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REVIEW ARTICLE

Acute kidney injury in adults receiving extracorporeal membrane oxygenation

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Extracorporeal membrane oxygenation (ECMO) has been utilized for critically ill patients such as patients with postcardiotomy cardiogenic shock or life-threatening respiratory failure. Acute kidney injury (AKI) that develops during ECMO is associated with a very poor outcome, possibly because of accumulated extravascular water causing interstitial overload, impaired oxygen transport through tissues, and increased extravascular lung water volume with impaired O_2 transport. Increased water is associated with subsequent organ dysfunction, particularly of the heart, lungs, and brain. Based on single-center studies, the incidence of AKI is 70—85% in ECMO patients. Therefore, renal replacement therapy is required in approximately 50% of these patients. This review summarizes three modalities that can be used to introduce renal replacement therapy to patients on ECMO, the pathophysiology of AKI in ECMO, and the impact of AKI on mortality. This review also identifies specific research-focused questions that need to be addressed to predict AKI early and to improve outcomes in this at-risk adult population.

Introduction

Critically ill patients frequently require mechanical ventilation, circulatory support, and other assistant devices. Extracorporeal membrane oxygenation (ECMO) is recommended for patients with acute, potentially reversible, life-threatening respiratory failure that is unresponsive to conventional therapy. Treatment by ECMO may also be effective in patients with severe reversible myocardial dysfunction (e.g., myocarditis or postoperative cardiogenic

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shock) or acute respiratory distress syndrome (ARDS); it may also provide temporary support prior to another treatment modality (e.g., heart transplant).[1–5] The type of ECMO administered will depend on the patient's underlying cardiac function. Venovenous (VV) ECMO (VV-ECMO) is usually administered for isolated respiratory failure, whereas venoarterial (VA) ECMO (VA-ECMO; i.e., full cardiopulmonary bypass) is administered for combined cardiac and respiratory failure. Table 1 lists the indications and contraindications for VV-ECMO and VA-ECMO support.[6,7] The algorithm in Fig. 1 simplifies the understanding about the choice of the type of VV-ECMO or VA-ECMO in clinical settings. Circuit flow may be achieved by a centrifugal or roller pump or by a patient's arteriovenous (AV) pressure gradient (i.e., pumpless). The AV-ECMO system is characterized by a membrane gas exchange device integrated into a pumpless AV circuit, which is established by the cannulation of the femoral artery and vein. The circuit provides a small amount of oxygenation, but mostly carbon dioxide removal, as the arterial blood is returned to the venous side. Arteriovenous ECMO is primarily useful in patients with severe hypercapnia, respiratory acidosis, and moderate hypoxemia. The pumpless circuit makes this device simple to use, but cardiac function must be preserved for the patient's blood to be effectively pumped (i.e., a cardiac index of at least 2.5 L/minute/m^2). However, high mortality has been reported in ARDS patients who are on AV-ECMO and some patients may require conversion from AV-ECMO to VV-ECMO or to VA-ECMO.[8,9]

Acute kidney injury (AKI) that develops during ECMO is associated with very poor outcome (i.e., patients who develop AKI have high mortality rates and resource utilization).[1,2,10] Most studies demonstrate that patients exhibiting renal failure signs [e.g., increased serum

Table 1 Indications and contraindications for VA-ECMO and VV-ECMO.

Indications

VA-ECMO

- Cardiogenic shock: AMI and complications (e.g., wall rupture, papillary muscle rupture, refractory VT/VF) that are refractory to conventional therapy such as IABP
- Postcardiac surgery: unable to wean safely from cardiopulmonary bypass using conventional supports
- Drug overdose with profound cardiac depression
- Acute myocarditis
- Early graft failure: postheart transplant or postheart-lung transplant
- As a bridge to cardiac transplantation
- Intractable arrhythmia
- Pulmonary hypertension (after pulmonary endarterectomy)

VV-ECMO

- Any potentially reversible acute respiratory failure
- ARDS that is associated with pneumonia (viral or bacterial)
- Failed lung transplant graft
- Trauma (pulmonary contusion)
- Pulmonary embolism (if patient has acceptable cardiac function)

Contraindications

Contraindications to all forms of ECMO

- Any condition or organ dysfunction that would limit the likelihood of overall benefit from ECMO such as severe, irreversible brain injury or untreatable metastatic cancer
- Patient has contraindications to anticoagulation therapy
- ECMO as a bridge to heart or lung transplantation if transplantation will not be considered
- Limited vascular access

VA-ECMO

- Severe aortic regurgitation
- Aortic dissections

VV-ECMO

- Severe pulmonary hypertension (mPAP $>$ 50 mmHg)
- Severe right or left heart failure (EF $<$ 25%)
- Cardiac arrest

AMI = acute myocardial infarction; ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; EF = ejection fraction; IABP = intra-aortic balloon pump; mPAP = mean pulmonary artery pressure; VA = venoarterial; VF = ventricular fibrillation; VT = ventricular tachycardia; VV = venovenous.

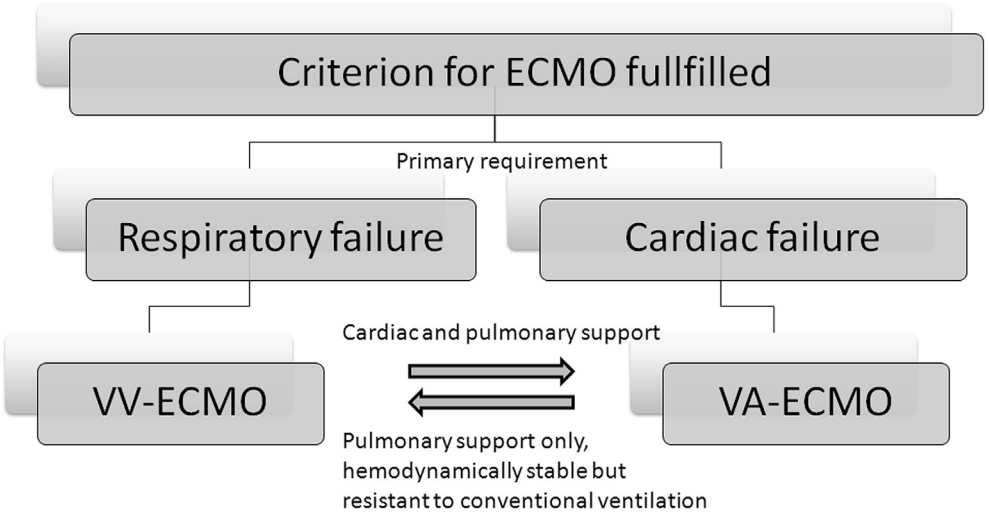

Figure 1 The choice of extracorporeal membrane oxygenation. ECMO = extracorporeal membrane oxygenation; VA = venoarterial; VV = venovenous.

creatinine (SCr) level and/or oliguria] typically respond poorly to ECMO. Acute kidney injury and its complications such as volume overload and azotemia are common in this situation. Some epidemiological studies show that more than 75% of the patients requiring ECMO therapy develop AKI. Renal replacement therapy (RRT) is required in approximately 50% of these patients. The management of patients with AKI is principally supportive with RRT indicated for patients with severe kidney injury. Table 2 lists the interaction between the RRT circuit and the ECMO circuit and the indications for initiating dialysis.[11,12] Fig. 2 illustrates the inclusion of continuous renal replacement therapy (CRRT) device in the peripheral VA-ECMO circuit.

Pathophysiology of AKI in ECMO

Prior to the initiation of ECMO, the etiology of AKI in these patients is almost always because of multiple factors such as sepsis, low cardiac output syndrome, exposure to nephrotoxic agents, and high intrathoracic pressures. Acute kidney injury, a manifestation of multiple organ system failure (OSF), is associated with underlying decompensated heart failure and sepsis and is aggravated by complications such as surgical site bleeding during ECMO support.[13] Whether AKI directly produces these adverse outcomes remains unclear; however, increased infection and new-onset sepsis, congestive heart failure, and fluid overload may contribute to AKI.[14]

Hypotension is associated with worsening renal function for patients on ECMO. Damaged cardiac function (which creates a condition of low cardiac output and therefore hypoperfusion), if not promptly corrected, can allow pre-renal AKI to progress to intrinsic AKI and cortical necrosis, which results in irreversible loss of renal function.[15]

During the first 24—48 h on ECMO, oliguria and acute tubular necrosis associated with capillary leakage and intravascular volume depletion are common because ECMO triggers an acute inflammatory-like reaction. Decreased urine output (UO) represents renal hypoperfusion resulting from low cardiac output (i.e., cardiogenic shock) or systemic vasodilatation (i.e., sepsis). Decreased UO also leads to fluid overload that impairs tissue oxygenation and oxygen transport in the lungs. This eventually leads to organ dysfunction of the heart, brain, and lungs. Fluid overload further increases preload and may contribute to circulatory failure. Circulatory failure may further aggravate in-hospital mortality.[1,8,16,17]

In VA ECMO, cardiac output is a mixture of native cardiac (i.e., pulsatile) flow and ECMO pump (i.e., nonpulsatile) flow. The mechanical flow may be nonpulsatile, although institution of VA-ECMO usually raises blood pressure and flow to the vital organs, including the kidneys. Venovenous ECMO maintains native pulsatile cardiac output, and changes in renal perfusion are less in VA-ECMO. After the initiation of ECMO, oxygenation improves, oxygen consumption reduces, and hemodynamics improves in most patients. The initiation of ECMO (especially in neonates and children) with subsequent adjustments in vasopressor drugs and inotropic drugs can nevertheless cause rapid hemodynamic fluctuations that alter renal blood flow and lead to ischemia- and reperfusion-associated AKI.[18,19]

Other factors associated with ECMO initiation predispose patients to incident AKI or exacerbation of AKI. Blood exposure to artificial surfaces causes systemic inflammation and hemoglobinuria-induced renal injury due to different degrees of hemolysis occur in the extracorporeal circuit.[19]

Impact of AKI on mortality

Patients on ECMO

Lin et al[1] retrospectively applied the risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage renal failure (RIFLE) criteria to evaluate 46 critically ill patients treated by ECMO. Most of them had postcardiotomy cardiogenic shock. In 2004, the Acute Dialysis Quality Initiative Group published the RIFLE criteria in an attempt to standardize AKI research.[20] It

Table 2 Modalities of RRT on ECMO and indications.

Modalities of ECMO plus RRT
- A double-lumen catheter can be used to connect the RRT circuit to part of the ECMO circuit
- A series circuit (e.g., SCUF or CAVH) can be used
- A connection can be created between the RRT machine and the ECMO circuit

Indications for ECMO plus RRT
- Anuria (>12 h), unresponsive to high doses of diuretics
- Oliguria (>12 h), unresponsive to high doses of diuretics
- AKI in progression
- Oliguria/AKI with metabolic acidosis
- Oliguria/AKI with hyperkalemia
- Oliguria/AKI with pulmonary edema

AKI = acute kidney injury; CAVH = continuous arteriovenous hemofiltration; ECMO = extracorporeal membrane oxygenation; RRT = renal replacement therapy; SCUF = slow continuous ultrafiltration.

classified AKI into three categories (risk, injury, and failure), based on the status of the SCr level and UO. The RIFLE criteria were assessed only during the first day of ECMO support. A progressive and significant increase in mortality among all patients was associated with increasing RIFLE categories. At the 6-month follow-up, cumulative survival rates differed significantly ($p < 0.05$) for non-AKI versus RIFLE-Injury and RIFLE-Failure, and for RIFLE-Risk versus RIFLE-Failure.

The authors further reviewed the medical records of 78 critical ill patients on ECMO support.[2] The RIFLE criteria classified 78.2% of the patients as having AKI. Multivariate analysis indicated that Acute Physiology, Age, Chronic Health Evaluation (APACHE) IV, and the RIFLE classification had independent prognostic significance (Table 3).

The RIFLE criteria can precisely predict hospital mortality in this subset of critically ill patients on ECMO Day 1. The influence of other factors (e.g., advanced age, type of

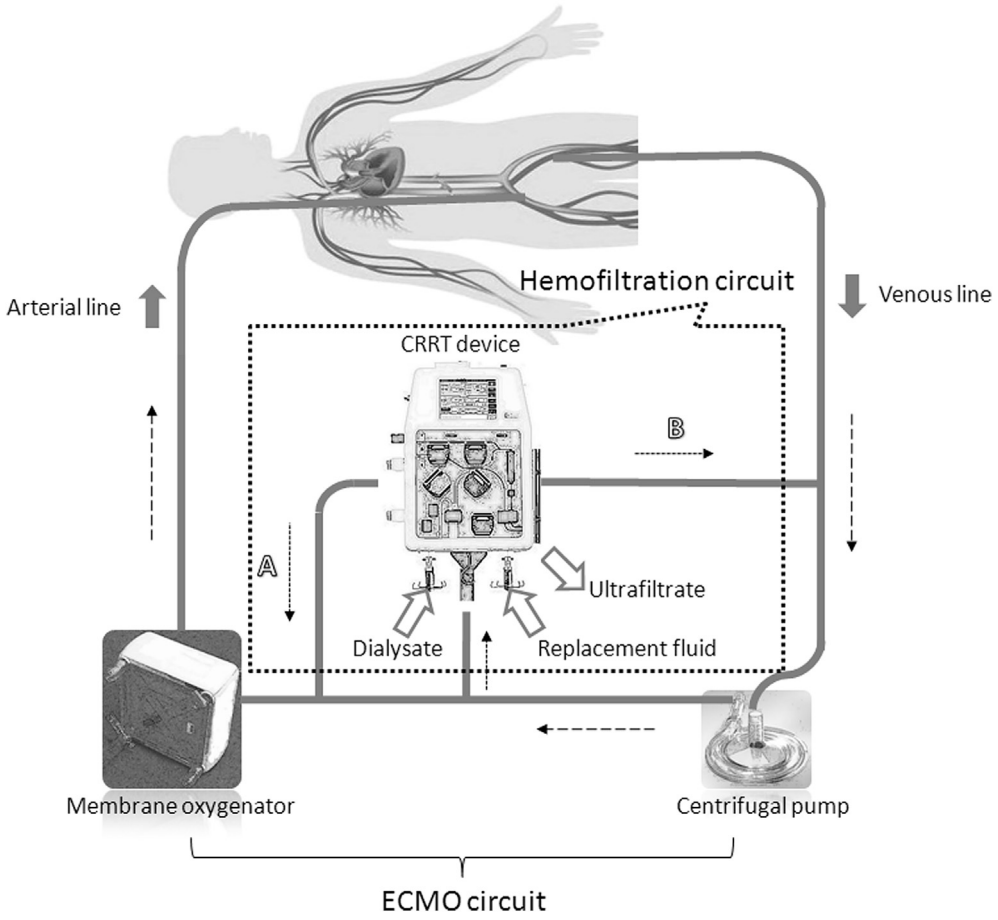

Figure 2 Incorporation of an integrated continuous renal replacement therapy (CRRT) system with an extracorporeal membrane oxygenation (ECMO) circuit. Blood is delivered to the CRRT device from the postpump limb of the ECMO circuit and returned (A) to the postpump limb of roller pump circuits or (B) to the venous limb of centrifugal pump circuits.

Table 3 Variables predicting in-hospital mortality at different stages of ECMO treatment.

	n	Independent predictors	Study period	Refs
On ECMO	78	• APACHE IV • RIFLE	March 2002—October 2005	2
Post-ECMO 48-hour	102	• AKIN48-hour • Age • GCS score on ECMO	March 2002—January 2008	10
RRT on ECMO	123	• Age • MAP on RRT • OSF number on RRT	March 2003—August 2010	11
Off ECMO	119	• Daily UO on the second day of ECMO removal ($UO_{24-48\ hour}$) • MAP off ECMO • SOFA off ECMO	July 2006—October 2010	16
ARDS on ECMO	81	• APACHE II • MAP • Platelet count • UO	May 2006—December 2011	32

AKIN = Acute Kidney Injury Network; APACHE = Acute Physiology, Age, Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; GCS = Glasgow Coma Scale; MAP = mean arterial pressure; OSF = organ system failure; RIFLE = risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage renal failure; RRT = renal replacement therapy; SOFA = Sequential Organ Failure Assessment; UO = urine output.

surgery, history of chronic disease, hemodynamics, neurological factors, or respiratory factors) on the morbidity and mortality of critically ill patients on ECMO are not measured by the RIFLE score. The failure to measure such extrarenal parameters in the RIFLE classification may explain its inferiority to APACHE IV, APACHE III, APACHE II, and Sequential Organ Failure Assessment (SOFA) scores in discriminative capability.[2]

Post-ECMO 48-hour

Chen et al[10] evaluated the outcomes of 102 patients treated with ECMO and identified the relationship between prognosis and Acute Kidney Injury Network (AKIN) scores obtained at pre-ECMO support (AKIN0-hour); and at 24 hours post-ECMO support (AKIN24-hour) and 48 hours post-ECMO support (AKIN48-hour).[10] In 2007, the AKIN group proposed a modified version of the RIFLE criteria. In AKIN stage-1 (analogous to RIFLE-Risk), a smaller change within 48 hours in the SCr level—0.3 mg/dL (26.2 μmol/L) or greater—was suggested as the AKI threshold. In addition, patients receiving RRT were reclassified as AKIN stage-3 (i.e., RIFLE-Failure). Finally, the "loss" and "end-stage kidney disease" categories were eliminated in the AKIN classification.[21] The overall in-hospital mortality rate was 57.8%. The AKIN0-hour, AKIN24-hour, and AKIN48-hour scoring systems also had excellent areas under the receiver operating characteristic curve (AUROCs) (0.804 ± 0.046, 0.811 ± 0.045, and 0.858 ± 0.040, respectively). Furthermore, multiple logistic regression analysis indicated that AKIN48-hour score, age, and Glasgow Coma Scale score on the Day 1 of intensive care unit admission were independent risk factors for hospital mortality (Table 3). Cumulative survival rates at the 6-month follow up after hospital discharge differed significantly for AKIN48-hour stage 0 versus AKIN48-hour stages 1, 2, and 3, and for AKIN48-hour stages 1 and 2 versus AKIN48-hour stage 3 ($p < 0.05$). During ECMO support, the AKIN48-hour scoring system proved to be a reproducible evaluation tool with an excellent prognostic ability for these patients.

The AKIN group aimed to improve the sensitivity and reproducibility of the AKI criteria and define the AKIN classification. However, some studies indicate that the AKIN criteria may not improve sensitivity and predictive ability.[22–24] The AKIN stage-1 is notably similar to RIFLE-Risk, but includes abrupt (i.e., within 48 hours) reduction in kidney function (indicated by an increase in the SCr level of 0.3 mg/dL or greater). In addition, stage 3 encompasses patients who require RRT at any stage. Emerging evidence suggests that even small increases in SCr levels after cardiac surgery significantly increase mortality. Several studies document a high mortality rate for patients treated with ECMO and RRT.[1–3]

RRT on ECMO

In a study by Morris et al,[25] all 13 children managed with ECMO and slow continuous ultrafiltration died. In such patients, a fatal outcome is often associated with the progression of conduction disturbance to electromechanical dissociation and asystole.[25] In a study by Balasubramanian et al,[26] 30 pediatric surgical cardiac patients requiring RRT while on ECMO had a high risk of hospital mortality. Kolovos et al[27] also demonstrated that children who underwent postcardiotomy ECMO requiring hemofiltration had a mortality rate five times that of patients without AKI. Wu et al[12] proved that independent predictors for hospital mortality among ECMO patients on dialysis were high central venous pressure, high APACHE IV score when initializing dialysis, and latency from hospital admission to dialysis.

In a previous study by our study group, 21 AKI patients treated by ECMO and continuous arteriovenous

hemofiltration (CAVH) died during hospitalization.[2] In a subsequent study, two patients with myocardial dysfunction survived following ECMO and CAVH treatment.[3] Early diagnosis and aggressive treatment of patients with fewer than three failed organs resulted in a favorable outcome. Timely administration of ECMO and CAVH is effective in supporting circulation and renal function for myocardial dysfunction that is refractory to conservative treatment. These will likely be the standard treatments in the near future. These studies indicate that advanced cardiac failure may require more aggressive and earlier initiation of ECMO support before AKI develops.

Tsai et al[11] reviewed the medical records of 123 critically ill patients on ECMO plus CAVH support. The overall in-hospital mortality rate was 85.4%. The most common condition requiring ECMO plus CAVH support was cardiogenic shock and anuria. The goodness-of-fit was good for OSF number. The OSF number also had good AUROC curve (0.758 ± 0.057). Multiple logistic regression analysis also indicated that age, mean arterial pressure (MAP), and OSF number on the 1st day of ECMO plus CAVH were independent risk factors for hospital mortality (Table 3). Cumulative survival rates at the 6-month follow up after hospital discharge differed significantly ($p < 0.05$) for patients with an OSF number of 4 or less versus patients with OSF number of 4 or greater.[11]

Survival when on ECMO generally decreases as the patient's age increases. Nehra and colleagues[28] reported a bimodal distribution of survival with respect to patient age, with the highest survival in groups aged 0–9 years and 30–39 years. This distribution was noted previously and has been confirmed by data from the Extracorporeal Life Support Organization database.[29] For patients treated with ECMO and CAVH, Tsai et al[11] adopted the best Youden index and established a cut-off value of 50 years of age. Hospital mortality rates differed significantly, according to the best Youden index below and above the cutoff of 50 years of age (75.4% vs. 93.9%, $p = 0.005$).

Patients off ECMO

Chang et al[16] reviewed the medical records of 119 critically ill patients who were successfully weaned from ECMO. Successful weaning was defined as weaning from ECMO support after a survival longer than 48 hours.[16] The overall in-hospital mortality rate was 26%. The most common condition requiring ECMO support was cardiogenic shock. By using the AUROC curve, the SOFA score displayed good discriminative power (AUROC was 0.805 ± 0.055; $p < 0.001$). In addition, multiple logistic regression analysis indicated that daily UO on the 2nd day of ECMO removal ($UO_{24-48\ hour}$), MAP, and the SOFA score on the day of ECMO removal were independent predictors of hospital mortality (Table 3). Cumulative survival rates at the 6-month follow up differed significantly for patients with a SOFA score of 13 or less, compared to the survival rate for patients with a SOFA score greater than 13 ($p < 0.001$).

Urine volume is a more sensitive marker than the SCr level for the early detection of AKI. Decreased urine volume on the day of ECMO removal is attributed to decreased cardiac output after decannulation, and is correlated with acute cardiorenal syndrome type 1.[30] For patients with improved systolic function, the urine volume may increase gradually in the following days. For other patients, decreased urine volume progresses and causes fluid overload, which likely increases preload and may contribute to circulatory failure. In addition, loop diuretics were usually prescribed for better diuresis in patients with decreased urine volume. Metra et al[31] identified the use of loop diuretics as a modifiable in-hospital determinant of acute cardiorenal syndrome type 1, which probably occurs by further activation of the renin-angiotensin-aldosterone system and worsening of intrarenal hemodynamics. Circulatory failure may further aggravate in-hospital mortality. For patients weaned from ECMO, Chang et al[16] adopted the best Youden index and established a cut-off urine volume of 1468 mL. Hospital mortality rates below and above the cutoff value of 1468 mL of daily urine volume on the 2nd day of ECMO removal were 59.5% (22 of 37 patients) and 12.5% (9 of 72 patients; $p < 0.001$), respectively.[16]

ECMO for ARDS

Hsiao et al[32] reviewed the medical records of 81 ARDS patients after ECMO support. The overall in-hospital mortality rate was 55.5%. A multiple logistic regression analysis indicated that the APACHE II score, MAP, platelet count, and UO on Day 1 of ECMO support were independent risk factors for hospital mortality (Table 3). By using the AUROC curve, UO obtained on the 1st day of ECMO support demonstrated good discriminative power (AUROC was 0.754 ± 0.056; $p < 0.001$). Urine output had the best discriminative power, the best Youden index, and the highest overall correctness of prediction. Cumulative survival rates at the 6-month follow up differed significantly ($p < 0.001$) for a UO of 1432 mL or greater on Day 1 of ECMO support versus the survival rate of patients with a UO of less than 1432 mL on Day 1 of ECMO support. Urine output obtained on the 1st day of ECMO is related to the severity of the underlying critical illness affecting the ARDS patient.

Predicting the outcome after ARDS onset is difficult because ARDS occurs in patients with various profiles and diverse disease etiologies.[33,34] The APACHE system assumes that the core mission of intensive care is treating the disease and maintaining physiological homeostasis. Physiological abnormalities are common among intensive care unit patients, and the extent of derangement is an objective and reproducible measure of illness severity. The SOFA score ignores diagnosis, age, and comorbid conditions. This could, at least partially, explain the superiority of APACHE II to SOFA.

Future research needs

Renal failure is common in critically ill patients on ECMO. It has an extremely high mortality rate. New classification systems for AKI may enhance standardization of the diagnosis and staging of this clinical syndrome. Novel biomarkers for the early diagnosis of AKI may represent a breakthrough for clinicians—if the biomarkers are accurate, reproducible, and applicable in different settings.

There are no specific therapeutic interventions for patients with established AKI.[35—37]

During ECMO support, the AKIN48-hour scoring system proved to be a reproducible evaluation tool with an excellent prognostic ability for these patients. Several studies have shown that AKI biomarkers increase significantly in patients with AKI 24—48 hours before an increase in the SCr level is detectable.[38—40] Based on the aforementioned findings, a well-powered trial is required to examine this issue, which may require an early intervention guided by novel AKI biomarkers on the 1st day of a patient on ECMO.[38—40]

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References

1. Lin CY, Chen YC, Tsai FC, Tian YC, Jenq CC, Fang JT, et al. RIFLE classification is predictive of short-term prognosis in critically ill patients with acute renal failure supported by extracorporeal membrane oxygenation. *Nephrol Dial Transplant* 2006;**21**:2867—73.
2. Lin CY, Tsai FC, Tian YC, Jenq CC, Chen YC, Fang JT, et al. Evaluation of outcome scoring systems for patients on extracorporeal membrane oxygenation. *Ann Thorac Surg* 2007;**84**:1256—62.
3. Lin CY, Chen YC, Tsai FC, Tian YC, Jenq CC, Huang CC, et al. Continuous renal replacement therapy combined with extracorporeal membrane oxygenation in advanced cardiac failure patients. *J Nephrol* 2008;**21**:789—92.
4. Journois D. Hemofiltration during cardiopulmonary bypass. *Kidney Int Suppl* 1998;**66**:S174—7.
5. Peng CC, Wu SJ, Chen MR, Chiu NC, Chi H. Clinical experience of extracorporeal membrane oxygenation for acute respiratory distress syndrome associated with pneumonia in children. *J Formos Med Assoc* 2012;**111**:147—52.
6. Butt W, Maclaren G. Extracorporeal membrane oxygenation. *F1000Prime Rep* 2013;**5**:55.
7. Brodie D, Bacchetta M. Extracorporeal membrane oxygenation for ARDS in adults. *N Engl J Med* 2011;**365**:1905—14.
8. Flörchinger B, Philipp A, Klose A, Hilker M, Kobuch R, Rupprecht L, et al. Pumpless extracorporeal lung assist: a 10-year institutional experience. *Ann Thorac Surg* 2008;**86**:410—7.
9. Martinez G, Vuylsteke A. Extracorporeal membrane oxygenation in adults. *Cont Edu Anaesth Crit Care and Pain* 2012;**12**:57—61.
10. Chen YC, Tsai FC, Chang CH, Lin CY, Jenq CC, Juan KC, et al. Prognosis of patients on extracorporeal membrane oxygenation: the impact of acute kidney injury on mortality. *Ann Thorac Surg* 2011;**91**:137—42.
11. Tsai TY, Tsai FC, Chang CH, Jenq CC, Hsu HH, Chang MY, et al. Prognosis of patients on extracorporeal membrane oxygenation plus continuous arteriovenous hemofiltration. *Chang Gung Med J* 2011;**34**:636—43.
12. Wu VC, Tsai HB, Yeh YC, Huang TM, Lin YF, Chou NK, et al. Patients supported by extracorporeal membrane oxygenation and acute dialysis: acute physiology and chronic health evaluation score in predicting hospital mortality. *Artif Organs* 2010;**34**:828—35.
13. Yap HJ, Chen YC, Fang JT, Huang CC. Combination of continuous renal replacement therapies (CRRT) and extracorporeal membrane oxygenation (ECMO) for advanced cardiac patients. *Ren Fail* 2003;**25**:183—93.
14. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. *N Engl J Med* 1999;**341**:577—85.
15. Metra M, Nodari S, Parrinello G, Bordonali T, Bugatti S, Danesi R, et al. Worsening renal function in patients hospitalized for acute heart failure: clinical implications and prognostic significance. *Eur J Heart Fail* 2008;**10**:188—95.
16. Chang WW, Tsai FC, Tsai TY, Chang CH, Jenq CC, Chang MY, et al. Predictors of mortality in patients successfully weaned from extracorporeal membrane oxygenation. *PLoS One* 2012;**7**:e42687.
17. Chou YH, Chen YF, Lin SL. More is not better: fluid therapy in critically ill patients with acute kidney injury. *J Formos Med Assoc* 2013;**112**:112—4.
18. Keckler SJ, Laituri CA, Ostlie DJ, St. Peter SD. A review of venovenous and venoarterial extracorporeal membrane oxygenation in neonates and children. *Eur J Pediatr Surg* 2010;**20**:1—4.
19. Askenazi DJ, Selewski DT, Paden ML, Cooper DS, Bridges BC, Zappitelli M, et al. Renal replacement therapy in critically ill patients receiving extracorporeal membrane oxygenation. *Clin J Am Soc Nephrol* 2012;**7**:1328—36.
20. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, Acute Dialysis Quality Initiative Workgroup. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004;**8**:R204—12.
21. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007;**11**:R31.
22. Bagshaw SM, George C, Bellomo R. A comparison of the RIFLE and AKIN criteria for acute kidney injury in critically ill patients. *Nephrol Dial Transplant* 2008;**23**:1569—74.
23. Lopes JA, Fernandes P, Jorge S, Goncalves S, Alvarez A, Costa e Silva Z, et al. Acute kidney injury in intensive care unit patients: a comparison between the RIFLE and the Acute Kidney Injury Network classifications. *Crit Care* 2008;**12**:R110.
24. Chang CH, Lin CY, Tian YC, Jenq CC, Chang MY, Chen YC, et al. Acute kidney injury classification: comparison of AKIN and RIFLE criteria. *Shock* 2010;**33**:247—52.
25. Morris MC, Ittenbach RF, Godinez RI, Portnoy JD, Tabbutt S, Hanna BD, et al. Risk factors for mortality in 137 pediatric cardiac intensive care unit patients managed with extracorporeal membrane oxygenation. *Crit Care Med* 2004;**32**:1061—9.
26. Balasubramanian SK, Tiruvoipati R, Amin M, Aabideen KK, Peek GJ, Sosnowski AW, et al. Factors influencing the outcome of paediatric cardiac surgical patients during extracorporeal circulatory support. *J Card Surg* 2007;**2**:4.
27. Kolovos NS, Bratton SL, Moler FW, Bove EL, Ohye RG, Bartlett RH, et al. Outcome of pediatric patients treated with extracorporeal life support after cardiac surgery. *Ann Thorac Surg* 2003;**76**:1435—41.
28. Nehra D, Goldstein AM, Doody DP, Ryan DP, Chang Y, Masiakos PT. Extracorporeal membrane oxygenation for non-neonatal acute respiratory failure: the Massachusetts General Hospital experience from 1990 to 2008. *Arch Surg* 2009;**144**:427—32.
29. Masiakos PT, Islam S, Doody DP, Schnitzer JJ, Ryan DP. Extracorporeal membrane oxygenation for nonneonatal acute respiratory failure. *Arch Surg* 1999;**134**:375—80.
30. Ronco C, McCullough P, Anker SD, Anand I, Aspromonte N, Bagshaw SM, et al. Cardio-renal syndromes: report from the

consensus conference of the acute dialysis quality initiative. *Eur Heart J* 2010;**31**:703—11.
31. Metra M, Nodari S, Parrinello G, Bordonali T, Bugatti S, Danesi R, et al. Worsening renal function in patients hospitalized for acute heart failure: clinical implications and prognostic significance. *Eur J Heart Fail* 2008;**10**:188—95.
32. Hsiao CC, Chang CH, Fan PC, Ho HT, Jenq CC, Kao KC, et al. Prognosis of patients with acute respiratory distress syndrome on extracorporeal membrane oxygenation: the impact of urine output on mortality. *Ann Thorac Surg* 2014;**97**:1939—44.
33. Lin CY, Kao KC, Tian YC, Jenq CC, Chang MY, Chen YC, et al. The RIFLE score increases the accuracy of outcome prediction in patients with acute respiratory distress syndrome undergoing open lung biopsy. *Respiration* 2009;**77**:398—406.
34. Lin CY, Kao KC, Tian YC, Jenq CC, Chang MY, Chen YC, et al. Outcome scoring systems for acute respiratory distress syndrome. *Shock* 2010;**34**:352—7.
35. Chen YC, Fang JT, Yang CW. Acute kidney injury biomarkers. *Taiwan Crit Care Med* 2009;**10**:121—8.
36. Chen TH, Chang CH, Lin CY, Jenq CC, Chang MY, Tian YC, et al. Acute kidney injury biomarkers for patients in a coronary care unit: a prospective cohort study. *PLoS One* 2012;**7**:e32328.
37. Lin CY, Chang CH, Fan PC, Tian YC, Chang MY, Jenq CC, et al. Serum interleukin-18 at commencement of renal replacement therapy predicts short-term prognosis in critically ill patients with acute kidney injury. *PLoS One* 2013;**8**:e66028.
38. Chou YH, Pan SY, Yang CH, Lin SL. Stem cells and kidney regeneration. *J Formos Med Assoc* 2014;**113**:201—9.
39. Lin LY, Chen YC, Fang JT, Yang CW. Renal replacement therapy in acute kidney injury. *Acta Nephrologica* 2013;**27**:63—9.
40. Chen YC, Fang JT, Yang CW. The use of RIFLE classification in critically ill patients. *Int J Intensive Care* 2008; **15**:83—6.