO) as a bridge to lung transplantation (BTT) has increased over time. While 1-year and overall survival have been reported to be similar with non-ECMO transplant recipients, there are limited data on major adverse cardiovascular and cerebrovascular events (MACCE) and clinically relevant bleeding (CRB) events. In this study, we sought to evaluate the incidence of perioperative MACCE and CRB in lung transplant recipients who underwent ECMO BTT.

METHODS: Using the National Inpatient Sample from 2008-2019, we identified 5,254 lung transplant recipients who either received or did not require pretransplant ECMO. Perioperative MACCE and CRB were compared between the 2 cohorts.

RESULTS: Patients with ECMO BTT had a higher incidence of MACCE compared to non-ECMO patients (35% vs 13.3%, $p < 0.0001$) and CRB (34.5% vs 12.9%, $p < 0.0001$). Recipients of pretransplant ECMO for double lung transplant ($n = 158$) were more likely to have perioperative MACCE and CRB as opposed to patients without pretransplant ECMO ($n = 3,584$) (adjusted odds ratio 2.69, $p < 0.0001$; 95% confidence interval 1.86-3.80). The ECMO BTT cohort was notably younger with less cardiac comorbidities and higher diagnoses of cystic fibrosis and interstitial lung disease.

CONCLUSIONS: Our data indicate that lung transplant recipients who required ECMO BTT are at significantly higher risk of MACCE and bleeding events despite being younger with less comorbidities as opposed to those who did not require ECMO.

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Background

Lung transplantation is an established treatment option for patients suffering from end-stage lung disease despite optimal medical therapies. As more patients undergo evaluation and await a lung transplant, extracorporeal membrane oxygenation (ECMO) is increasingly utilized as a bridge to lung transplantation (BTT) in those with refractory respiratory failure.[1] The International Society of Heart and Lung Transplantation proposes that extracorporeal life support should be recommended in patients with young age, absence of multiorgan dysfunction, and good potential for rehabilitation.[2] Recent studies have found that more than 55.6% of patients were successfully bridged to transplant with satisfactory 1-year post-transplant survival of 69% and higher.[3-8] Conditional survival analysis has shown that candidates who survived to transplant after receiving ECMO BTT have statistically similar 1-, 3-, and 5-year survival outcomes, similar to the non-ECMO transplant recipients.[5,9,10] Several centers even report better outcomes with ECMO when compared to mechanical ventilation (MV) alone, with some suggesting the combination of ECMO and MV is a superior modality to MV alone while others favor awake ambulatory ECMO as a viable method to delay deconditioning in critically ill patients.[5,11,12]

Studies report favorable survival outcomes in patients who receive ECMO as BTT.[3,5,9] However, most of these studies primarily focus on mortality rather than morbidity outcomes. ECMO support has its own innate risks of bleeding, kidney failure, infection, stroke, and thrombotic events.[13] Individual centers have reported various incidences of bleeding, renal injury, cardiac arrest, cerebrovascular insults, and in-hospital mortality in patients who required ECMO as BTT.[3-5,7,8] Major cardiovascular events and cerebrovascular events and clinically relevant bleeding (CRB) remain important causes of perioperative morbidity and mortality in lung transplant recipients and in patients who require ECMO as a BTT.[13-16]

In this study, we use the National Inpatient Sample (NIS) data to investigate the incidence of perioperative major adverse cardiovascular and cerebrovascular events (MACCE) and CRB in lung transplant recipients who received and did not receive ECMO BTT. We hypothesized that patients requiring ECMO as BTT will have worse outcomes and higher incidences of MACCE and CRB compared to the non-ECMO cohort.

Material and methods

Using the NIS from 2008-2019, we compared baseline characteristics and in-hospital outcomes of patients who received pretransplant ECMO and those who did not receive pretransplant ECMO. NIS is a database of inpatient hospital admissions as part of the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality. It includes data from 45 states in compliance with the principles of the International Society of Heart and Lung Transplantation Statement on Transplant Ethics.[17] These samples are designed to provide both unweighted and weighted national estimates of inpatient stays. Perioperative MACCE was defined as in-hospital death, myocardial infarction, cardiogenic shock, or ischemic stroke. CRB was defined as events requiring blood transfusions or surgical interventions, such as hemothorax, hemoperitoneum, hemopericardium, pulmonary hemorrhage, intracranial bleed, and gastrointestinal and skin hemorrhage.

All continuous variables are presented as mean ± standard deviation or median (interquartile range) unless otherwise stated. Categorical variables were compared using Pearson chi-square test. Odds ratios were calculated for MACCE and CRB using logistic regression analysis and adjusted for age, gender, race, Charlson comorbidity index (CCI), cardiovascular risk factors [hypertension, hyperlipidemia, diabetes mellitus type 2, atrial fibrillation, coronary artery disease, and obesity], use of anticoagulation and antiplatelet use, acute kidney injury (AKI) and diagnosis [pulmonary hypertension, cystic fibrosis, interstitial lung disease, and chronic obstructive pulmonary disease]. All statistical tests are 2-tailed, and p-values of less than 0.05 were considered to indicate statistical significance. Statistical analyses were performed using STATAv14.

Results

We identified 5,254 index hospitalizations who underwent lung transplantation. Within this cohort, 5,083 patients were transplanted without the use of ECMO (non-ECMO group), and 171 patients underwent ECMO as BTT (ECMO BTT group) (Figure 1). The mean age in the non-ECMO and ECMO BTT cohorts were 55.8 + 14.03 and 45.05 + 15.7 years, respectively ($p < 0.0001$). Over two-thirds of patients in both cohorts were identified as White with over 50% identified as males (Table 1). There were no statistical differences between the 2 cohorts by CCI, obesity (body mass index > 30), chronic use of antiplatelet or anticoagulation, or gender ($p > 0.05$) (Table 1).

On chi-square analysis, the non-ECMO and ECMO BTT cohorts had differences in comorbidities. Non-ECMO patients had higher rates of cardiovascular risk factors including age, hypertension, diabetes, atrial fibrillation, coronary artery disease, and hyperlipidemia but less rates of AKI (Table 1). The ECMO BTT cohort was younger, had higher rates of cystic fibrosis (14.5% vs 4.28%, $p < 0.001$), higher rates of interstitial lung disease (22.82% vs 13.44%, $p < 0.001$), lower rates of chronic obstructive pulmonary disease (8.21% vs 13.43%, $p < 0.05$), and had lower clinically significant comorbidities as opposed to the non-ECMO cohort. There was no difference in the diagnosis of pulmonary hypertension (33.58% vs 36.24%, $p > 0.05$) among the 2 groups (Table 1).

Perioperative MACCE occurred in 738 (14%) hospitalizations and CRB occurred in 717 (13.64%) hospitalizations. The ECMO BTT cohort had higher overall rates of MACCE compared to non-ECMO (35% vs 13%, $p < 0.0001$) with significantly higher cardiogenic shock

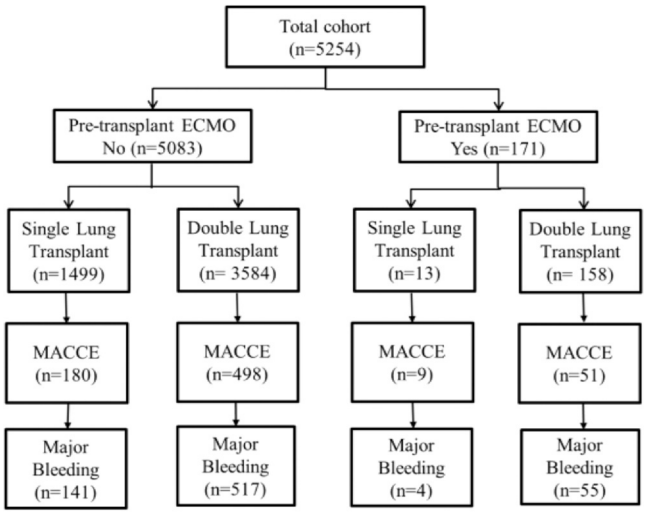

Figure 1 Study cohort outcomes and groups based on pre-transplant ECMO status, single/double lung transplant, MACCE, and major bleeding events. ECMO, extracorporeal membrane oxygenation; MACCE, major adverse cardiovascular and cerebrovascular events.

(16.37% vs 5.37%, $p < 0.0001$), in-hospital death (9.27% vs 4.9%, $p < 0.05$), and ischemic stroke (7.6% vs 1.61%, $p < 0.0001$) (Table 2, Figure 2). Moreover, the ECMO BTT cohort had higher overall CRB when compared to non-ECMO cohort (34% vs 12%, $p < 0.0001$) with greater incidences of hemothorax (11.15% vs 2.73%, $p < 0.0001$), pulmonary hemorrhage (11.74% vs 1.46%, $p < 0.0001$), and intracranial bleed (2.35% vs 0.53%, $p < 0.005$) (Table 2, Figure 3).

Within the ECMO BTT group, patients who received double lung transplantation ($n = 158$) were more likely to have complications of perioperative MACCE and CRB as opposed to the non-ECMO cohort ($n = 3,584$, adjusted odds ratio (aOR) 2.69, $p < 0.0001$; (95% confidence interval [CI] 1.86-3.80) (Figure 1). Similar findings were seen in ECMO BTT for single lung transplantation ($n = 13$; aOR 1.99, $p = 0.193$) but not statistically significant.

Independent risk factors for developing MACCE included ECMO BTT (aOR 2.74, $p < 0.0001$; 95% [CI] 2.07-3.62), higher CCI (aOR 1.23, $p < 0.05$; 95% [CI] 1.12-1.35), and AKI during the hospital course (aOR 2.15, $p < 0.05$; 95% [CI] 1.69-2.72). Anticoagulation had an aOR of 0.41 ($p < 0.05$; 95% [CI] 0.20-0.76) for MACCE.

Discussion

To our knowledge, our study is the first to use a large national database to assess perioperative morbidity in ECMO

Table 1 Characteristics of Lung Transplant Recipients in the National Inpatient Stratified by No Pretransplant ECMO or Use of Pretransplant ECMO

Variables	No pretransplant ECMO (n = 5,083; 96.74%)	Pretransplant ECMO (n = 171; 3.26%)	p-value
Age (mean, SD)	55.80 ± 14.03	45.05 ± 15.70	< 0.0001
Charlson comorbidity index (median 25%, 75%)	1 (0. 2)	1(0. 2)	0.996
Female	2,029 (39.91%)	74 (43.26%)	0.358
Race			0.035
White	4,011 (78.90%)	121 (70.65%)	
Black	451 (8.88%)	19 (11.00%)	
Hispanic	397 (7.82%)	19 (11.01%)	
Asian or Pacific Islander	83 (1.63%)	2 (1.22%)	
Native American	15 (0.30%)	0 (0%)	
Other	125 (2.46%)	10 (6.12%)	
Cardiovascular risk factors			
Hypertension	1,757 (34.56%)	34 (19.96%)	0.0003
Diabetes mellitus type 2	967 (19.03%)	15 (8.88%)	0.0007
Hyperlipidemia	1,234 (24.27%)	20 (11.74%)	0.0001
Atrial fibrillation	1,086 (21.37%)	17 (9.93%)	0.0008
Obesity (BMI > 30)	344 (6.76%)	11 (6.36%)	0.8694
Acute kidney injury	1,755 (34.52%)	115 (67.22%)	< 0.0001
Chronic use of anticoagulation	150 (2.96%)	2 (1.17%)	0.1674
Chronic use of antiplatelet	371 (7.29%)	4 (2.35%)	0.0108
Coronary artery disease	1,051 (20.68%)	16 (9.34%)	0.0005
Transplant diagnosis			
COPD	683 (13.43%)	14 (8.21%)	0.0452
Pulmonary hypertension	1,707 (33.58%)	62 (36.24%)	0.4624
Cystic fibrosis	218 (4.28%)	25 (14.50%)	< 0.0001
ILD	683 (13.44%)	39 (22.82%)	0.0002

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; ILD, interstitial lung disease; SD, standard deviation.

Table 2 MACCE and CRB Outcomes of Lung Transplant Recipients in the National Inpatient Sample Stratified by No Pretransplant ECMO or Use of Pretransplant ECMO

	No pretransplant ECMO ($n = 5,083$; 96.74%)	Pretransplant ECMO ($n = 171$; 3.26%)	p-value
MACCE	678 (13.34%)	60 (35.01%)	< 0.0001
Acute myocardial infarction	74 (1.45%)	3 (1.75%)	0.7658
Cardiogenic shock	273 (5.37%)	28 (16.37%)	< 0.0001
Ischemic stroke	82 (1.61%)	13 (7.60%)	< 0.0001
In-hospital death	249 (4.90%)	16 (9.27%)	0.0096
CRB	658 (12.94%)	59 (34.50%)	< 0.0001
Gastrointestinal hemorrhage	15 (0.29%)	2 (1.13%)	0.0146
Postoperative skin hemorrhage	374 (7.35%)	13 (7.63%)	0.9025
Hemothorax	139 (2.73%)	19 (11.15%)	< 0.0001
Hemoperitoneum	22 (0.44%)	0 (0%)	0.4259
Hemopericardium	7 (0.14%)	1 (0.59%)	0.1367
Pulmonary hemorrhage	74 (1.46%)	20 (11.74%)	< 0.0001
Intracranial bleed	27 (0.53%)	4 (2.35%)	0.0027

Abbreviations: CRB, clinically relevant bleeding; ECMO, extracorporeal membrane oxygenation; MACCE, major adverse cardiovascular and cerebrovascular events.

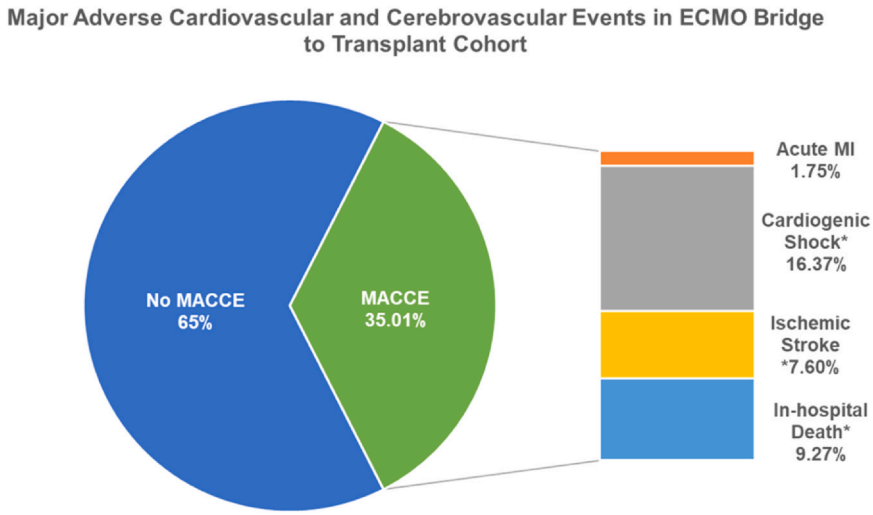

Figure 2 Bar of pie chart of major adverse cardiovascular and cerebrovascular events (MACCE) and no MACCE in ECMO bridge to transplantation (BTT) in lung transplant recipients stratified by acute myocardial infarction (MI), cardiogenic shock, ischemic stroke, and in-hospital death; *$p < 0.05$. ECMO, extracorporeal membrane oxygenation.

BTT in lung transplant recipients. This retrospective study showed that despite optimal age and with less comorbidities, patients successfully bridged to lung transplantation have higher rates of MACCE and bleeding. Risk factors for MACCE were identified as ECMO BTT, higher CCI, and AKI. Moreover, the highest at-risk for perioperative MACCE and CRB patients were those who underwent double lung transplantation on ECMO BTT.

ECMO continues to be a viable treatment as BTT in select patients, but complications, such as bleeding and thrombotic events, can occur at any point due to factors such as circuit malfunction, exposure to nonbiologic circuit components, activation of coagulation system, and mechanical hemolysis.[18,19] Patients have an increased predisposition to primary graft dysfunction, bleeding, hemodialysis, tracheostomies, longer intensive care unit and hospital length of stay, and mortality.[7,20] Despite similar rates of survival post-transplant in ECMO BTT and non-ECMO cohorts,[3,21–23] our study shows significant morbidity and mortality associated with patients who required pretransplant ECMO BTT. It is unclear the exact timing of when MACCE and CRB events occurred during the transplant process, but ECMO BTT was an independent risk factor for developing MACCE. As MACCE events can preclude delisting or withdrawal of life-sustaining therapies, it can be suspected that these events occurred after transplantation during the perioperative/postoperative care.

A recent study utilizing the United Network for Organ Sharing database found risk factors for reduced waitlist survival in ECMO BTT patients that included extended duration of ECMO support, ECMO support in redo-lung transplant recipients, and center volume.[24] After successful BTT, there was no difference in survival based on low or high lung transplant volume centers.[24] Several other studies have reported increased morbidity and mortality associated with greater duration of ECMO (14 and 29 days) before transplantation and improved BTT success with ECMO use

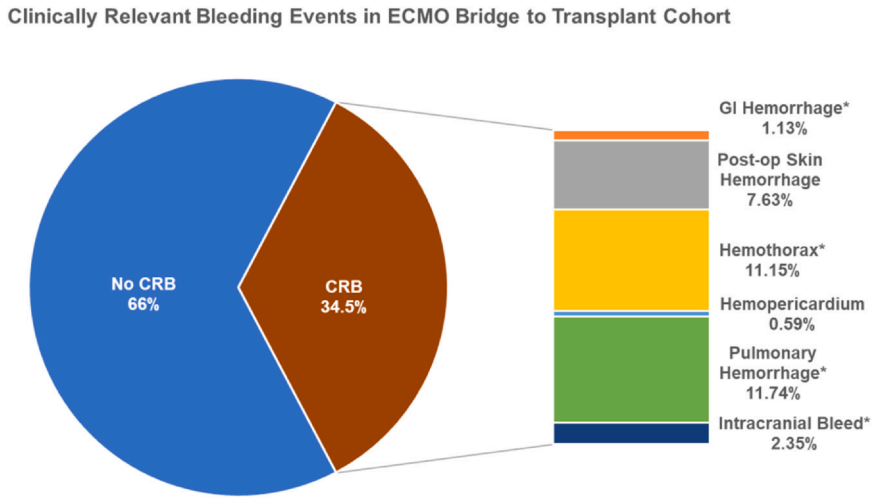

Figure 3 Bar of pie chart of clinically relevant bleeding (CRB) events and no CRB events in ECMO as bridge to transplantation (BTT) in lung transplant recipients stratified by gastrointestinal (GI) hemorrhage, postoperative skin hemorrhage, hemothorax, hemopericardium, pulmonary hemorrhage, and intracranial bleed; $*p < 0.05$. ECMO, extracorporeal membrane oxygenation.

less than 14 days.[25-27] Though our patient population only includes those successfully bridged to transplantation, the duration of ECMO therapy may certainly have contributed to the results of CRB and MACCE within this cohort.

ECMO BTT patients in this study were younger than the non-ECMO cohort with lower rates of cardiovascular comorbidities. Moreover, these patients had higher diagnoses of cystic fibrosis and interstitial lung disease. A single-center retrospective study found similar significant differences in age and diagnoses leading to transplant in their cohort of BTT patients, but on propensity-matched analysis, they did not find any significant difference in survival between the 2 cohorts except for higher lung allocation scores in BTT.[3] Moreover similar to our study, there were increased incidences of MACCE and CRB in ECMO BTT to double lung transplant as opposed to the non-ECMO double lung transplant cohort. This finding may be attributed to the use of ECMO and the intrinsic risk of ECMO-associated complications but also increased intraoperative blood loss, ischemic time, ischemic-reperfusion injury, larger incisions, and complexity of surgical technique.[28-30]

On multivariate regression analysis for MACCE alone, AKI and rising CCI were associated with higher rates of MACCE. Renal injury has been reported to occur in up to 60% of patients on ECMO due to critical illness, comorbidities, and acute insults affecting hemodynamic, hormonal, inflammatory, and circuit-related variables.[31,32] Several studies report a high incidence rate of AKI, high odds ratio for death, and failure to wean from ECMO when initiating renal replacement therapy.[33-35] Though there are no studies assessing CCI with ECMO morbidity, CCI is a widely used comorbidity index in the medical literature to assess mortality.[36] Higher CCI was associated with increased MACCE events. Lastly, chronic use of anticoagulation was associated with lower MACCE events which could be related to decreased systemic and mechanical thrombosis within the ECMO circuit.[37]

The primary strength of this study is the use of a national database and a very large number of patients over a decade. These results provide insights into individual MACCE and CRB incidence rates, giving more relevant utility in perioperative and early postoperative settings limited to transplant recipients and excluding those who died while awaiting lung transplantation. There are limitations to this study. The registry does not include granular data about individual lung allocation scores, ECMO configuration, use of intraoperative ECMO or cardiopulmonary bypass, or duration of ECMO therapy, or other factors that may have contributed to the increased risk of MACCE or CRB. The registry is limited to self-reporting by individual centers. Moreover, information on disease-specific therapy, ECMO practice patterns/protocols, and center-specific information (high vs low volume transplant or ECMO center) are not available. Our data comprise transplant recipients nationwide and cannot be generalized to individual lung transplant candidates. Lastly, the landscape of lung transplantation and utilization of ECMO as a BTT underwent significant transformations during the years 2008-2019. Practice patterns surrounding ECMO utilization including indication, duration, and weaning protocols have advanced to minimize complications and maximize likelihood of successful transplantation outcomes. Our data are a combined pool of data from 2008-2019 and do not delve into trends over time in the number of BTT or complications.

Conclusions

Our analysis shows that patients requiring ECMO BTT are at increased risk of developing MACCE and CRB despite having been of optimal patient criteria. Detailed preoperative risk assessment and close perioperative care are necessary to recognize and treat MACCE and major bleeding complications.

Disclosure statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

F.A. participated in research design. J.K., D.F., R.M., G.C., and F.A. participated in the writing of the paper. F.A. participated in the performance of the research. J.K., F.A., and R.M. contributed new reagents or analytic tools. F.A. and R.M. participated in data analysis. J.K. and D.F. wrote the manuscript. R.M. and F.A. acquired, analyzed, and interpreted the data. G.C. and F.A. reviewed and revised the manuscript. F.A. designed and supervised the study.

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