Outcomes After Respiratory Extracorporeal Life Support in Teens and Young Adults: An Extracorporeal Life Support Organization Registry Analysis*

Stephanie R. Brown, MBBS, MS[1,2]
Jana Assy, MD[3]
Michael P. Anderson, PhD[4]
Ravi R. Thiagarajan, MBBS[5,6]
Thomas V. Brogan, MD[7,8]

OBJECTIVES: A recent study from Germany found that survival after respiratory extracorporeal life support (ECLS) was lower among patients 10–20 years old than 20–30 years old. The objective of this study was to compare survival between teenage and young adult patients who receive respiratory ECLS.

DESIGN: Retrospective cohort study.

SETTING: Extracorporeal Life Support Organization registry, an international prospective quality improvement database.

PATIENTS: All patients ages 16–30 years cannulated for respiratory indications from 1990 to 2020 were included. Patients were divided into two groups, teens (16–19 yr old) and young adults (20–30 yr old).

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Primary outcome was survival to discharge. Variables were considered for the multivariate logistic regression model if there was both a statistically significant difference ($p \leq 0.05$) and a clinically meaningful absolute difference between the groups. A total of 5,751 patients were included, of whom 1,653 (29%) were teens and 4,098 (71%) were young adults. Survival to discharge was higher in young adults than teens, 69% versus 63% ($p < 0.001$). Severity of illness was higher among teens; however, survival within each stratum defined by Pa_{O_2}/F_{IO_2} ratio was higher in young adults than in teens. Use of venoarterial ECLS was higher in teens than in young adults, 15% versus 7%, respectively. Teens were more likely to receive high-frequency oscillatory ventilation and this therapy was associated with a longer time from admission to ECLS initiation. After adjusting for variables that differ significantly between the groups, the odds ratio for survival in young adults compared with teens was 1.14 (95% CI, 1.004–1.3).

CONCLUSIONS: In this large multicenter retrospective study, mortality was higher in teens than in young adults who received respiratory ECLS. This difference persisted after adjusting for multiple variables and the mechanism underlying these findings remains unclear.

KEY WORDS: adolescent; extracorporeal membrane oxygenation; respiratory distress syndrome; respiratory insufficiency; young adult

The use of extracorporeal life support (ECLS) for respiratory failure has increased throughout the world. In fact, over 40,000 patients received this therapy over the past 5 years (1). A recent study from Germany found that survival after respiratory ECLS was lower among patients 10–20 than 20–30 years old (2). The reasons for this difference in survival are unclear and studies rarely compare these two groups because the ECLS literature

DOI: 10.1097/CCM.0000000000006049

is typically divided into neonatal, pediatric, and adult studies (3–5). A direct comparison of teens with young adults is needed to confirm this earlier finding and to determine whether the groups differ by factors known to be associated with outcome after respiratory ECLS, including primary diagnosis, severity of illness at cannulation, and ECLS complications (6–8).

The primary objective of this study is to compare survival to hospital discharge after ECLS for respiratory failure between adolescents (age 16–19 yr) and young adults (age 20–30 yr). The secondary objectives include identifying patient and clinical characteristics that differ between the groups and that are associated with survival after ECLS in these populations.

MATERIALS AND METHODS

We performed a retrospective cohort study of patients in the Extracorporeal Life Support Organization (ELSO) registry database from 1990 to 2020 (9). We included the index course of ECLS for all patients 16–30 years old cannulated for respiratory indications. We divided our cohort into groups based on the previous study describing different outcomes for patients 10 to less than 20 years old versus 20–30 years old and older (2). The finding of greater mortality in ECLS patients who were 10–20 years old compared with those 20–30 years old seemed surprising; our goal was to confirm this finding. We compared two groups in this study, teens (16–19 yr old) and young adults (20–30 yr old). We chose patients 16 to less than 20 years as the teen group because theoretically they should have greater physiologic similarities to patients in their 20s compared with patients less than 16, who may be more similar to young children. We also felt that teenagers are a distinct group to study because they are likely to have fewer comorbid conditions at ECLS deployment than adults and potentially have better outcomes. Furthermore, very few studies focus on teenaged patients on ECLS as a separate group and often combine them with pediatric or adult cohorts. We felt that this study adds to medical knowledge by considering teenage patients supported with ECLS as a distinct cohort. Data for this study were obtained from the ELSO registry, an international prospective quality improvement database (9). This study was reviewed by the Seattle Children's Hospital Institutional Review Board (IRB) and labeled not human research (IRB: 00003233).

The primary outcome was survival to hospital discharge. The secondary outcomes included patient and clinical characteristics that differ between the groups and characteristics associated with survival to hospital discharge. Patient demographics, laboratory values, support modalities, and ECLS complications are defined per the ELSO registry data classifications (10). We collapsed the original 21 primary diagnosis classifications into 14 categories for the multivariable analysis. We calculated oxygenation index (OI) using the following equation: OI = (Fio_2 × mean airway pressure × 100)/Pao_2 (11). We calculated the Pao_2/Fio_2 (P/F) ratio from the blood gas data (12). Illness severity was based on P/F ratio with greater than 200 defined as mild, greater than 100–200 as moderate, and 100 or less as severe. We defined CNS injury as the occurrence of CNS infarct, CNS ischemia, and/or CNS hemorrhage. We computed descriptive statistics for all demographic and clinical variables. We summarized categorical variables as frequencies and continuous variables as medians with interquartile ranges (IQRs). Continuous variables were assessed for normality using the Kolmogorov-Smirnov test. We compared categorical variables between the teen and young adult groups using a chi-square test or Fisher exact test, as appropriate. Continuous variables were assessed for normality as above within the teen and young adult groups and compared using Student *t* test or the Wilcoxon/Mann-Whitney *U* test, as appropriate.

We considered variables for inclusion in a multivariable logistic regression model of survival if there was a statistical difference ($p < 0.05$) between the two groups. We excluded variables from the model when the differences between the groups were less than 5%; two authors (S.R.B., T.V.B.) deemed this difference to be clinically insignificant. We also excluded variables if large amounts of data were missing (> 20%) or if the variable was colinear with another variable in the model. A posteriori, we performed a logistic regression comparing survival between groups stratified by: 1) illness severity as defined by P/F ratio and 2) difference between peak inspiratory pressure (PIP) and positive end-expiratory pressure (PEEP) of 18 cm H_2O or less (13). Since the ELSO registry does not collect plateau pressures, we used the difference between PIP and PEEP as an approximation of driving pressure, termed "modified driving pressure" (14). We also tested whether the time from admission to ECLS initiation and from intubation to ECLS initiation differed between groups, stratified by whether or not the patient received high-frequency oscillatory ventilation (HFOV).

RESULTS

A total of 5,751 patients received respiratory ECLS during the study period: 1,653 teens and 4,098 young adults. The median age of study participants was 23 years (IQR, 19–26 yr), 45% (2,496 patients) were female, and the most common diagnosis was acute respiratory distress syndrome (ARDS) (18%). The overall survival was 67% (3,831 patients). Patient demographics and outcomes are summarized by group in **Table 1**. Survival was lower among teens (63% [1,026 patients]) than young adults (69% [2,805 patients]; $p < 0.001$). **Table 2** summarizes the laboratory values, illness severity, and support before ECLS initiation. Hypotension was more common among the teen group than young adults (48% vs 42%; $p < 0.001$) as was the use of vaso-inotrope infusions (30% vs 23%; $p < 0.001$). Pulmonary vasodilator therapies were more frequently used among teens than young adults (25% vs 20%; $p < 0.001$) and a larger proportion of teens had severe illness by P/F ratio (82% vs 79%; $p = 0.028$). For patients in the mild category, the most common diagnosis was asthma, followed by acute respiratory failure and "other" (see **Supplemental Table 1**, http://links.lww.com/CCM/H421, for full details).

TABLE 1.
Patient Demographics

Variable	Teens, *n* (%)	Young Adults, *n* (%)	*p*
Total	1,653 (29)	4,098 (71)	
Sex (female)	736 (46)	1,760 (45)	0.5
Race			0.007
Asian	111 (7)	374 (9)	
Black	245 (15)	603 (15)	
Hispanic	147 (9)	385 (9)	
White	911 (55)	2,084 (51)	
Other	239 (14)	652 (16)	
Primary diagnosis			< 0.001
ARDS	262 (16)	753 (18)	
Acute respiratory failure	308 (19)	668 (16)	
Bacterial pneumonia	85 (5)	200 (5)	
Viral pneumonia	56 (3)	142 (4)	
Fungal pneumonia	12 (1)	19 (< 1)	
Pneumonia not otherwise specified	51 (3)	127 (3)	
Asthma	62 (4)	197 (5)	
COVID-19	12 (1)	51 (1)	
Influenza	59 (4)	200 (5)	
Sepsis	82 (5)	176 (4)	
Cystic fibrosis	70 (4)	197 (5)	
Transplant	24 (1)	82 (2)	
Pulmonary embolism	17 (1)	44 (1)	
Pulmonary hemorrhage	11 (1)	8 (< 1)	
Pulmonary hypertension	8 (< 1)	34 (1)	
Aspiration	36 (2)	86 (2)	
Trauma	153 (9)	342 (8)	
Trauma ARDS	11 (1)	29 (1)	
Lung contusion	17 (1)	27 (1)	
Submersion	27 (1)	27 (1)	
Other	290 (18)	689 (17)	

ARDS = acute respiratory distress syndrome.
p value is for comparison between teen and young adult groups.

The mode, duration, and complications experienced during the ECLS course are summarized in **Table 3**. Teens were more likely to receive venoarterial ECLS than young adults (15% vs 7%; $p < 0.001$). They were

TABLE 2.
Illness Severity and Support at Extracorporeal Life Support Initiation

Variable	Teens	Young Adults	p
pH[a]	7.23 (7.12–7.33)	7.24 (7.13–7.33)	0.06
Pa_{CO_2}[a]	60 (45–80)	59 (46–79)	0.19
Pa_{O_2}[a]	59 (47–77)	63 (49–82)	< 0.001
Venous oxygen saturation[a]	70 (54–86)	67 (55–79)	0.13
Presence of hypotension[b]	559 (48)	1,136 (42)	< 0.001
Severity of illness (defined by Pa_{O_2}/F_{IO_2} ratio)			0.028
Mild[b]	81 (6)	214 (7)	
Moderate[b]	160 (12)	446 (14)	
Severe[b]	1,073 (82)	2,476 (79)	
Vaso-inotrope infusion[b]	504 (30)	932 (23)	< 0.001
Pulmonary vasodilator[b]	415 (25)	833 (20)	< 0.001
Renal replacement therapy[b]	59 (4)	179 (4)	0.17
Ventilatory support			
Positive end-expiratory pressure[a]	12 (9–15)	12 (10–16)	0.015
Peak inspiratory pressure[a]	36 (30–45)	36 (31–41)	0.0029
Mean arterial pressure[a]	24 (19–30)	23 (19–28)	< 0.001
High-frequency oscillatory ventilation[b]	211 (13)	165 (4)	< 0.001
Neuromuscular blockade[b]	817 (49)	1,850 (45)	0.003
Prone positioning[b]	61 (4)	237 (6)	0.001
Steroids[b]	185 (11)	490 (12)	0.4

[a]Median (interquartile range).
[b]*n* (%).
Pa_{O_2}/F_{IO_2} ratio data available in 1,281 teens and 3,021 young adults. *p* value is for comparison between teen and young adult groups.

also more likely to have an ECLS mode conversion and to experience complications. Time from admission to cannulation was 60 hours longer in teens who received HFOV compared with those who did not, whereas this difference was only 18 hours in young adults (**Supplemental Table 2**, http://links.lww.com/CCM/H421).

The multivariable logistic regression model for survival to hospital discharge included group, race, primary diagnosis, vaso-inotrope infusion, HFOV, ECLS mode, and hemorrhagic complication. After adjusting for the other variables in the model, the odds ratio (OR) for survival was higher in young adults than teens (OR, 1.14; 95% CI, 1.004–1.3; $p = 0.04$). All variables in the model were associated with survival and the results of the multivariable logistic regression are summarized in **Tables 4** and **5**. Modified driving pressure data was available for 910 teens and 2,340 young adults. A modified driving pressure of 18 cm H_2O or less was present in 28% of teens and 31% of young adults and was associated with increased survival compared with modified driving pressure greater than 18 cm H_2O. After adjusting for group, the odds of survival among patients with modified driving pressure greater than 18 cm H_2O is 0.84 (95% CI, 0.71–0.99) compared with 18 cm H_2O or less. Survival was higher in young adults than teens after adjusting for severity of illness defined by P/F (OR, 1.33; 95% CI, 1.17–1.53) (**Fig. 1**). After adjusting for group, receiving HFOV was associated with a 12 hours ($p < 0.0001$) longer time from admission to cannulation and 29 hours ($p < 0.0001$) longer time from intubation to cannulation.

DISCUSSION

In this large multicenter cohort, survival after respiratory ECLS is lower among teens than young adults. This

TABLE 3.
Extracorporeal Life Support and Complications

Variable	Teens, *n* (%)	Young Adults, *n* (%)	*p*
Mode			< 0.001
Venovenous	1,213 (73)	3,469 (85)	
Venoarterial	248 (15)	303 (7)	
Veno-veno-arterial	19 (1)	40 (1)	
Conversion	105 (6)	140 (3)	
Other	68 (4)	146 (4)	
Time from admission to ECLS (hr)[a]	18 (2–119)	16 (1–111)	0.09
Time from intubation to ECLS (hr)[a]	32 (9–114)	35 (9–121)	0.27
Duration of ECLS (hr)[a]	180 (92–358)	180 (91–342)	0.96
Complications			
Mechanical	301 (18)	625 (15)	0.006
Circuit change	55 (3)	149 (4)	0.57
Hemorrhage	372 (23)	707 (17)	< 0.001
CNS injury	80 (5)	173 (4)	0.3
Infection	189 (11)	431 (11)	0.31
Arrest on ECLS	105 (6)	194 (5)	0.012

ECLS = extracorporeal life support.

[a]Median (interquartile range).

p value is for comparison between teen and young adult groups. CNS injury defined as CNS infarct, ischemia, and/or hemorrhage.

TABLE 4.
Outcomes After Respiratory Extracorporeal Life Support

Outcome	Teens, *n* (%)	Young Adults, *n* (%)	*p*
Survival to discharge	1,026 (63)	2,805 (69)	< 0.001
Length of stay (d)[a]	24 (22–44)	23 (12–41)	0.18

[a]Median (interquartile range).

p value is for comparison between teen and young adult groups.

difference persists after adjusting for race, primary diagnosis, mode of ECLS, use of HFOV, use of vaso-inotrope infusion, and occurrence of a hemorrhagic complication, all of which are also associated with lower survival. Additionally, when all patients were considered, mortality was greater in those who had a pre-ECLS difference between PIP and PEEP of more than 18 cm H_2O.

The mechanisms underlying the greater mortality in teens compared with young adults remain unclear. Teens had higher rates of HFOV, use of venoarterial ECLS and mode change. Venoarterial ECLS support and mode change is known to be associated with higher odds of mortality including in this cohort (15). Although we do not know why a particular mode of ECLS was chosen, the higher use of venoarterial ECLS among teens may reflect an overall higher illness severity in these patients. Alternatively, this may reflect differences in ECLS physician or surgeon preference between pediatric and adult practitioners. Additionally, HFOV was associated with longer time to ECLS initiation and higher mortality in this study. Guidelines for the use of HFOV exist only for adults, as studies to compare it to conventional mechanical ventilation have yet to be performed in pediatrics (16). However, the Prone and Oscillation Pediatric Clinical Trial (PROSpect) trial of use prone positioning and HFOV in pediatric ARDS patients is currently ongoing (17). We were surprised by the very low rate of prone positioning in both groups before cannulation for ECLS. Although there is not currently evidence to support routine prone positioning in pediatrics, the use of prone positioning is recommended for adults with moderate to severe ARDS (11, 18).

TABLE 5.
Multivariable Analysis for Survival After Respiratory Extracorporeal Life Support

Variable	OR (95% CI)	*p*
Group (young adult vs teen)	1.14 (1.004–1.3)	0.049
Race		< 0.0001
White	Reference	
Black	0.78 (0.66–0.93)	
Hispanic	0.77 (0.63–0.95)	
Asian	0.58 (0.47–0.71)	
Other	0.86 (0.72–1.03)	
Primary diagnosis		< 0.0001
Acute respiratory distress syndrome	Reference	
Acute respiratory failure	0.96 (0.79–1.17)	
Aspiration	2.01 (1.23–3.3)	
Pneumonia	0.91 (0.74–1.13)	
Asthma	4.59 (2.82–7.49)	
Influenza	1.17 (0.86–1.6)	
COVID-19	1.12 (0.62–2.03)	
Cystic fibrosis	0.56 (0.42–0.75)	
Sepsis	0.56 (0.42–0.74)	
Pulmonary embolus	1.94 (1.03–3.65)	
Submersion	0.84 (0.47–1.52)	
Trauma	0.81 (0.64–1.02)	
Transplant	0.65 (0.42–1.001)	
Other	0.72 (0.6–0.87)	
Vaso-inotrope infusion at cannulation	1.19 (1.04–1.36)	0.014
High-frequency oscillatory ventilation	1.28 (1.02–1.62)	0.034
Hemorrhagic complication	1.52 (1.31–1.75)	< 0.0001
Mode		< 0.0001
Venovenous	Reference	
Venoarterial	0.5 (0.41–0.61)	
Veno-veno-arterial	0.29 (0.17–0.49)	
Conversion	0.34 (0.26–0.44)	
Other/unknown	0.47 (0.47–0.64)	

OR = odds ratio.

ORs, 95% CIs, and *p* values were calculated using multivariable logistic regression comparing survivors and nonsurvivors. Values are adjusted for all other variable in the multivariable model.

We found a statistical difference between the two groups in primary diagnosis but this was small and probably not responsible for the important difference in survival. It is also possible that teens and young adults receive different pre-, intra-, and/or post-ECLS management. The teen groups are more likely to receive care in a pediatric center than young adults, many of which have lower ECLS volumes than adult centers. Higher center volume is associated with lower mortality, so this may explain some of the difference in mortality (19). Although the groups in our study are physiologically similar, they

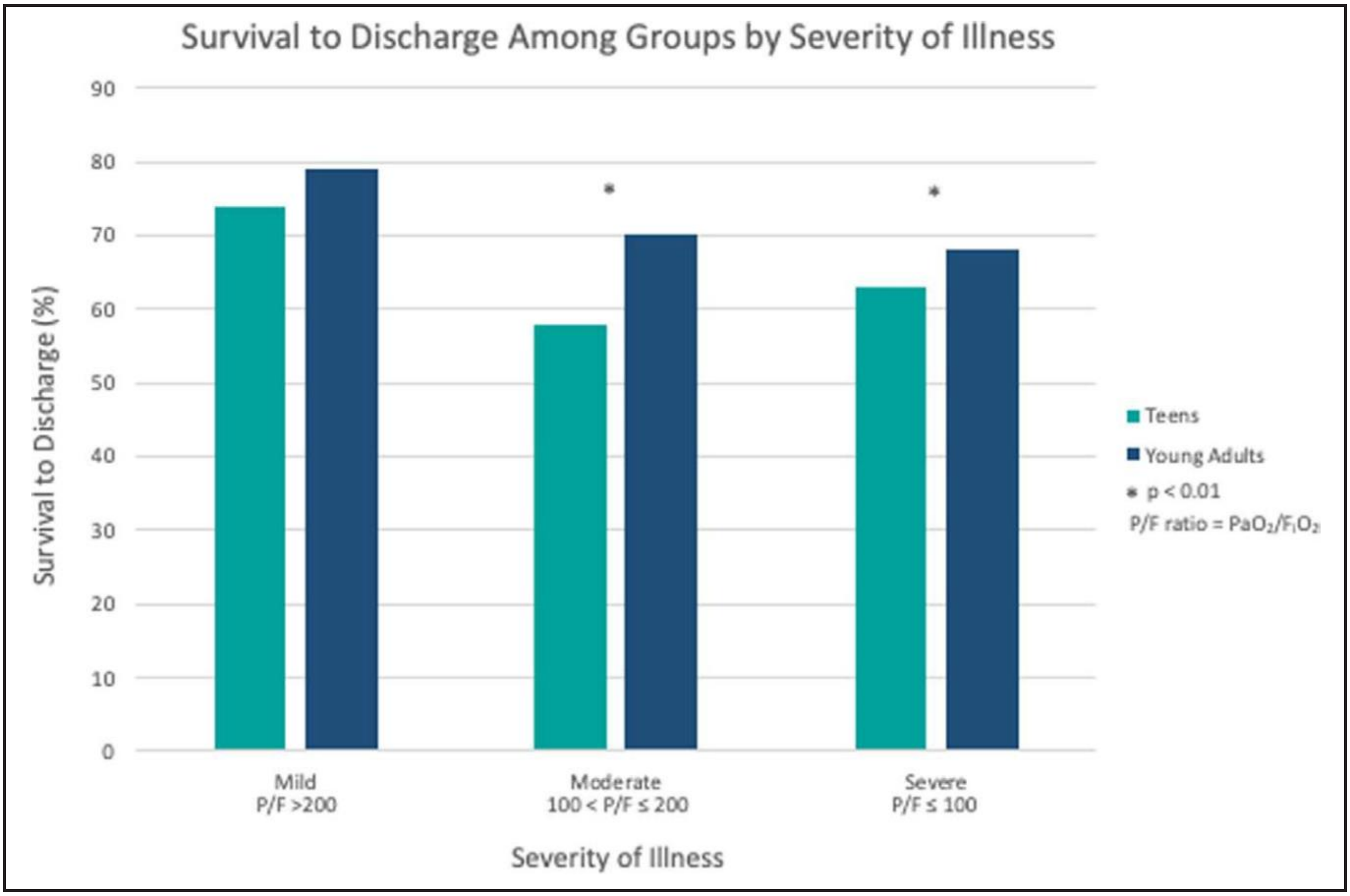

Figure 1. Survival after respiratory extracorporeal life support by group and illness severity. *p* values compare survival rates between teens and young adults within the same severity category. P/F = Pa_{O_2}/F_{IO_2} ratio.

may receive different c are d epending o n w hether they are in an adult or pediatric center. Pediatric and adult intensivists have different guidelines to define and manage ARDS, so they are likely to have different management strategies of many areas of patient care (mobilization, nutrition, anticoagulation, etc.) accordingly (11, 18). In particular, adult guidelines recommend the use of prone positioning and against routine use of HFOV, whereas pediatric guidelines do not recommend routinely using prone positioning and recommend a trial of HFOV if PIP greater than 28 (11, 18). The ELSO registry provides limited data on the factors that lead to application of ECLS support. Further insight into differences in management of these two groups might help improve care for the younger group of patients.

High-modified driving pressures (> 18 c m H_2O) were associated with increased mortality among the entire cohort. This finding accords with existing literature demonstrating higher morbidity and mortality with higher driving pressure or delta pressure (13, 14,
20). The ELSO registry does not record plateau pressure, driving pressure, or ventilator mode so we chose the modified driving pressure measure as a surrogate. Since this analysis uses PIP and not plateau pressure, the presence of significant airway resistance could falsely elevate this value. Of note, the pre-ECLS ventilator settings and time of mechanical intubation before ECLS cannulation were similar between teens and young adults. Further insight into pre-ECLS ventilator strategies could help elucidate differences between these two groups. We found that a larger proportion of teens had severe illness, as measured by P/F ratio, than young adults; however, both groups had a significant portion of patients with mild or moderate illness. It is unclear why these patients required extracorporeal membrane oxygenation (ECMO) despite higher P/F ratios, we presume that there were other factors, such as hemodynamic instability, involved in the decision. This is consistent with a recent study of pediatric respiratory ECLS patients in the ELSO registry, which also found a large proportion of patients with

more mild disease as measured by OI than might be expected (21).

We also found that non-White race was associated with higher mortality after respiratory ECLS, even after adjusting for variables associated with survival including diagnosis, age group, and mode of ECLS. Race is a social construct and any disparity in outcome between groups defined by race is not due to genetic background but rather reflects the impact of systemic racism on health (22, 23). Elucidating the mechanisms underlying this disparity requires data on other important social variables, including geographic location, income and access to care, which are not collected in the ELSO registry currently (22). The relationship between race and health outcomes is complex and is influenced by the presence of systemic racism in many communities globally (22). Understanding the association between race and respiratory ECMO outcomes will require prospectively collecting data on the myriad social factors which mediate this relationship (23, 24).

This study has the following strengths. First, the use of data from an international registry provided large numbers of patients in both populations. Second, we compared teens and young adults directly using the same data source. Last, these patients represent a heterogeneous group with a variety of diagnoses across a range of illness severity. This improves the generalizability of the findings from this study.

However, this study also has several important limitations. First, there were a large proportion of patients missing data required to calculate OI and P/F ratios. This prevented us from including illness severity in the multivariable model. Second, we did not have data on comorbid conditions, medical complexity or cause of death for this study which may have an impact on outcome. Third, we do not know whether patients received their care at adult or pediatric centers and center type may impact management and outcome of these patients. Finally, the data used for this study represents a snapshot of patient status at a single point in time preceding ECLS initiation and contains a limited set of variables. There may be important differences in unmeasured variables or the remainder of patient care course that is not accounted for by this analysis.

This study provides an important direct comparison of teens and young adults who received respiratory ECLS. After adjusting for factors that differ between the groups, survival remains lower among teens than in young adults. These findings highlight the need for further investigation of comparing these populations to understand best practices. In particular, there is a need to report outcomes for these two groups of patients within broader pediatric and adult studies.

CONCLUSIONS

In this large multicenter retrospective study, mortality was higher in teens than in young adults who received respiratory ECLS. This difference persisted after adjusting for multiple variables and the mechanism underlying these findings remains unclear. Further investigation is required to understand this important disparity in outcome.

1 Division of Pediatric Critical Care Medicine, Oklahoma Children's Hospital, Oklahoma City, OK.
2 Department of Pediatrics, University of Oklahoma Health Sciences Center, Oklahoma City, OK.
3 Department of Pediatrics, Division of Pediatric Critical Care, Centre Hospitalier Universitaire de Liège, Liège, Belgium.
4 Department of Biostatistics and Epidemiology, University of Oklahoma Health Sciences Center, Oklahoma City, OK.
5 Cardiac Intensive Care Unit, Boston Children's Hospital, Boston, MA.
6 Department of Cardiology, Harvard Medical School, Boston, MA.
7 Division of Pediatric Critical Care Medicine, Seattle Children's Hospital, Seattle, WA.
8 Department of Pediatrics, University of Washington, Seattle, WA.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Dr. Thiagarajan's institution received funding from the U.S. Department of Defense; he received funding from the Extracorporeal Life Support Organization and the Society of Critical Care Medicine. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: stephanie.brown@choa.org

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