Extracorporeal Membrane Oxygenation in Pregnancy: An Analysis of the Extracorporeal Life Support Organization Registry

Kollengode Ramanathan, MD, FCICM, FCCP[1,2]; Chuen Seng Tan, PhD[2,3]; Peter Rycus, MPH[4]; Marc Anders, MD, FCICM[5]; Roberto Lorusso, PhD[6]; John J. Y. Zhang, MBBS[2]; Graeme MacLaren, MBBS, MSc, FCCM[1,2,7]

Objectives: We examined data from the International Registry of the Extracorporeal Life Support Organization to identify risk factors for mortality in pregnant and peripartum patients receiving extracorporeal membrane oxygenation.

Design: Retrospective analysis.

Setting: International Registry of Extracorporeal Life Support Organization.

Patients: We collected de-identified data on all peripartum patients who needed extracorporeal membrane oxygenation between 1997 and 2017 using *International Classification of Diseases*, 9th and 10th Edition criteria.

Interventions: Our primary outcome measure was in-hospital mortality. We also collected data on demographics, preextracorporeal membrane oxygenation ventilator, hemodynamic and biochemical parameters, extracorporeal membrane oxygenation mode, duration, and complications. Initial bivariate analysis assessed potential associations between survival and various preextracorporeal membrane oxygenation as well as extracorporeal membrane oxygenation-related factors. Variables with p values of less than 0.1 were considered for logistic regression analysis which identified predictors of mortality.

Measurements and Main Results: There were 280 peripartum patients who received extracorporeal membrane oxygenation. Overall maternal survival was 70%, with observed mortality for these patients decreasing over the 21-year time period. Multivariate regression identified extracorporeal cardiopulmonary resuscitation (odds ratio, 3.674; 95% CI, 1.425–9.473; overall $p = 0.025$), duration of extracorporeal membrane oxygenation (< 66 hr: odds ratio, 1; 66–128 hr: odds ratio, 0.281; 95% CI, 0.101–0.777; $p = 0.014$; 128–232 hr: odds ratio, 0.474; 95% CI, 0.191–1.174; $p = 0.107$; and > 232 hr: odds ratio, 1.084; 95% CI, 0.429–2.737; $p = 0.864$; overall $p = 0.017$), and renal complications on extracorporeal membrane oxygenation (odds ratio, 2.346; 95% CI, 1.203–4.572; $p = 0.012$) as significant risk factors for mortality. There was no statistically significant difference in mortality between venovenous versus venoarterial versus mixed group extracorporeal membrane oxygenation (23.9 vs 34.4 vs 29.4%; $p = 0.2$) or between pulmonary versus cardiac indications (1.634; 95% CI, 0.797–3.352; $p = 0.18$) for extracorporeal membrane oxygenation.

Conclusions: On analysis of this multicenter database, pregnant and peripartum patients with refractory cardiac or respiratory failure supported on extracorporeal membrane oxygenation had survival rates of 70%. We identified preextracorporeal membrane oxygenation as well as extracorporeal membrane oxygenation-related factors that are associated with mortality. (*Crit Care Med* 2020; 48:696–703)

Key Words: complications; extracorporeal; pregnancy

The use of extracorporeal membrane oxygenation (ECMO) for critical cardiopulmonary failure has been rising over the past few years (1). Despite increases in the overall use of ECMO, its use in the management of refractory cardiopulmonary failure in pregnant patients is currently limited to case reports, case series, and a few select systematic reviews on specific infections in pregnancy (2). A recent analysis of the National Inpatient Service database showed that there are increasing rates of cardiogenic shock (CS) among peripartum patients during a 12-year period; the prevalence of

[1]Cardiothoracic ICU, Department of CTVS, National University Heart Centre, Singapore.

[2]Yong Loo Lin School of Medicine, National University of Singapore, Singapore.

[3]Swee Saw School of Public Health, National University of Singapore, Singapore.

[4]University of Michigan, Ann Arbor, MI.

[5]Department of Pediatrics, Baylor College of Medicine, Houston, TX.

[6]Department of Cardiothoracic Surgery, Maastricht University Medical Centre, Cardiovascular Research Institute Maastricht, Maastricht, The Netherlands.

[7]Paediatric ICU, Royal Children's Hospital, University of Melbourne, Melbourne, VIC, Australia.

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CS was 3.8 per 100 000 pregnancy-related hospitalizations in the United States. This contributed to 18.81% of all maternal mortalities as compared 0.02% in patients with no CS and was associated with a higher occurrence rate of adverse outcomes including cardiac arrest (pregnant patients with and without CS: 16.35% vs 0.01%) and intrauterine fetal death (pregnant patients with and without CS: 1.38% vs 0.1%) (3). Similar data from the United Kingdom identified deaths attributable to cardiac disease as the most common overall cause for maternal death; peripartum cardiomyopathy contributed to 25% of this mortality (4). The use of mechanical cardiac support in pregnancy as bridge to recovery or transplant has been shown to be feasible in patients with peripartum cardiomyopathy with relatively low mortality rates (3, 5). However, the use of ECMO in severe cardiac failure during pregnancy has not been fully elucidated. In addition to supporting patients with cardiomyopathy, ECMO has also been used to salvage peripartum patients with cardiovascular collapse from massive pulmonary embolism (PE), rheumatic heart disease, and amniotic fluid embolism (6).

Similarly, the benefits of ECMO over conventional lung-protective ventilation techniques in acute respiratory failure remain controversial (7, 8), and uncertainty remains over the role of ECMO in pregnant and postpartum patients. The occurrence rate of acute respiratory distress syndrome (ARDS) in pregnant patients requiring mechanical ventilation has increased from 36.5 cases per 100,000 live births to 59.6 cases per 100,000 live births in the United States, during a 7-year period from 2006 to 2012, with an overall mortality of 9% (9). Although infection remains the most common cause of ARDS in pregnancy, maternal mortality ranges from 10% to more than 50% and is complicated by prolonged ventilation and a higher occurrence of perinatal asphyxia (10–12). The Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries in the United Kingdom (MBRRACE-UK) report of 2016, which detailed on Confidential Enquiry into Maternal Deaths in United Kingdom from 2009 to 2014, recommended early ECMO referral for peripartum patients with severe respiratory failure (4, 13). A recently published randomized controlled study done by the ECMO to Rescue Lung Injury in Severe ARDS Trial Group showed reduction in treatment failure with use of ECMO; however, they excluded pregnant patients from the study (14). The use of ECMO in pregnant patients with H1N1 pneumonia showed that ECMO support for severe respiratory failure is technically feasible in pregnant and postpartum patients with survival rates of up to 66% (2). The utility of ECMO in pregnant patients with severe respiratory failure is thus, not fully established.

The Extracorporeal Life Support Organization (ELSO) has maintained an international registry of patients on ECMO since 1989 and collects data from over 300 international pediatric and adult centers. Given the limited evidence for ECMO therapy in pregnancy, we sought to examine this registry to analyze all pregnant patients treated with ECMO, in order to establish the epidemiological characteristics, clinical features, survival to discharge and complication rates, and risk factors associated with mortality.

MATERIALS AND METHODS

Patient Selection

After approval from the Institutional Review Board, we collected data from the ELSO registry on all female patients between 15 and 49 years old, who had a diagnosis of pregnancy-related diseases based on *International Classification of Diseases*, 9th Edition (ICD-9) and *International Classification of Diseases*, 10th Edition (ICD-10) coding and who received ECMO between 1997 and 2017. The codes pertaining to primary as well as secondary diagnoses of pregnancy-related diseases were examined independently by two investigators (K.R., P.R.). Any disagreements were resolved by a third investigator (G.M.). The codes were also used to look at the common clinical indications for ECMO. Brain-dead patients were excluded from analysis because it was difficult to determine the timing of brain death from the registry, which reported brain death as a neurologic complication. Patients with multiple ECMO runs had only their first run included for analysis.

The primary outcome measure was in-hospital mortality and risk factors. The mortality trend was compared during the period between 1997 and 2017 at 5-year intervals. We also analyzed the various complications on ECMO in addition to looking at common indications for ECMO based on ICD-9 and ICD-10 codes as well as the cannulation strategies in the peripartum population. Variables collected from the registry included demographic information, pre-ECMO ventilation parameters (Pao_2/Fio_2 [P/F] ratio, peak inspiratory pressure, and positive end-expiratory pressure [PEEP]) and biochemical parameters (pH, Pao_2, $Paco_2$), pre-ECMO hemodynamic variables, pre-ECMO inotrope requirements (use of dopamine, adrenaline, noradrenaline, dobutamine, or vasopressin), renal function, ECMO mode, duration, and complications. Patients who needed conversion from venovenous ECMO to venoarterial ECMO or vice versa and those who needed hybrid configurations (e.g., veno-arterial-venous) were categorized into the mixed group. Use of adjunctive therapies such as nitric oxide, corticosteroids, sodium bicarbonate, neuromuscular blockers, and high frequency oscillation was also recorded from the database. We performed a univariate analysis to assess for potential associations between survival and specific risk factors: demographic variables, pre-ECMO ventilator, hemodynamic and biochemical parameters, ECMO mode, duration, and complications. All continuous variables were categorized into four groups using cutoffs from the first to fourth quartiles to allow for nonlinear effects. Sensitivity analyses were performed to account for the effect of age on the association of relevant univariates like systolic, diastolic, and mean arterial blood pressure and mortality. Complications on ECMO were identified from the registry and were classified under eight subgroups as entered into the registry (**Supplementary Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/F332). Complication rates among survivors versus

nonsurvivors were then computed. The chi-square or Fisher exact test was used in the univariate analysis where appropriate, and counts and proportion were reported for nonsurvivors and survivors.

A multiple logistic regression model for nonsurvivors was developed to identify risk factors for mortality. Variables that had *p* values of less than 0.1 in the univariate analysis were considered for the multiple logistic regression models. A stepwise variable selection model building approach using Akaike information criteria (AIC) was used to construct the multiple logistic regression model where the model with the lowest AIC is the best model (15, 16).

All analyses were performed using R statistical language (R Foundation for Statistical Computing, Vienna, Austria). *p* values of less than 0.05 were considered significant.

RESULTS

From the 281 pregnant and peripartum patients who were supported on ECMO, we had complete data for 277 patients for their first run. There were 13 patients who were brain dead; one patient had missing mortality data. Data of 263 patients were eventually analyzed. Overall, maternal survival was 70% over the 20-year period. Venoarterial ECMO was the predominant mode used (128/258 patients—49.6%); 43.8% (113/258 patients) received venovenous ECMO; 17 patients needed either a hybrid mode or conversion from one mode to another while data on the mode of ECMO was not available in five patients (**Table 1**). The majority of patients (52.5%) needed ECMO for pulmonary indications; 83 patients (31.5%) needed ECMO for cardiac indications while 16% of pregnant and peripartum patients had extracorporeal cardiopulmonary resuscitation (ECPR) (Table 1). Sixty-two pregnant/parturient patients who needed ECMO had cardiomyopathy; 48 patients had peripartum cardiomyopathy. Twenty-three patients (37.1%) with cardiomyopathy eventually died. There were 62 peripartum patients with PE during this period of which 12 patients had amniotic fluid embolism. Fourteen patients with PE (22.6%) did not survive. Among patients with pulmonary indications for ECMO, 98 out of 180 peripartum patients had unclassified complications of labor or pregnancy with an overall mortality of 30.9%; 54 patients had pneumonia or influenza with 22.2 % mortality while 20 of them had sepsis or septic shock, of which seven patients (35%) did not survive. Other pulmonary indications for ECMO in pregnant and postpartum females included hypertensive disorders of pregnancy, fluid overload, PE, asthma, and aspiration pneumonia. The number of pregnant and peripartum patients who were initiated on ECMO increased after 2006 with a marked rise in the last 6 years (2012–2017), with a nonsignificant reduction

TABLE 1. Univariate Analysis of Demographic and Extracorporeal Membrane Oxygenation Variables and Mortality in Peripartum Patients

Variable	Categories	Alive/Dead	Mortality (%)	*p*
Age, yr	< 24.1	45/23	33.8	0.429
	24.1–30.2	50/15	23.1	
	30.2–36.5	41/22	34.9	
	> 36.5	48/19	28.4	
Weight, kg	< 63	44/21	32.3	0.748
	63–75	43/21	32.8	
	75–90.9	43/14	24.6	
	> 90.9	42/19	31.1	
Mode	Mix	12/5	29.4	0.205
	Venoarterial	84/44	34.4	
	Venovenous	86/27	23.9	
Duration of extracorporeal membrane oxygenation, hr	< 66	35/25	41.7	**0.003**
	66–128	54/9	14.3	
	128–232	48/18	27.3	
	> 232	41/26	38.8	
Indication	Cardiac	56/27	32.5	**0.026**
	Extracorporeal cardiopulmonary resuscitation	23/19	45.2	
	Pulmonary	105/33	23.9	

Boldface values indicate $p < 0.05$ were considered significant.

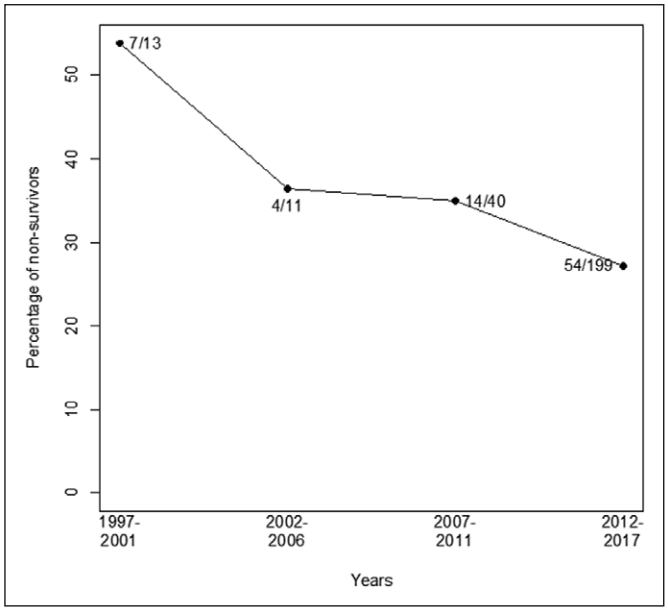

Figure 1. Overall mortality of peripartum patients on extracorporeal membrane oxygenation (ECMO) over a 20-yr period from 1997 to 2017. The number of patients who died during the 5-yr periods has also been represented against the total number of pregnant patients on ECMO during that period.

in overall mortality over the 21-year period (mortality: 1997–2001 vs 2002–2006 vs 2007–2011 vs 2012–2017: 53.85% vs 36.36% vs 35.00% vs 27.14; $p = 0.156$) (**Fig. 1**). Data on cannulation was available in 244 patients. One-hundred seventy-five of 244 (71.7%) had percutaneous peripheral cannulation while 21 patients (8.6%) had central cannulation. Femoral artery was the most common site accessed for arterial cannulation (110/244 patients) while femoral vein was the preferred venous cannulation site (178/244 patients).

Pre-ECMO Factors

Pre-ECMO factors associated with mortality on univariate analysis included the indication for ECMO and need for hemofiltration (**Tables 1–3**; and **Supplementary Table 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/F333). There was no difference in mortality in terms of mode of ECMO used. (mortality: venovenous vs venoarterial vs mixed: 23.9% vs 34.4% vs 29.4%; $p = 0.21$). Pregnant patients who needed ECMO for pulmonary indications had 76.1% survival rates while 42 of 263 pregnant patients had ECPR with survival rates of 54.8%. Other biochemical parameters (e.g., pH, Po_2, Pco_2), ventilator parameters (e.g., PIP, P/F ratio, PEEP), hemodynamic variables (e.g., mean arterial pressure, systolic blood pressure) (Table 2), or use of pre-ECMO adjunctive therapies (e.g., inotropes, nitric oxide, high frequency ventilation) (Table 3) did not have any significant association with mortality.

ECMO Factors

ECMO factors associated with nonsurvival included duration of ECMO and presence of ECMO complications (neurologic, pulmonary, cardiovascular, renal, infectious, and hemorrhagic) (Table 1; Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/F332; and **Supplementary Table 3**, Supplemental Digital Content 3, http://links.lww.com/CCM/F334). Duration of ECMO was significantly associated with mortality where patients with shorter (< 66 hr) and longer duration of ECMO (> 232 hr) run had higher mortality than the rest. (duration of ECMO: < 66 vs 66–128 vs 128–232 vs > 232 hr and mortality: 41.7% vs 14.3% vs 27.3% vs 38.8%; $p = 0.003$) (Table 1). Cardiovascular (49.8%), renal (42.9%), and hemorrhagic complications (37.3%) occurred more frequently; cannulation site bleeding accounted for less than 50% (47/98 patients) of the hemorrhagic complications.

Multiple Regression

Multiple regression analysis identified ECPR, duration of ECMO, and renal complications as risk factors for mortality in pregnant and peripartum patients who needed ECMO. Although ECPR had 3.7 times odds of mortality compared with pulmonary indications for ECMO, the presence of renal complications increased the likelihood of mortality by 2.35 in pregnant patients (**Table 4**).

DISCUSSION

Our analysis of the international ELSO registry revealed that pregnant and peripartum patients supported on ECMO had survival rates of 70%. More pregnant patients had ECMO initiated in the last few years with a trend toward reduced mortality over the 20-year period. The data from the ELSO registry remains the largest cohort of pregnant and peripartum patients whose outcomes on ECMO have been analyzed.

Outcomes of ECMO in peripartum patients has been limited to case reports, case series, and selective systematic reviews. A recent meta-analysis that reported outcomes for ECMO in pregnant and postpartum patients with H1N1-related ARDS demonstrated maternal and fetal survival rates of more than 60% (2). Although maternal respiratory failure secondary to infection and ARDS is a major indication for ECMO, ECMO is also commonly used to salvage peripartum patients with massive PE, peripartum cardiomyopathy, and amniotic fluid embolism (6). Given that up to 40% of maternal deaths are potentially preventable in peripartum women, it is important for physicians to be cognizant of the outcomes of ECMO in this patient group (17).

The notable features of this analysis include the fact that there was no difference in maternal mortality on ECMO for pulmonary versus cardiac indications (odds ratio, 1.634; 95% CI, 0.797–3.352; $p = 0.18$). This contrasts with what has been reported from the ELSO registry, where patients needing ECMO for respiratory indications have better survival rates that those with cardiac indications (1). However, this may be related to the relatively limited number of patients and inadequate power of our cohort. We also observed that mechanical ventilation prior to ECMO in this group might have been suboptimal, with the majority of patients having a higher range of Pco_2 expected for pregnancy, as well as high peak inspiratory pressures and hypoxemia. Targeting lower airway pressures during

TABLE 2. Univariate Analysis of Preextracorporeal Membrane Oxygenation Biochemical, Ventilatory, and Hemodynamic Variables and Mortality in Peripartum Patients

Variable	Categories	Alive/Dead	Mortality (%)	*p*
pH	< 7.1	32/21	39.6	0.205
	7.1–7.22	40/17	29.8	
	7.22–7.36	36/19	34.5	
	> 7.36	44/12	21.4	
Pco_2, mm Hg	< 36	45/18	28.6	0.058
	36–48	42/12	22.2	
	48–60	36/15	29.4	
	> 60	30/25	45.5	
Po_2, mm Hg	< 51.6	38/15	28.3	0.401
	51.6–67	40/21	34.4	
	67–96.7	32/20	38.5	
	> 96.7	43/14	24.6	
Bicarbonate, mmol/dL	< 16.7	31/19	38	0.154
	16.7–20.1	37/13	26	
	20.1–24.7	37/13	26	
	> 24.7	27/21	43.8	
Peak inspiratory pressure, cm H_2O	< 26	26/12	31.6	0.100
	26–32	32/6	15.8	
	32–38	28/10	26.3	
	> 38	23/16	41	
Positive end-expiratory pressure, cm H_2O	< 7	29/17	37	0.689
	7–10	29/11	27.5	
	10–16	34/16	32	
	> 16	26/9	25.7	
Pao_2/Fio_2 ratio	< 53	34/13	27.7	0.895
	53–69	34/16	32	
	69–100	33/17	34	
	> 100	35/14	28.6	
Systolic blood pressure, mm Hg	< 79	35/16	31.4	0.847
	79–92	39/14	26.4	
	92–110	38/15	28.3	
	> 110	31/16	34	
Diastolic blood pressure, mm Hg	< 42.2	40/9	18.4	0.229
	42.2–52	34/19	35.8	
	52–65	34/17	33.3	
	> 65	34/14	29.2	
Mean arterial pressure, mm Hg	< 56.2	34/15	30.6	0.597
	56.2–67	40/12	23.1	
	67–78.2	31/17	35.4	
	> 78.2	37/15	28.8	

TABLE 3. Univariate Analysis of Preextracorporeal Membrane Oxygenation Adjuvant Therapies and Mortality in Peripartum Patients

Pre-Extracorporeal membrane oxygenation Adjuvant Therapies	Categories	Alive/Dead (*n*)	Mortality (%)	*p*
Inotropes	No	51/18	26.1	0.496
	Yes	133/61	31.4	
High frequency ventilation	No	173/76	30.5	0.564
	Yes	11/3	21.4	
Nitric oxide	No	150/68	31.2	0.471
	Yes	34/11	24.4	
Steroids	No	168/67	28.5	0.178
	Yes	16/12	42.9	
Bicarbonate/Tris hydroxyl acetone maleate	No	157/64	29	0.489
	Yes	27/15	35.7	
Hemofiltration	No	8/10	28.2	**0.029**
	Yes	176/69	55.6	
Neuromuscular blockers	No	126/56	30.8	0.809
	Yes	58/23	28.4	

Boldface value indicates $p < 0.05$ was considered significant.

TABLE 4. Multivariate Analysis Showing Risk Factors for Mortality in Peripartum Patients

Risk Factors	OR (95% CI)	*p*	Overall *p*
Pre-ECMO factors			
Indications			
Pulmonary	1		**0.025**
Cardiac	1.634 (0.797–3.352)	0.18	
Extracorporeal cardiopulmonary resuscitation	3.674 (1.425–9.473)	**0.007**	
Hemofiltration	2.758 (0.857–8.878)	0.089	
ECMO factors			
Duration of ECMO, hr			
< 66	1		**0.017**
66–128	0.281 (0.101–0.777)	**0.014**	
128–232	0.474 (0.191–1.174)	0.107	
> 232	1.084 (0.429–2.737)	0.864	
Renal complications	2.346 (1.203–4.572)	**0.012**	
Neurologic complications	2.345 (0.805–6.836)	0.118	

ECMO = extracorporeal membrane oxygenation, OR = odds ratio.
Boldface values indicate $p < 0.05$ were considered significant.

mechanical ventilation may not be easily feasible in pregnant patients where intra-abdominal pressure would be increased physiologically (18, 19). This makes early referral for ECMO imperative in this subgroup as highlighted by the MBBRACE UK report that recommended prompt ECMO referral for peripartum patients with severe cardiopulmonary failure (4, 13). Pregnant and parturient patients who underwent ECPR following cardiac arrest had a survival of 54.8%; the survival rates are comparable to that of non-ECMO peripartum patients (58%) (20). However, peripartum patients with cardiac arrest had better survival rates compared to 29% survival reported from the ELSO registry for ECPR in other cohorts (1). Bleeding

complications in pregnant patients undergoing ECMO have been frequently reported and has been attributed to the interaction between pregnancy-related coagulation changes with the ECMO circuit. Our data analysis showed that 37.3% of patients who underwent ECMO had hemorrhagic complications and this was associated with mortality on univariate analysis; however, less than 50% of these complications were attributable to cannulation. This correlates closely with the findings from other case series published on ECMO and pregnancy (21, 22), where a higher occurrence rate of hemorrhage has been reported based on individual institutional or regional experience. Our analysis did not identify bleeding complications on ECMO to be a risk factor for mortality, suggesting that bleeding should not be considered a contraindication to initiating ECMO in this critically ill population. Our analysis identified renal complications on ECMO as a risk factor for mortality. This correlates well with existing literature where acute kidney injury has been shown to be an independent risk factor for mortality in ECMO patients and other critically ill patients, in single-center studies (23), as well as during analysis of ELSO registry (24). Pregnant patients who had shorter and longer duration of ECMO run had a higher mortality than the rest; this is consistent with recently published data from both national and ELSO registries for other specific cohorts (25–27), where patients with shorter and longer ECMO runs had higher mortality. The increased mortality could be attributed to very sick patients who had shorter runs (e.g., received ECMO late) with rapid progression to death or brain death or to higher number of complications when they had longer runs. It has to be acknowledged that peripartum patients who deteriorate to the point of needing ECMO are susceptible to the natural course of disease-related severity and complications and the presence of a correlation or statistical association (e.g., pre-ECMO renal dysfunction or ECPR) should not be interpreted as a recommendation to avoid ECMO initiation under such circumstances.

The overall survival rate of 70% reported in our study of ECMO in pregnant and peripartum patients is better than the survival rates reported for ECMO in the general population. The ELSO registry reports an overall survival of 59% in adults with respiratory failure, and while those with cardiac indications remained low at 42% (1). This is very likely from the fact that pregnant patients are young with limited or no comorbidities and clinicians tend to be aggressive with their management. They are monitored during frequent antenatal visits as well as during delivery, which allows for early detection of deterioration and timely intervention. The diseases that necessitate ECMO in pregnancy tend to have a short natural history, which explains their good outcomes.

The limitations of this study include its retrospective nature and lack of standardized criteria for application of ECMO. Many variables including some patient comorbidities and selection criteria are not included in the ELSO database and are center-specific. Center specific data was not available from the registry. The registry does not capture data on timing of ECMO initiation; hence, it remains unknown as to how many received ECMO during pregnancy and postpartum period. Fetal survival rates are also not captured. Use of ICD-9 codes for inclusion has inherent limitations. Data coding and entry are performed at each institution, and some fields remain empty at the time of data submission. Changes to ECMO management over the years with newer pump technologies and varying management guidelines in addition to advances in management of critically ill patients during this period could have had an impact on outcomes. However, this remains the largest cohort of peripartum patients on ECMO that has been analyzed and sheds light on outcomes and risk factors for mortality in pregnant patients receiving ECMO support. We believe that the findings of the study would be useful to both experienced and less experienced ECMO centers in dealing with critically ill pregnant patients who need timely referral and initiation of ECMO, as well as understanding the common indications, the outcomes, and its risk factors.

CONCLUSIONS

In this analysis of an international, multicenter database, peripartum patients supported with ECMO achieved 70% survival to hospital discharge. Peripartum patients with ECPR, shorter or prolonged ECMO runs as well as those with renal complications had a higher odds of mortality. The use of ECMO in severe cardiorespiratory failure associated with pregnancy is feasible with outcomes similar to or better than other cohorts of patients supported on ECMO for other etiologies.

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For information regarding this article, E-mail: ram_ramanathan@nuhs.edu.sg

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