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ORIGINAL RESEARCH

Clinical characteristics and outcomes of extracorporeal membrane oxygenation used in a non-cardiac surgical intensive care unit: Siriraj experiences and literature review

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ABSTRACT:

Background: Extracorporeal membrane oxygenation (ECMO) has substantially increased in frequency of use over the past decades. Occasionally, patients who require ECMO support are admitted to an ICU rather than medical or cardiac ICU, where physicians may be not familiar with the process of how to care for ECMO patients. The aims of this case series were to explore the utilization of ECMO support in a non-cardiac general surgical ICU (SICU) in terms of indications, ECMO-related complications and clinical outcomes.

Methods: Adult patients admitted to the SICU from January 2014 to June 2021 who received ECMO support were included. Demographic data, data regarding ECMO utilization and clinical outcomes were described. Current evidence and updated literature were also researched and reviewed.

Results: A total of 18 patients were admitted to the SICU and received ECMO support, but four died within four hours of SICU admission. The most common reason for ECMO support was extracorporeal cardiopulmonary resuscitation (ECPR) (9 cases, 50.0%), followed by cardiac and/or respiratory support. The majority of patients received venoarterial ECMO support (15 cases, 83.3%). Unfractionated heparin was used in 10 cases (71.4%) and the anticoagulant effect was monitored with aPTT, which was maintained at a lower range (30–50 seconds). There was no thromboembolic event, and four patients (28.6%) developed major bleeding. The overall hospital mortality was as high as 77.8%.

Conclusion: There was a small volume of cases receiving ECMO support in the SICU. ECPR was the most common reason for ECMO support in these patients. Overall, the hospital mortality was 77.8%. To improve outcomes in these patients, appropriate patient selection, well-organized protocols, and a multidisciplinary approach are mandatory.

Keywords: ECMO, ECPR, ICU, Mortality, Perioperative period, Surgical patients

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is an extracorporeal life support technique that has become increasingly utilized in the past decades [1,2]. The first successful use of ECMO in clinical practice was reported in patients with acute respiratory distress syndrome (ARDS) in the 1970s [1-4]. Since then, its use has grown to include other clinical conditions, and is not only limited to patients with ARDS [5]. Instead, it also covers cardiogenic shock [6] and refractory cardiac arrest during cardiopulmonary resuscitation or extracorporeal cardiopulmonary resuscitation (ECPR) [7]. Moreover, its use and application has grown from intensive care units (ICU) to operating theaters for surgical patients undergoing complex airway or intrathoracic surgery, pregnant patients with severe cardiopulmonary diseases during the peripartum period, or high-risk patients undergoing cardiac interventions such as percutaneous coronary intervention or transcatheter aortic valve replacement [8,9].

At Siriraj Hospital, one of the largest tertiary university-based hospitals in Thailand, there are multiple special ICUs, including medical, cardiac, respiratory, neurological, general surgical, cardiothoracic surgery, neurosurgical, pediatric and trauma. Each unit is run by their specialists. For general surgical ICU (SICU), patients undergoing non-cardiac and non-neurological surgery as well as surgical patients who require perioperative intensive care are admitted to this unit. The SICU is a closed ICU and is regulated 24/7 by anesthesiology-based intensivists, critical care fellows and anesthesiology residents. Occasionally, patients requiring ECMO support with a unique indication are admitted to this SICU rather than a medical or cardiac ICU where physicians may be not familiar with the process for caring of ECMO patients. Furthermore, there is limited data regarding ECMO use in general non-cardiac SICU such as indications, ECMO-rated complications and clinical outcomes. Therefore, we conducted this case series to explore the utilization of ECMO at this SICU in terms of indications for ECMO support, ECMO-related complications, and patients' clinical outcomes. In addition, we performed literature review focusing on anticoagulation and mechanical ventilation management in patients receiving ECMO support.

MATERIALS AND METHODS

Setting and patient population

This case series was conducted at a SICU at the tertiary university-based hospital in Bangkok, Thailand. The protocol was reviewed by the institutional review board of the hospital and approval was obtained prior to enrollment (COA no. Si 662/2020), with a waiver of written informed consent as a retrospective chart review. All patients aged ≥18 who were admitted to the SICU between January 2014 and June 2021 were screened and those requiring ECMO support during admission were included in this case series.

KEY MESSAGES:

- In a non-cardiac general surgical ICU, a small number of patients required ECMO support.
- Half of these patients received ECMO support for ECPR and the rest for cardiac and/or respiratory support.
- Anticoagulation management during ECMO support in the perioperative setting was challenging.
- Overall, the hospital mortality in these patients was as high as almost 80%.

Data collection

Of those who were included, their medical records were reviewed and data retrieved including demographic data, comorbidities, Charlson comorbidity index [10], diagnosis at SICU admission, reasons for SICU admission (either planned or unplanned SICU admission following elective or emergency surgery or admission due to a medical condition) Acute Physiology and Chronic Health Evaluation (APACHE) II score [11], Sequential Organ Failure Assessment (SOFA) score [12,13], presence of sepsis/septic shock according to Sepsis-3 definition [13], ARDS according to the Berlin definition [14], acute kidney injury according to the KDIGO definition [15] at SICU admission, and management of mechanical ventilation. Data about ECMO utilization, type of ECMO support (either venoarterial or venovenous and central or peripheral cannulation), anticoagulation management, duration of ECMO support, ECMO-related complications such as ischemic/hemorrhagic stroke, myocardial ischemia/infarction, arrhythmias, hemorrhage, arterial and venous thromboembolism, infection, and limb ischemia was collected. For clinical outcomes, length of SICU and hospital stay, status at SICU and hospital discharge was also collected.

Study endpoints

The primary endpoint of this study was the mortality rate in patients admitted to the SICU who received ECMO support. The secondary endpoints were the indications for ECMO use, the management of anticoagulation and mechanical ventilation during ECMO support, and ECMO-related complications.

Statistical analysis

Descriptive statistics were used to analyze the data. Data was expressed as mean with standard deviation, median with interquartile range (IQR) and number with percentage as appropriate. Data was prepared and analyzed using Microsoft® Excel for Mac Version 16.63.1 (Microsoft, California, USA).

Table 1. Details of 18 patients included in the case series.

Gender	Age	Diagnosis	Reasons for ECMO	Type of ECMO	Discharge status
F	70	Intraoperative cardiac arrest due to massive pulmonary tumor emboli; renal cell carcinoma with renal vein thrombosis and lung metastasis scheduled for open radical nephrectomy.	ECPR	VA ECMO	Deceased
M	67	Cardiac arrest due to type 2 myocardial infarction; postoperative day 2 for robotic-assisted laparoscopic radical prostatectomy for prostate cancer.	ECPR	VA ECMO	Deceased
F	70	Intraoperative cardiac arrest due to unknown causes; pelvic organ prolapse stage 3 scheduled for vaginal hysterectomy.	ECPR	VA ECMO	Deceased
F	52	Intraoperative cardiac arrest due to severe pulmonary hypertension; interstitial lung disease overlapping systemic lupus erythematosus with necrotizing fasciitis at foot with septic shock scheduled for debridement.	ECPR	VA ECMO	Deceased
M	58	Intraoperative cardiac arrest due to acute right ventricular dysfunction after reperfusion; familial amyloidosis scheduled for orthotopic liver transplantation.	ECPR	VA ECMO	Deceased
M	68	Cardiac arrest due to NSTEMI with cardiogenic shock; postoperative day 2 for anterior cervical discectomy and fusion for cervical spondylotic myelopathy at 4th – 7th cervical vertebrae.	ECPR	VA ECMO	Deceased
F	35	Cardiac arrest due to severe pulmonary hypertension and hemorrhagic shock from incomplete abortion; severe rheumatic mitral stenosis with left atrial thrombus.	ECPR	VA ECMO	Alive
F	67	Cardiac arrest due to hypoxemia from upper airway obstruction; postoperative day 3 for fiberoptic bronchoscopy evaluation for tracheal stenosis.	ECPR	VA ECMO	Deceased
M	69	Cardiac arrest due to pulmonary embolism at bifurcation of pulmonary artery extended to left and right pulmonary artery; fall with closed fracture left pelvis and left acetabulum	ECPR	VA ECMO	Deceased
F	65	Intraoperative submassive pulmonary embolism; degenerative scoliosis scheduled for corrective scoliosis with rod and screw fixation	Cardiac	VA ECMO	Alive
M	79	NSTEMI with cardiogenic shock; postoperative day 3 for wedge resection for hepatocellular carcinoma.	Cardiac	VA ECMO	Deceased
M	48	Massive pulmonary embolism with right ventricular dysfunction; postoperative day 1 for radical nephrectomy with pancreaticoduodenectomy for renal cell carcinoma with pancreatic metastasis.	Cardiac	VA ECMO	Deceased
F	56	Severe ARDS following post intraoperative cardiac arrest due to hypoxemia; ureteric stone scheduled for ureteroscopic lithotripsy.	Respiratory	VV ECMO	Alive
M	59	Severe ARDS following massive transfusion; chronic hepatitis C with hepatocellular carcinoma scheduled for orthotopic liver transplantation.	Respiratory	VV ECMO	Deceased
M	57	Severe ARDS following massive transfusion, post intraoperative cardiac arrest due to hemorrhagic shock; hepatocellular carcinoma scheduled for hepatectomy.	Respiratory	VV ECMO	Deceased
F	57	Septic shock due to Klebsiella pneumoniae necrotizing pneumonia with severe hypoxemic respiratory failure.	Both cardiac and respiratory	VA ECMO	Deceased
F	82	Intraoperative massive pulmonary embolism, post intraoperative cardiac arrest; closed fracture of neck of femur scheduled for hemiarthroplasty.	Both cardiac and respiratory	VA ECMO	Alive
F	23	Post intraoperative cardiac arrest due to acute right ventricular failure immediate after transplantation; Budd-Chiari syndrome scheduled for orthotopic liver transplantation.	Both cardiac and respiratory	VA ECMO	Deceased

ARDS, acute respiratory distress syndrome; NSTEMI, non-ST segment elevation myocardial infarction; VA ECMO, venoarterial extracorporeal membrane oxygenation; VV ECMO, venovenous extracorporeal membrane oxygenation

Table 2. Demographic data of 18 patients included in the case series.

Age, year	60.1 ± 14.5
Male gender	8 (44.4)
Comorbidities	
- Cerebral vascular disease	1 (5.6)
- Hypertension	8 (44.4)
- Coronary artery disease	1 (5.6)
- Diabetes mellitus	2 (11.1)
- Liver cirrhosis	3 (16.7)
- Chronic kidney disease	1 (5.6)
Charlson comorbidity index	0 (0, 1)
Reasons for SICU admission[a]	
- Unplanned admission following elective surgery	5 (35.7)
- Medical conditions	5 (35.7)
- Planned admission following emergency surgery	3 (21.4)
- Planned admission following elective surgery	1 (7.1)
APACHE II at SICU admission[a]	25.9 ± 6.2
SOFA at SICU admission[a]	12 (10, 14)
Septic shock[b] at SICU admission[a]	2 (14.3)
Severe ARDS[c] at SICU admission[a]	3 (21.4)
AKI[d] required RRT at SICU admission[a]	7 (50.0)

Data are presented as mean ± standard deviation, median (interquartile range) or number (percentage), as appropriate.
[a] n = 14; 4 patients deceased within 4 hours after SICU admission and are excluded.
[b] Septic shock defines according to the Sepsis-3 definition [13].
[c] ARDS defines according to the Berlin definition [14].
[d] AKI defines according to the KDIGO definition [15].
AKI, acute kidney injury; APACHE II, Acute Physiology and Chronic Health Evaluation II score; ARDS, acute respiratory distress syndrome; RRT, renal replacement therapy; SICU, surgical intensive care unit; SOFA, Sequential Organ Failure Assessment score.

RESULTS

Between January 2014 and June 2021, 18 patients were admitted to the SICU and received ECMO support. The diagnosis at time of SICU admission, details of ECMO support and hospital discharge status of each patient is shown in Table 1. Of these, their mean age was 60.1 ± 14.5 years old, median Charlson comorbidity index was 0 (IQR 0, 1), and eight (44.4%) were male (Table 2). Four patients were deceased within four hours of SICU admission and, therefore, there were only 14 patients left for exploring their course in the SICU. The top reasons for SICU admission were as follows: unplanned admission following elective surgery and medical conditions, followed by planned admission following emergency and elective surgery (Table 2). At the time of SICU admission, the mean APACHE II score was 25.9 ± 6.2, and the median SOFA score was 12 (IQR 10, 14) (Table 2).

Table 3 shows data regarding ECMO management. The most common reason for ECMO support in this case series was ECPR (9 cases, 50%), followed by cardiac, respiratory and both cardiac and respiratory support. The majority of patients received VA ECMO support (15 cases, 83.3%). For patients receiving ECPR, the average time from CPR to initiation of ECPR was 101.2 ± 82.8 minutes (median 90 minutes, IQR 30-101 minutes). Regarding anticoagulation management, unfractionated heparin (UFH) was used in 10 (71.4%) cases as follows: three patients (30%) started on day 1, day 2 and day 3 of ECMO support, respectively, and one (10%) patient started on day 4 of ECMO support. The activated partial thromboplastin time (aPTT) was used to monitor the anticoagulant effect and was maintained between the median 33 seconds (IQR 29.5, 41.1) to median 51.4 seconds (IQR 41.1, 120.1) during ECMO support. The median duration of ECMO support was 60 (IQR 33, 144) hours.

Table 4 presents data regarding management of mechanical ventilation during ECMO support. Mechanical ventilation with a tidal volume of <8 ml/kg of predicted body weight combined with low to moderate level of positive end-expiratory pressure (PEEP) was exclusively used during ECMO support. The airway pressure did not change much, and the driving pressure seemingly reduced after ECMO day 3, with mechanical power decreasing by half after ECMO day 2. Although the fraction of inspired oxygen (FiO_2) used during ECMO support trended higher during the early days, it subsequently decreased to its usual level later. There was no problem with oxygenation and ventilation and the ratio of the partial pressure of oxygen in arterial blood (PaO_2) to FiO_2 (PF ratio) was maintained above 150 during ECMO support.

Table 5 presents the overall outcomes. During ECMO support, there were no thromboembolic events reported in any patient. Meanwhile, there were four (28.6%) patients developed at least one major bleeding including bleeding from the cannulation site, bleeding at the surgical site, intraabdominal bleeding, and intracranial hemorrhage. The median SICU and hospital length of stay was nine (IQR 5, 24) days and 13.5 (IQR 6, 28) days, respectively. Overall, seven (50.0%) out of 14 patients died in SICU and 14 (77.8%) out of 18 patients died in the hospital.

Table 3. Data regarding extracorporeal membrane oxygenation in 18 patients included in the case series.

Reasons for ECMO support	
- ECPR	9 (50.0)
- Cardiac support	3 (16.7)
- Respiratory support	3 (16.7)
- Both cardiac and respiratory support	3 (16.7)
Day of ECMO from SICU admission[a], day	0 (0, 1)
APACHE II day on ECMO[a]	26.6 ± 5.9
SOFA day on ECMO[a]	13 (11, 14)
ECMO configuration	
- VA ECMO	15 (83.3)
- VV ECMO	3 (16.7)
Site of ECMO	
- Peripheral	17 (94.4)
- Central	1 (5.6)
Unfractionated heparin used[a]	10 (71.4)
- On Day 1 of ECMO	3 (30.0)
- On Day 2 of ECMO	3 (30.0)
- On Day 3 of ECMO	3 (30.0)
- On Day 4 of ECMO	1 (10.0)
APTT[b], second	
- Day 1 of ECMO	47.6 (38.8, 125.8)
- Day 2 of ECMO	45.2 (34.1, 162.3)
- Day 3 of ECMO	51.4 (41.1, 120.1)
- Day 4 of ECMO	37.6 (34.7, 44.3)
- Day 5 of ECMO	37.9 (25.8, 45.8)
- Day 6 of ECMO	35.9 (25.7, 47.0)
- Day 7 of ECMO	33.0 (29.5, 41.1)
Duration of ECMO support[a], hour	60 (33, 144)

Data are presented as mean ± standard deviation, median (interquartile range) or number (percentage), as appropriate.
[a] n=14; 4 patients deceased within 4 hours after ICU admission and are excluded.
[b] Patients received ECMO on day 1, n = 14; day 2, n = 11; day 3, n = 10; day 4, n = 7; day 5, n = 6; day 6 and 7, n = 4.
APACHE II, Acute Physiology and Chronic Health Evaluation II score; APTT, activated partial thromboplastin time; ECMO, extracorporeal membrane oxygenation; ECPR, Extracorporeal cardiopulmonary resuscitation; SICU, surgical intensive care unit; SOFA, Sequential Organ Failure Assessment score; VA ECMO, venoarterial extracorporeal membrane oxygenation; VV ECMO, venovenous extracorporeal membrane oxygenation.

Table 4. Data regarding management of mechanical ventilation in 14 patients[a,b].

	SICU admit	ECMO day 1	ECMO day 2	ECMO day 3	ECMO day 4	ECMO day 5	ECMO day 6	ECMO day 7
Exhaled TV, ml	397.5 (315.5, 427.5)	380 (315.5, 415.5)	280 (187.5, 418.5)	304 (231.75, 374.75)	322 (202, 341)	302.5 (182.5, 346)	213.5 (171, 258.5)	279.5 (230, 296.25)
TV per kg PBW, ml/kg	7.9 (6.7, 9.1)	7.3 (6.7, 8.4)	6.5 (3.5, 7.3)	5.8 (4.6, 7.3)	5.7 (4.2, 7.3)	5.8 (4.0, 7.6)	4.4 (3.3, 5.8)	5.7 (4.7, 6.3)
PIP, cmH_2O	26 (20, 30)	25 (20, 30)	24 (22, 27)	23 (18,27)	25 (24, 25)	23 (18, 25)	26 (22, 28)	27 (23, 29)
Driving pressure, cmH_2O	18 (14, 21)	17 (14, 19)	18 (11, 19)	14 (11, 19)	16 (12, 18)	9 (6, 14)	11 (7, 16)	14 (7, 21)
PEEP, cmH_2O	7 (5.25, 9.5)	8.5 (5, 10)	7 (5, 11)	6 (5, 11)	7 (7, 12)	9.5 (7, 15)	10.5 (5, 16.5)	8.5 (5, 14)
MV, L/min	7.4 (5.8, 9.9)	8.1 (5.8, 10.5)	3.5 (1.9, 8.0)	4.8 (3.2, 7.0)	5.6 (2.7, 6.4)	4.8 (2.2, 6.2)	4.6 (1.4, 7.6)	5.8 (3.3, 8.0)
Mechanical power[48], J/min	10.7 (7.9, 17.3)	10.6 (7.9, 18.7)	4.9 (3.3, 8.8)	6.0 (4.0, 9.4)	8.2 (4.6, 9.1)	5.6 (3.6, 8.3)	4.7 (3.0, 7.5)	8.2 (6.2, 9.6)
pH	7.25 (7.10, 7.29)	7.23 (7.09, 7.30)	7.43 (7.32, 7.47)	7.42 (7.37, 7.43)	7.44 (7.36, 7.47)	7.46 (7.44, 7.47)	7.47 (7.43, 7.48)	7.50 (7.45, 7.53)
PaO_2, mmHg	95.2 (79.7, 151.4)	102.3 (73.9, 164.4)	96.5 (85.2, 152.7)	107.0 (89.7, 146.2)	122.0 (96.5, 130.9)	149.0 (141.2, 155.0)	125.5 (113.7, 201.8)	96.9 (85.2, 124.6)
$PaCO_2$, mmHg	42.3 (38.9, 48.2)	42.9 (39.3, 48.2)	35.2 (30.9, 39.4)	38.5 (31.9, 42.0)	38.0 (33.4, 40.8)	33.1 (32.0, 37.8)	32.6 (27.6, 37.6)	34.3 (25.9, 42.9)
FiO_2	0.7 (0.4, 1.0)	0.7 (0.4, 1.0)	0.6 (0.4, 0.6)	0.6 (0.4, 0.6)	0.4 (0.4, 0.6)	0.4 (0.4, 0.6)	0.4 (0.4, 0.5)	0.4 (0.4, 0.5)
PF ratio	182.3 (96.7, 346.6)	185.6 (75.0, 346.6)	164.3 (138.3, 253.0)	221.0 (159.9, 284.6)	265.6 (213.0, 288.3)	309.4 (224.2, 387.4)	313.8 (278.5, 371.3)	242.3 (213.1, 270.4)

[a] Of 18 patients included in the case series, there were 4 patients who deceased within 4 hours after ICU admission and are excluded.
[b] Patients received ECMO on day 1, n = 14; day 2, n = 11; day 3, n = 10; day 4, n = 7; day 5, n = 6; day 6 and 7, n = 4.
ECMO, extracorporeal membrane oxygenation; MV, minute ventilation; PBW, predicted body weight; PEEP, positive end-expiratory pressure; PF ratio, ratio of PaO_2 to FiO_2; PIP, peak airway pressure; TV, tidal volume; SICU, surgical intensive care unit.
Data presented in median (interquartile range)

Table 5. Clinical outcomes of 18 patients included in the case series.

Major bleeding[a]	4 (28.6)
- Cannulation site	2 (14.3)
- Surgical site	2 (14.3)
- Intraabdominal	2 (14.3)
- Gastrointestinal	1 (7.1)
- Intracranial	1 (7.1)
SICU-acquired infection[a]	6 (42.9)
- Bloodstream and CRBSI	5 (35.7)
- Pneumonia	4 (28.6)
- Surgical site	2 (14.3)
- Intraabdominal	2 (14.3)
Acute kidney injury after SICU admission[a]	3 (21.4)
Duration of mechanical ventilation[a], hour	215 (119, 429)
SICU length of stay[a], day	9 (5, 24)
SICU mortality[a]	7 (50.0)
Hospital length of stay, day	13.5 (6, 28)
Hospital mortality	14 (77.8)

Data are presented as median (interquartile range) or number (percentage), as appropriate.
[a] n=14; 4 patients deceased within 4 hours after ICU admission and are excluded from analysis.
CRBSI, catheter-related bloodstream infection; SICU, surgical intensive care unit.

DISCUSSION

This case series included 18 patients who required ECMO support during their stay in the SICU. ECPR was the most common reason for the application of ECMO in these patients. Other reasons included cardiovascular and/or respiratory support. The overall hospital mortality was as high as 77.8%. The indications for ECMO used, management of anticoagulation and mechanical ventilation will be discussed as follow.

Indication for ECMO: ECPR

A growing body of evidence supports the use of ECMO in patients with refractory cardiac arrest during CPR or ECPR [16-18]. In one meta-analysis [19], Kim et al. demonstrated that both in-hospital and out-of-hospital cardiac arrest patients receiving ECPR had a better survival rate and neurological outcome, especially at 3-6 months after cardiac arrest, compared to those receiving conventional CPR. In another recent meta-analysis focusing on in-hospital cardiac arrest patients receiving ECPR [20], Gravesteijn et al. reported that 84% of surviving patients had favorable neurological outcomes defined as a cerebral performance category score of 1 or 2, or Glasgow Outcome Scale score of 4 or 5. The survival rate of in-hospital cardiac arrest patients who received ECPR reported in these two meta-analyses was approximately 30% [19,20], which is higher than the 11.1% (one out of nine cases) hospital survival rate in patients receiving ECPR in our case series. Patient selection appears to be the most important factor determining clinical outcomes. In general, a CPR duration >10-30 minutes, advanced age, advanced malignancy, terminal illness, irreversible brain damage, uncontrolled bleeding or trauma were considered contraindications for ECPR in most studies [20]. In our case series, the average time from CPR to initiation of ECPR was longer than the suggested time associated with favorable outcomes. A possible reason for this delayed ECPR initiation was due to lack of a written ECPR protocol in our hospital. Hence, physicians might focus on ongoing CPR without being aware of the potential role of ECPR in patients with refractory cardiac arrest. Moreover, unexpected cardiac arrest in surgical patients, especially those following elective surgery, is considered catastrophic. In some cases, ECPR, even with delayed initiation, was still initiated as a bridge for family counselling. Besides, the presence of only some factors should not preclude the application of ECPR in these patients. Shin et al. demonstrated that neurological outcomes and survival rate at 6 months did not differ in patients with and without active cancer who developed in-hospital cardiac arrest and received ECPR [21]. Recently, Tonna et al. [22] developed a model for predicting mortality in in-hospital cardiac arrest patients receiving ECPR which showed good discrimination. In conjunction with the multidisciplinary team approach, these prediction models should help clinicians make decisions about whether to apply ECPR in patients with refractory cardiac arrest. In our hospital, the development of the comprehensive protocol for ECPR involving multidisciplinary team including cardiologists, cardiothoracic surgeons, vascular surgeons, intensivists, anesthesiologists, and perfusionists is ongoing. Once the protocol is implemented, the process of care of these patients should be improved.

Indication for ECMO: pulmonary embolism

In this case series, four patients developed acute massive pulmonary embolism and received VA ECMO support. The latest practice guidelines [23] recommend that ECMO may be considered in patients with acute pulmonary embolism suffering refractory circulatory collapse or cardiac arrest. In this scenario, ECMO can help to reduce right ventricular load, maintain oxygenation and serve as a bridge for further management such as

thrombolysis or thromboembolectomy [24]. In a recent large cohort including patients with pulmonary embolism suffering cardiac arrest, Hobohm et al. [25] demonstrated that application of ECMO with or without reperfusion with thrombolysis or thromboembolectomy was associated with lower risk of in-hospital mortality compared to administration of thrombolysis alone. Meanwhile, a beneficial effect on mortality was not observed if patients presented with unstable hemodynamic without cardiac arrest [25]. In contrast, a meta-analysis, including 29 observational studies consisting of 1,947 patients with pulmonary embolism did not demonstrate any advantage of ECMO use for short-term survival [26]. The hospital survival rate in our case series was 50% (two out of four cases), which was comparable to the 50%-60% survival rate reported in recent publications in patients with pulmonary embolism related to cardiac arrest managed with VA ECMO [26,27]. An age of >60-65 and ECPR were reported as factors associated with decreased survival, while surgical thromboembolectomy was associated with increased survival in these patients [26,27]. In this case series, there was only one patient who received pulmonary thromboembolectomy and none received thrombolysis due to its contraindication in a perioperative setting.

Indication for ECMO: refractory cardiogenic shock

Refractory cardiogenic shock is another clinical condition which VA ECMO plays an important role [16,28-30]. VA ECMO can help supporting either left, right or biventricular dysfunction as a bridge for recovery or decision for further advanced management such as heart transplantation [16,28-30]. A recent meta-analysis of patients with cardiogenic shock who received ECMO support demonstrated that overall survival-to-discharge and neurological dysfunction rates were 43% and 12.5%, respectively [17]. In this case series, we reported three cases of postoperative myocardial infarction and two cases of acute right ventricular dysfunction immediately after reperfusion during an orthotopic liver transplantation requiring VA ECMO support due to refractory cardiogenic shock. Unfortunately, all five patients did not survive to discharge. Thus, appropriate patient selection may be an important factor in determining a good outcome. By using a large international ECMO database, Schmidt et al. [31] created the SAVE-score to predict survival in patients with refractory cardiogenic shock receiving VA ECMO. This will help clinicians make a decision whether to initiate VA ECMO in patients with this condition. On the other hand, the outcome of ECMO use in patients with refractory septic shock is scattered. Survival rates reported in previous studies widely range from 7% to 90% [32-35], and is higher in patients with septic cardiomyopathy than distributive septic shock [34,35]. In this case series, we reported one case of septic shock due to Klebsiella pneumoniae necrotizing pneumonia with severe hypoxemic respiratory failure receiving VA ECMO support. Unfortunately, the patient did not survive to hospital discharge. We had no information regarding cardiac evaluation or cardiac function in this case and the patient might receive ECMO as a salvage therapy for refractory severe hypoxemia. Therefore, the decision to initiate ECMO support in patients with septic shock should be carefully assessed.

Indication for ECMO: ARDS

The application of VV ECMO in patients with severe ARDS and refractory hypoxemia has been studied for decades [1,2,5]. Recently, updated clinical practice guidelines for VV ECMO management in adult patients with respiratory failure has become available [36]. A recent meta-analysis [37], which included two landmark randomized controlled trials, the CESAR [38] and EOLIA [39], showed a significant decrease in 60-day-mortality in patients with severe ARDS who received ECMO support compared with conventional management (34% vs 47%, relative risk 0.73, 95% CI 0.58-0.92, P=0.008). Unlike the CESAR [38] and EOLIA [39] trials, in which the majority of patients had pneumonia, we reported on two cases of severe ARDS following intraoperative massive transfusion and one case following post intraoperative cardiac arrest.The pathophysiology of ARDS in these circumstances differ from that of primary ARDS resulting from pneumonia, which were transfusion-related acute lung injury and the 2-hit theory in case of massive transfusion [40] and ischemia-reperfusion injury in case of post cardiac arrest [41]. A subgroup analysis of the EOLIA trial [39] focused on the principal causes of ARDS either bacterial or viral pneumonia or other causes did not show any difference in 60-day mortality when compared to patients who received ECMO support and those who received conventional management. To date, reports of ECMO use in secondary ARDS linked to specific conditions, like in our case series, are very scattered. The decision to initiate ECMO support in these three cases was due to the failure of conventional management to improve oxygenation. Unfortunately, only one patient (33.3%) survived to hospital discharge.

Anticoagulation management

Anticoagulation management is one of the most debated issues during ECMO application. Until now, there has been no definite consensus on the choice of anticoagulant, method to monitor anticoagulant effect and optimal anticoagulation level. There is also a large variety between VA ECMO and VV ECMO [42]. UFH is the most widely used anticoagulant during ECMO support [42]. The disadvantage of UFH is the variation in pharmacokinetics due its ability to bind to not only antithrombin, but also other plasma proteins, endothelial cells and macrophages, resulting in altered patient-dose response. In addition, in some critically ill patients who have a low plasma concentration of antithrombin, heparin resistance can occur. Heparin induced thrombocytopenia develops in 0.2-5% of adult patients who receive UFH [42]. Alternatively, bivalirudin or argatroban, which are direct thrombin inhibitors, can be used during ECMO in cases where heparin is contraindicated [2,42]. Monitoring the anticoagulant effect is challenging during ECMO support. The activated clotting times, which have been used for decades, are affected by numerous factors independent of UFH, such as quality and quantity of platelets, coagulation factors and fibrinogen, body temperature, or hemodilution [42,43]. Consequently, discordance between activated clotting times and heparin concentration is likely to occur [43]. aPTT is a plasma-based coagulation test currently used worldwide [43]. However, it may have high intrapatient

and interpatient variability, especially in critically ill patients [42]. The current guidelines [42] does not mention optimal levels of aPTT during ECMO support. A recent review by Chlebowski et al. [43] recommended aPTT ranged between 60 and 80 seconds for patients with standard bleeding risk and between 40 to 60 seconds for those with high bleeding risk during ECMO support. The anti-Xa assay, a direct measurement of the ability of UFH to inhibit factor Xa, is now being increasingly used for monitoring the anticoagulant effect of UFH during ECMO support [42,43]. Chlebowski et al. [43] recommends anti-Xa levels to range between 0.3 and 0.7 IU/mL during ECMO support. The viscoelastic hemostatic assays allow global assessment of clotting formation, including initiation, strength, and stabilization. Nevertheless, the current guidelines [42] do not recommended use of these assays in routine clinical practice. With the advancement of technology, such as heparin-coated circuits or high pump flow machine, it is feasible and safe to apply VV ECMO support with either low or even no anticoagulation [42]. On the other hand, systemic anticoagulation for VA ECMO is still recommended given that the potential risks of systemic emboli [42]. All patients in our case series were in the perioperative setting, and thus, the risk of bleeding was a major concern if systemic anticoagulation had to be administered. Of these, 10 (71.4%) of 14 patients received UFH for systemic anticoagulation during ECMO support and aPTT levels were monitored and maintained within the lower ranges. Although there was no thromboembolic event in any patient, four patients (28.6%) experienced major bleeding, which was in concordance to the approximately 30% of incidence of bleeding in patients receiving ECMO support as reported in literature [44,45]. The specific protocol for anticoagulation in patients receiving ECMO during perioperative period is warranted to guide appropriate management balancing risks of bleeding and risks of thromboembolism.

Mechanical ventilation management

The recent guidelines for management of adult patients receiving VV ECMO [36] recommend mechanical ventilation, with a plateau pressure < 25 cmH_2O, PEEP ≥10 cmH_2O, RR 4 – 15 /min, and FiO_2 0.3 – 0.5 or as low as possible to maintain oxygen saturation. For management of patients receiving VA ECMO, the guidelines [30] recommend a lung protective mechanical ventilation strategy with relatively high PEEP. The latter helps not only recruit alveoli, but also counterbalances pulmonary edema which may be developed during VA ECMO. In our case series, all patients received lung protective ventilation with a low tidal volume of <8 ml/kg of predicted body weight, and relatively lower PEEP than recommendation. In this circumstance, PEEP should be carefully titrated to avoid undesirable adverse effects such as increased right ventricular afterload or compromised hemodynamic. After initiation of ECMO support, we observed a decrease in mechanical power, which was likely the result of its ability to reduce both tidal volume and respiratory rate. Mechanical power as of late has garnered attention as a growing body of evidence suggests its association with clinical outcomes in mechanically ventilated patients [46-48]. In a multicenter prospective cohort study of 350 ARDS patients who received ECMO support, Schmidt et al. [49] demonstrated that the tidal volume per predicted body weight, plateau pressure, driving pressure, respiratory rate and mechanical power significantly reduced after the initiation of ECMO support when compared to values before. Nevertheless, these changes in respiratory mechanics during ECMO support were apparently not linked to a higher six-month survival [49].

Limitations

First, there was a small volume of cases in this case series. From January 2014 to June 2021, only 18 patients received ECMO support in our SICU, which represented approximately three cases per 1,000 admissions. This limited statistical analysis to compare any treatment effect or outcomes. Second, we did not have a written protocol for ECMO care in our unit, especially the inclusion and exclusion criteria for initiation of ECMO. Most of the management was based on the discretion of primary physicians, SICU attending staff and the consultation teams. Therefore, we are currently developing a multidisciplinary protocol for perioperative ECPR as this represents the majority of cases at our SICU. Lastly, most cases included in this case series were before 2021. Some management practices may differ from current guidelines and recommendations [30,36].

CONCLUSION

In this case series, we reported our experience in taking care of patients receiving ECMO support due to various indications in a perioperative setting. The most common reason for ECMO support in these patients was ECPR, followed by cardiac and/or respiratory support. Anticoagulation management during ECMO support in the perioperative setting was somewhat challenging. Overall, the hospital mortality was as high as 80%. Appropriate patient selection, well-organized protocols, and a multidisciplinary approach are necessary for improving outcomes in these patients.

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AUTHORS' CONTRIBUTIONS

(I) Conceptualization: AP, SK, OC; (II) Data curation: AP; (III) Formal analysis: AP; (IV) Methodology: AP, SK, OC; (V) Project administration: AP; (VI) Visualization: AP, SK, OC; (VII) Writing – original draft: AP; (VIII) Writing – review & editing: P, SK, OC.

SUPPLEMENTARY MATERIALS

None

ABBREVIATIONS

APACHE II, Acute Physiology and Chronic Health Evaluation II score; aPTT activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; AUC, area under the receiver operating characteristic curve; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; ELSO, Extracorporeal Life Support Organization; ICU, intensive care unit; IQR, interquartile range; PEEP, positive end-expiratory pressure; PF ratio, ratio of PaO_2 to FiO_2; SICU, surgical intensive care unit; SOFA, Sequential Organ Failure Assessment score; UFH, unfractionated heparin; VA ECMO, venoarterial extracorporeal membrane oxygenation; VV ECMO, venoveno extracorporeal membrane oxygenation.

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