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Similarities in extracorporeal membrane oxygenation management across intensive care unit types in the United States:

An analysis of the Extracorporeal Life Support Organization Registry

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Address for Correspondence: Clark G. Owyang, MD, 1305 York Avenue, Y-1047, Box 96, New York, NY 10021, Telephone: 916-761-8681, clo9021@med.cornell.edu, Twitter: @clark_owyang, Tweet: In >10,000 ECMO runs, @ELSOOrg's Registry shows ECMO in US mainly within CTICUs. But, the majority of ECMO is NOT related to cardiac surgery procedures. @clark_owyang @JoeTonnaMD @HBGMD @MayHuaMD @NidaQadirMD @ClaireDonnat.

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Abstract

Background: Extracorporeal membrane oxygenation (ECMO) use in the United States occurs often in cardiothoracic ICUs (CTICU). It is unknown how it varies across ICU types.

Methods: We identified 10,893 ECMO runs from the Extracorporeal Life Support Organization (ELSO) Registry across 2018 and 2019. Primary outcome was ECMO case volume by ICU type (CTICU vs. non-CTICU). Adjusting for pre-ECMO characteristics and case mix, secondary outcomes were on-ECMO physiologic variables by ICU location stratified by support type.

Results: CTICU ECMO occurred in 65.1% and 55.1% (2018 and 2019) of total runs. A minority of total runs related to cardiac surgery procedures (CTICU: 21.7% [2018], 18% [2019]; non-CTICU: 11.2% [2018], 13% [2019]). After multivariate adjustment, non-CTICU ECMO for cardiac support associated with lower 4- and 24-hour circuit flow (3.9 liters per minute [LPM] vs. 4.1 LPM, $p<0.0001$; 4.1 LPM vs. 4.3 LPM, $p<0.0001$); for respiratory support, lower on-ECMO mean fraction of inspired oxygen ([F_iO_2], 67% versus 69%, $p=0.02$) and lower respiratory rate (14 versus 15, $p<0.0001$); and, for extracorporeal cardiopulmonary resuscitation (ECPR), lower ECMO flow rates at 24 hours (3.5 liters per minute [LPM] versus 3.7 LPM, $p=0.01$).

Conclusions: ECMO mostly remains in CTICUs though a minority is associated with cardiac surgery. Statistically significant but clinically minor differences in on-ECMO metrics were observed across ICU types.

Keywords

Critical care delivery; multidisciplinary critical care; epidemiology; healthcare delivery; cardiothoracic intensive care unit; cardiac intensive care unit; cardiac critical care; ECMO

Introduction/Background

As indications for extracorporeal membrane oxygenation (ECMO) have expanded, its use amongst different ICU settings has grown. (1–13) From its origins in cardiopulmonary bypass and the early respiratory support trials of the 1970s to the recent CESAR and EOLIA era, ECMO has typically been dichotomized into either cardiac or respiratory support.(14–16) As such, there is robust literature specific to its role in cardiac surgery and the cardiothoracic ICU (CTICU).(17, 18) Recent descriptions show a wide array of use beyond the paradigm of postcardiotomy shock in the CTICU as demonstrated by the advent of specialized respiratory ECMO units, mobile ECMO teams, and multidisciplinary shock teams. (1–13, 19–22) It is unknown how expanding indications and novel/non-CTICU locations may affect the delivery of ECMO given this historical context. Importantly, the hospital units where ECMO initiation and maintenance occur have increasingly included non-CTICU locations (i.e. respiratory ICUs, cardiac ICUs, medical ICUs, surgical ICUs and mixed ICUs), but data on how these systems factors may affect critical care delivery are scarce.(19, 20, 23–26) Recent literature has investigated the positive impact of multidisciplinary, intensivist-led ECMO teams and Extracorporeal Life Support

Organization (ELSO) recommendations advise this interdisciplinary team structure.(27, 28) As the COVID-19 pandemic has most immediately shown, the provision of ECMO across different ICU settings continues to rapidly evolve but the effect of ICU type remains incompletely described.(29)

Despite the expansion in locations providing ECMO care, large-scale research investigating how systems-based factors affect ECMO use remains limited.(19, 30) Investigation on ECMO delivery has been performed in relation to center-type but without more granular description of how ICU setting may affect ECMO management.(31–33) While healthcare delivery for procedures, mechanical ventilation and the individual intensivist services have been studied,(34–38) to our knowledge there is no research characterizing the delivery of ECMO within specific CTICU vs. non-CTICU settings. With the expansion of ECMO indications, it remains unknown how, under what circumstances, and for whom ECMO is implemented in non-CTICU locations. Specifically, it is unknown if ICU type has an association with clinical parameters (e.g., partial pressure of arterial oxygen [P_aO_2]) or management strategies (e.g., ECMO blood flow rate), within the same ECMO indication and for ECMO patients across different support types (i.e. cardiac, respiratory, and extracorporeal cardiopulmonary resuscitation [ECPR]).

Our group sought to primarily examine the use of ECMO outside traditional CTICU settings with specific attention to application outside its established role in postcardiotomy shock.(31, 32, 39) As cultural paradigms can drive critical care delivery,(38) we aimed to investigate the association of ICU type with on-ECMO management. We utilized the ELSO Registry comprehensive dataset of the United States to understand the volume of ECMO use and the characteristics of patients managed outside of the traditional CTICU setting. Our objectives were two-fold. We aimed to describe diagnoses and characteristics in ECMO use across the CTICU vs. non-CTICU settings. Secondly, we sought to describe the association of the non-CTICU location on patient clinical variables during ECMO. Exploratory analysis was performed on ECMO use in relation to cardiac surgery procedures across ICU types.

Methods

Our analysis is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.(40)

Study Population

All adult (age ≥18 years) subjects who had ICU location recorded in the ELSO Registry from January 1, 2018 to December 31, 2019 were included in the analysis. Patients requiring ECMO for cardiac, respiratory, or ECPR indications were included. In cases of more than one ECMO run per patient, we analyzed only the patient’s first run. We excluded patients outside of the United States, and those whose ECMO runs occurred primarily in the operating room, coronary catheterization lab or emergency department (as these environments are distinctly different than any ICU). These locations have a distinctly different goal than longitudinal ECMO care of an ICU. For all analyses, we stratified our population into three cohorts according to the ECMO support type as entered into Registry form: cardiac, pulmonary and ECPR. Support type does not necessarily correspond to the cannulation configuration (i.e. VV vs. VA); however, it describes the organ failure for which ECMO is initiated.

Data Source

The ELSO Registry is a voluntary international registry with approximately 500 contributing centers across 60 countries and containing >125,000 patients over >30 years.(41–43) Registry data are used for both quality improvement and research (44, 45) and have been used in over >300 publications in PubMed. Data submission via ELSO site managers requires passage of the data entry exam with subsequent guidance via detailed instructions and standardized database definitions. Point-of-entry data assessment with error and validity checks along with full record validation at time of submission ensure completeness of mandatory fields. Internal validation has shown that only 1% of 190 reported fields were incorrect.(46, 47) The Registry undergoes continuous multimodal auditing and has been previously validated.(46–48) Standardized case report forms submitted by ELSO site data managers detail basic demographic data (age, weight, sex, race), pre- and on-ECMO ventilation data and circuit parameters as well as ICU location. Since 2018, the type of ICU in which most or integral parts of ECMO care was delivered has been collected under the data field of “Unit where ECLS received.”(43)

Exposure

The exposure was ICU type which was available on Registry data forms beginning in 2018. For the purposes of analysis, ICU type was dichotomized into CTICU vs. non-CTICU. Non-CTICU included adult medical ICU, adult surgical ICU, cardiac ICU, extracorporeal life support ICU, burn ICU, or mixed ICU locations. Conceptually, the non-CTICU designation was based upon units that are not primarily related to cardiac surgery (e.g., the multi-specialty extracorporeal life support ICU and cardiac ICU were both classified as non-CTICU). Per the ELSO Registry form instructions, the “unit where ECMO received” was to be filled out as location where “majority or most integral aspect” of ECMO care took place, with careful consideration for the unit that decided to place the patient on ECMO.

Outcomes

Our primary outcome was US ECMO case volume distribution by ICU type, clustered into CTICU vs non-CTICU. Secondary outcomes were case mix-adjusted patient physiologic variables by CTICU vs. non-CTICU locations, stratified by cardiac, respiratory and ECPR support indications. Physiologic outcomes included the following variables at 24 hours of ECMO support: respiratory rate (RR), partial pressure of arterial oxygen (P_aO_2,) and carbon dioxide (P_aCO_2), fraction of inspired oxygen (F_iO_2), positive end-expiratory pressure (PEEP), mean airway pressure and systolic blood pressure (SBP). Details regarding identification of the variables at 24 hours have been previously described.(43) Specifically, these values are on-ECMO values closest to 24 hours and between 18 and 30 hours. We also considered ECMO blood flow rate at both 4 and 24 hours after ECMO initiation and duration from ECMO initiation to the start of enteral feeding as secondary outcomes. As an exploratory analysis into the use of ECMO within traditional cardiac surgery paradigms, we described the use of cardiac surgical procedures, defined using *Current Procedural Terminology* (CPT) codes for heart or pericardium (33016 – 33999) excluding runs solely associated with codes for ECMO cannulation or daily management (33946 – 33989), by ICU type. The goal of this analysis was to understand differences in ECMO use/application and management 24 hours after cannulation; as such, aggregate outcomes such as mortality and complications were not available for the purposes of this analysis.

Covariates

We *a priori* identified available pre-ECMO characteristics for adjustment that have been shown to be associated with survival in ECMO or cardiac arrest populations: age,(33, 49, 50) sex,(51) chronic comorbidities,(49, 50) and acute severity of illness.(48, 50) We additionally included pre-ECMO cardiac arrest, pre-ECMO arterial blood gases, pre-ECMO ventilator settings, planned cannulation for organ transplant (ECMO as bridge to transplant), and duration of mechanical ventilation prior to ECMO initiation.

To account for the influence of acute severity of illness on the probability of survival, we calculated a modified RESP score (for pulmonary support patients) and SAVE score (for cardiac and ECPR support patients).(48, 50) Diagnostic codes for use in each of these were classified according to the *International Classification of Diseases*, 10th Edition. To identify patients classified in the postoperative cardiac surgery procedure state, CPT procedures codes were used as described above. Each CPT code within heart or pericardium range was individually screened by two members of the research team (C.G.O. and J.E.T.) for determination of cardiac surgery classification (eTable 1 in Supplement). To account for the influence of chronic medical conditions on probability of survival, we calculated the Charlson Comorbidity Index (CCI) for all patients.(52) For ECPR patients, we additionally adjusted for the presence of pre-arrest/pre-ECMO mechanical ventilation.

Statistical Analysis

We fit a linear regression model predicting the outcome variable of interest based on both the covariates and the ICU location. We examined the association of non-CTICU location on several 24 hour on-ECMO metrics: P_aO_2, P_aCO_2, F_iO_2, PEEP, systolic blood pressure, mean airway pressure, time from ECMO until enteral feeding, pump blood flow rate (at 4 and 24 hours), and RR. We assessed this significance via a linear regression model where covariates controlled for are a mix of continuous and categorical variables (similar to ANCOVA [Analysis of Covariance]).

To control for initial physiologic differences between patients, we used a linear additive approach, modeling each of the on-ECMO output variables of interest (stratified and fitted independently for each support type) as a function of ICU location, age, gender, P_aO_2, PEEP, HCO_3^-, Charlson Comorbidity Index, time to intubation, pre-ECMO arrest, transplant status, and procedure/diagnosis groups. The following were used for each cohort: a modified RESP score for pulmonary support patients; a modified SAVE score and (binary yes/no) cardiac surgery variable for cardiac support patients; and modified SAVE score and mechanical ventilation status (binary yes/no) variable for ECPR patients.

Missing variables were imputed using multiple imputation with the MICE package in R.(53) Significance of the effect of the ICU type on the outcome was assessed through the regression coefficient's associated t-test, as well as with an F-test to compare the regression model with the nested model predicting the outcome solely based on the covariates. Since we examined multiple outcomes with independent models, we adjusted for multiple hypothesis testing using the Bonferroni procedure, which controls the family wise error rate. A p-value < 0.05 after Bonferroni correction, was considered statistically significant. All statistical analyses were conducted with R v3.6.2.

Data Sharing

Our analytic code is available in the Open Science Foundation repository (DOI:10.17605/OSF.IO/5WN6G, available at https://osf.io/5wn6g/) to facilitate research reproducibility, replicability, accuracy and transparency. Code was deidentified in accordance with section 164.514 of the Health Insurance Portability and Accountability Act. Data that support the findings of this work are available from ELSO and were used under license for the current study. The data can be requested from ELSO.

This analysis was approved by the ELSO Scientific Oversight Committee (ELSO, Ann Arbor, MI) and by the research ethics board of Stanford University (eProtocol #56562). As an analysis of deidentified data, it was determined to be exempt from human subjects review by the Institutional Review Board of Stanford University Medical Center.

Results

ECMO Case Volume and Distribution Across ICUs

ECMO Support Type by ICU—From January 1st, 2018 through December 31st, 2019, 10,893 unique ECMO runs were managed either in a CTICU or non-CTICU; CTICU: 59.9% (6,528), non-CTICU: 41% (4,365) (Figure 1). Of ECMO runs managed within the CTICU, 53.5% (3,491) were for cardiac indications, 33.2% (2,171) were for respiratory, and 13.3% (866) were for ECPR (Figure 2). In the non-CTICU setting, 41.2% (1,798) of ECMO runs were for cardiac support, 46.4% (2,025) for respiratory support, and 12.4% (542) were for ECPR.

Cardiac Surgery Procedures by ICU Type—Within the CTICU, 20.7% and 18.0% (2018 and 2019, respectively) of ECMO runs were associated with cardiac surgery procedures (Figure 3). Outside of the CTICU, 11.2% and 12.9% were associated with cardiac surgical procedures.

Patient Distribution by ECMO Support Type—Of all ECMO runs for cardiac support (5,289), 66% (3,491) were managed within the CTICU, with 34% (1,798) managed outside of the CTICU. Of all ECMO runs for respiratory support (4,196), 52% (2,171) were managed within the CTICU, with 48% (2,025) managed in the non-CTICU. Of all ECMO runs for ECPR (1,408), 61.5% (866) were managed within the CTICU, with 38.5% (542) managed outside of the CTICU (Figure 2).

Adjusted association of on-ECMO physiology by ICU type

Cardiac Support Runs—After multivariate adjustment, management within a non-CTICU (vs. CTICU) was associated with statistically significantly lower on-ECMO 4- and

24-hour blood flow rate (3.9 liters LPM vs. 4.1 LPM, $p<0.0001$; 4.1 LPM vs. 4.3 LPM, $p<0.0001$) (Figure 4 and eFigure 1a in Supplement). There were no statistically significant differences by ICU type in on-ECMO F_iO_2, mean airway pressure, P_aCO_2, PEEP, P_aO_2, RR, SBP or duration from ECMO initiation until enteral feeding (eFigure 1a in Supplement).

Pulmonary Support Runs—After multivariate adjustment, management within a non-CTICU (vs. CTICU) was associated with statistically significant differences in select on-ECMO physiologic variables of F_iO_2 (66.5 mmHg vs. 69.0 mmHg, $p=0.01$), and RR (14 BPM vs. 15 BPM, $p<0.0001$) (Figure 4 and eFigure 2a in Supplement). There were no statistically significant differences in mean airway pressure, P_aCO_2, PEEP, P_aO_2, flows, SBP or duration from ECMO initiation until enteral feeding (eFigure 2a in Supplement).

ECPR Support Runs—After multivariate adjustment, non-CTICU showed statistically significant difference in 24-hour ECMO blood flow rates (3.5 LPM vs. 3.7 LPM, $p=0.01$). No differences were found in F_iO_2, mean airway pressure, P_aCO_2, PEEP, P_aO_2, 4-hour blood flow rate, RR or duration from ECMO initiation until enteral feeding (eFigure 3a in Supplement).

Discussion

To our knowledge, this is the first large-scale, ELSO Registry-based study to characterize the use of ECMO outside the traditional CTICU in the United States. While non-CTICU ECMO is increasing, we observed that the majority of all ECMO runs in the United States from 2018 through 2019 still occur within a traditional CTICU (60%) even when stratified by support type. Compared to non-CTICU, a higher fraction of CTICU ECMO is for cardiac support (54% compared to 41% of non-CTICU). Combining these data with the increase in ECMO for postcardiotomy shock in the past decade would suggest that the provision of ECMO is still largely within traditional CTICU locations.(31, 32, 39) Despite growth in the breadth of ECMO applications in recent years,(8, 10, 54) our analysis shows that delivery of ECMO has not similarly diversified.(9, 55–57) Importantly, our study characterizes and defines to what extent ECMO has been provided in non-CTICU settings.

We found that non-CTICU settings have lower case numbers for all ECMO support types (cardiac, respiratory and ECPR) compared to CTICU. However, when comparing non-CTICU vs. CTICU ECMO unit settings, the non-CTICU setting has a higher proportion of respiratory support in comparison to that of CTICU. Furthermore, the percentage of ECMO for ARDS was higher for non-CTICU (52% vs. 45%) settings consistent with the increased proportion of respiratory support ECMO. These data would suggest that the provision of ECMO care by ICU type is still largely driven by indication with respect to primary organ failure. Of the non-CTICU ECMO, the largest fraction of runs are for respiratory support; in contrast, the largest proportion of CTICU ECMO runs are for cardiac support.

In contrast to the expected findings of primary organ system failure dictating ICU location, our analysis of ECMO and cardiac surgery procedures found lower than expected rates of perioperative ECMO.(39) A minority of ECMO across both CTICU and non-CTICU locations is actually primarily related to cardiac surgery (the highest percentage in our analysis was 20% of CTICU ECMO for 2018). Though cardiac surgery procedures ECMO was an exploratory analysis, this is an important finding of our descriptive study as there is a discrepancy between the provision of ECMO by unit type and the procedural indication. ECMO is still mostly within CTICUs when only a minority of ECMO runs are related to cardiothoracic surgery.

Further analysis of our data attempted to quantify the effect of non-CTICU management on selected on-ECMO metrics. As ECMO use expands but remains largely within the realm of CTICUs, our team asked whether location of ECMO patients within non-traditional units showed meaningful associations with differences in management. After adjustment, ECMO run characteristics and on-ECMO physiologic metrics differed statistically by ICU location but were clinically minimal. The differences in on-ECMO metrics, though statistically significant in our analysis, are clinically minimal often with changes of less than 5%. It is important to note the myriad of variability in circuit setups, cannula sizes and individual physiology preclude firmly drawing conclusions on the effect of ICU type. However, the variation in on-ECMO metrics between ICU types even after adjustment and within subgroups of support type across the large (> 10,000 ECMO runs) dataset suggests a signal for unit effect. Future research should now examine important subpopulations on a more focused level. We acknowledge that the groupings of CTICU vs non-CTICU are broad and rough--and may not reflect important differences in staffing or volume within each group. Our groupings do reflect historical, cultural and systems-based distinctions and are somewhat validated by our findings of consistent differences across years, despite adjustment. The large dataset showed CTICUs housed more ECMO related to cardiac support and cardiac surgery procedures than non-CTICUs, reflecting some validity to our choice in grouping heterogenous ICUs together as non-CTICUs in contrast to CTICU. As ECMO continues to expand in indication and location, our work provides descriptive analysis of the current state of ECMO delivery as it relates to heterogeneity within fields of cardiac and thoracic surgery.(58) In context of prior work on the provision of ECMO, our analysis shows how there are minimal differences in on-ECMO metrics across unit types.(20),(59, 60)

Study Limitations

Limitations of the analysis were driven by the constraints of data collection elements in the ELSO Registry and the availability of data for only 2 years. Though the COVID-19 pandemic has only strengthened the need for further research in the multidisciplinary provision of ECMO, the constraints of our data query limited us to pre-COVID-19 data (2018 and 2019). The subsequent research in the provision of ECMO during the pandemic only further supports our call for continued investigation in this area.(27, 61) Concluding trends from our analysis would be difficult with the limited 2-year time frame (this was all data available from ELSO at time of query approval); thus, our approach was primarily descriptive in nature. The most notable limitation to our analysis was the documentation method of the ICU location. We had no method of accounting for whether ICU location was entered as cannulation location or the subsequent management unit if they were different.

A limitation of this analysis was a focus on use and physiologic differences at 24 hours of ECMO support, rather than aggregate or other clinical outcomes such as mortality or complications. These outcome data were not available for this analysis but are a focus of future work.

Another limitation to the analysis in the provision of ECMO was the lack of granular physiologic data and only limited ventilator data (i.e., tidal volumes, static compliance, driving pressure and mechanical power were unavailable). Despite this lack of data, we were able to demonstrate that available physiologic metrics, after multivariate adjustment, were remarkably similar. Notably, drawing robust conclusions on effect of ICU type is limited when raw physiologic metrics like circuit flow aren't normalized to body surface area or cannula configuration. While this was a novel descriptive study of ECMO by ICU location, our conclusions about management are limited by Registry data in accurately capturing systems organization. It is impossible to tell the degree to which ICU location, primary teams and consultants affect on-ECMO parameters (e.g., a medical ICU where the cardiac surgery service is the primary team vs. the consultant in charge of ECMO management). Finally, outcomes and center-specific analysis for ECMO by ICU type was beyond the intended scope of this analysis. Despite our limitations, this work is a novel and important step in the description of the provision of ECMO across healthcare systems and ICU types.

Conclusion:

Evidenced in ELSO guidelines and international, large scale studies, ECMO is inherently multidisciplinary and resource-intensive yet remains ill-defined in terms of systems of care for its delivery.(16, 62) This study is the first to use large Registry data to characterize how systems-based, cultural, and ICU type factors may affect ECMO management within complex healthcare systems. The majority of ECMO care in the United States is still provided within cardiothoracic ICUs, but its use is expanding in non-CTICUs. A minority of runs are associated with primarily cardiac surgery indications. After multivariate adjustment, on-ECMO physiologic metrics are minimally different across ICU types.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ECMO	extracorporeal membrane oxygenation

CTICU	cardiothoracic intensive care unit
ELSO	extracorporeal life support organization
ECPR	extracorporeal cardiopulmonary resuscitation
VV	venovenous
VA	venoarterial
CPT	Current Procedural Terminology

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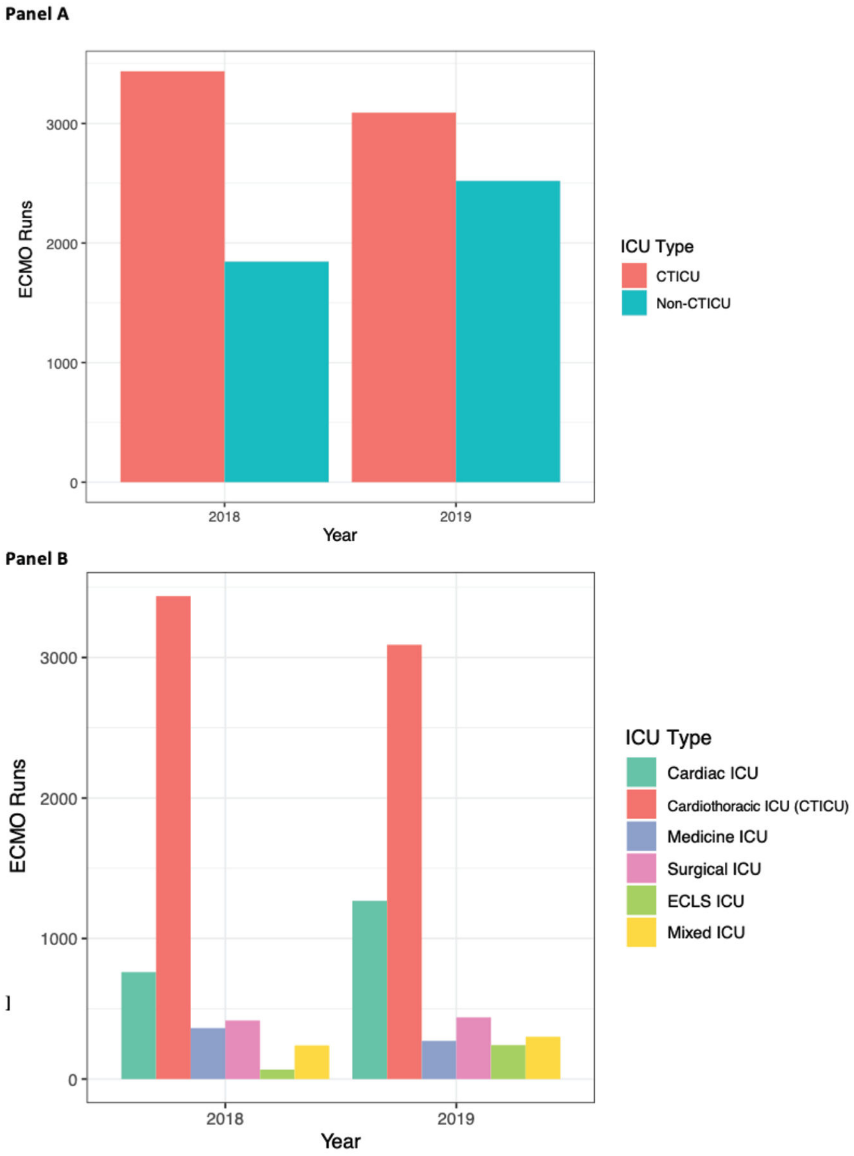
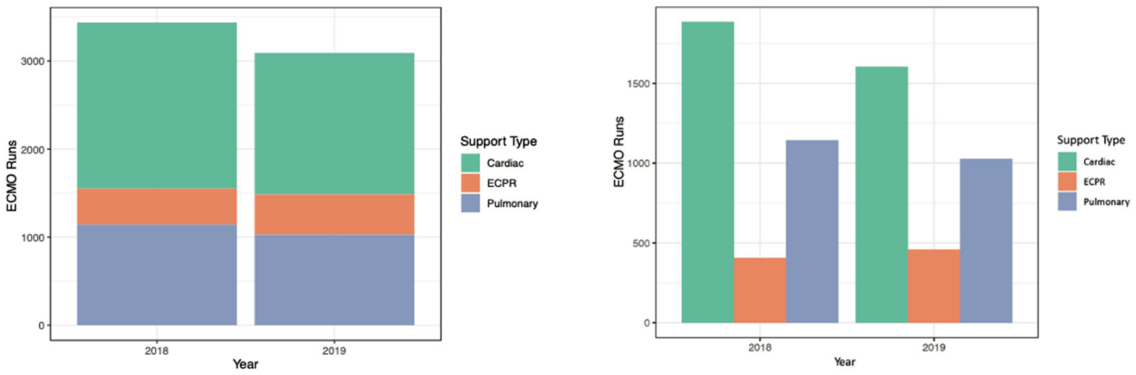


Central Illustration/Figure 1: ECMO runs by ICU type

Panel A shows distribution of ECMO amongst CTICU and non-CTICU settings over 2018 and 2019. Panel B describes the specific ICU types in which ECMO was managed over the same time period.

CTICU



Non-CTICU

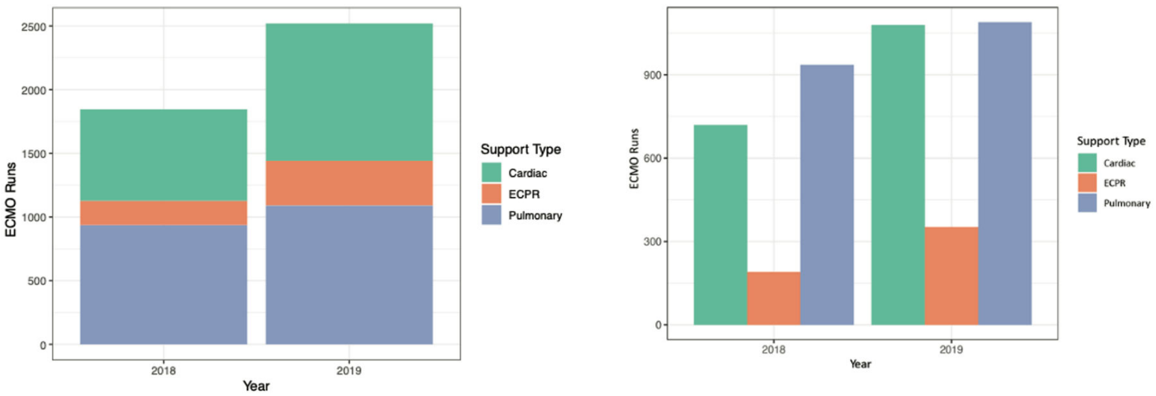


Figure 2:

ECMO case volume across the CTICU and non-CTICU by support type

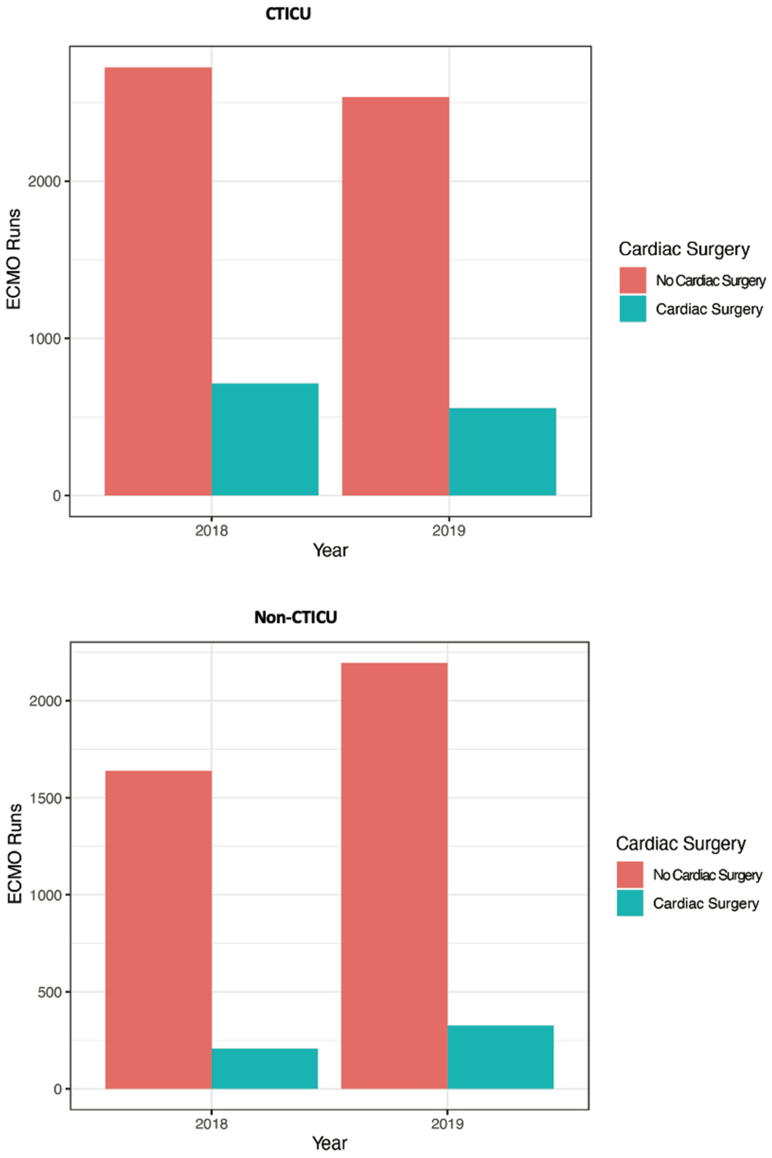


Figure 3:

ECMO associated with cardiac surgery procedures by ICU type

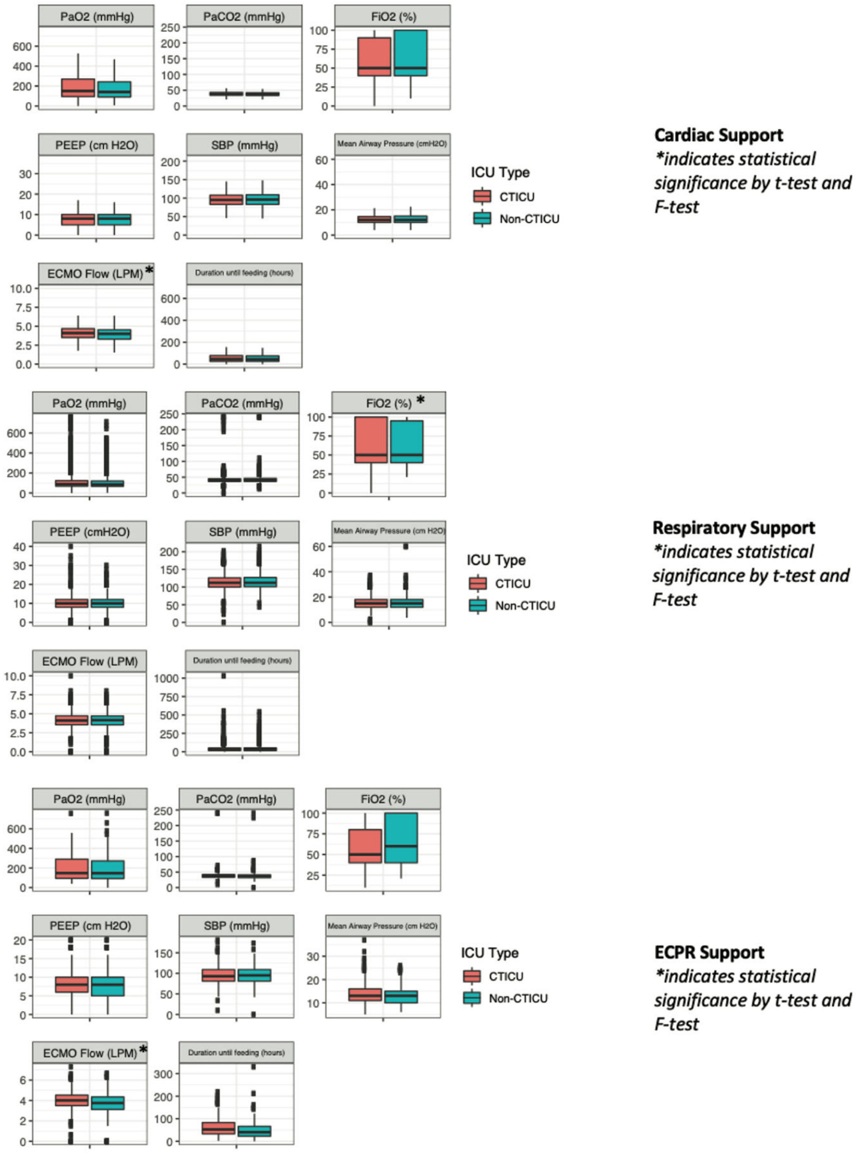


Figure 4:

On-ECMO metrics by ICU location for cardiac, respiratory and ECPR support

Table 1 –

Characteristics of CTICU and Non-CTICU by Support Type

	CTICU			Non-CTICU		
	Cardiac	**Respiratory**	**ECPR**	**Cardiac**	**Respiratory**	**ECPR**
Demographics						
No. of patients	3,491	2,171	866	1,798	2,025	542
Male, no.	2336	1328	576	1187	1235	359
Age, median (IQR), y	59 (48–68)	50 (36–61)	58 (47–67)	59 (48–67)	48 (35–59)	59 (47–67)
Cardiac surgery, no. (%)						
Yes	1,269 (19)			533 (12)		
No	5,259 (81)			3,832 (88)		
Major diagnoses, no. (%)						
ARDS	2,970 (45)			2,250 (52)		
Asthma	168 (3)			134 (3)		
Acute MI	1,062 (16)			551 (13)		
Aortic dissection	254 (4)			92 (2)		
Cardiomyopathy	808 (12)			379 (9)		
Cardiac surgery	1,269 (19)			533 (12)		
Heart failure	1,562 (24)			748 (17)		
Pulmonary embolism	398 (6)			271 (6)		
Sepsis	586 (9)			460 (11)		
Transplant	388 (6)			263 (6)		
Clinical data						
Charlson Comorbidity Index, mean	1	1	1	1	1	1
Modified RESP, mean (SD)	--	0.97 (3)	--	--	1.0 (3)	--
Modified SAVE, mean (SD)	−1.6 (4)	--	−3.7 (4)	−1.1 (4)	--	−3.2 (4)
ECMO, mean (SD), hours	164 (171)	251 (269)	120 (150)	160 (178)	275 (299)	101 (135)