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Acute kidney injury is a frequent complication in critically ill neonates receiving extracorporeal membrane oxygenation: a 14-year cohort study

Alexandra JM Zwiers[1,3*], Saskia N de Wildt[1], Wim CJ Hop[2], Eiske M Dorresteijn[3], Saskia J Gischler[1], Dick Tibboel[1] and Karlien Cransberg[3]

Abstract

Introduction: Newborns in need of extracorporeal membrane oxygenation (ECMO) support are at high risk of developing acute kidney injury (AKI). AKI may occur as part of multiple organ failure and can be aggravated by exposure to components of the extracorporeal circuit. AKI necessitates adjustment of dosage of renally eliminated drugs and avoidance of nephrotoxic drugs. We aimed to define systematically the incidence and clinical course of AKI in critically ill neonates receiving ECMO support.

Methods: This study reviewed prospectively collected clinical data (including age, diagnosis, ECMO course, and serum creatinine (SCr)) of all ECMO-treated neonates within our institution spanning a 14-year period. AKI was defined by using the Risk, Injury, Failure, Loss of renal function, and End-stage renal disease (RIFLE) classification. SCr data were reviewed per ECMO day and compared with age-specific SCr reference values. Accordingly, patients were assigned to RIFLE categories (Risk, Injury, or Failure as 150%, 200%, or 300% of median SCr reference values). Data are presented as median and interquartile range (IQR) or number and percentage.

Results: Of 242 patients included, 179 (74%) survived. Median age at the start of ECMO was 39 hours (IQR, 26 to 63); median ECMO duration was 5.8 days (IQR, 3.9 to 9.4). In total, 153 (64%) patients had evidence of AKI, with 72 (30%) qualifying as Risk, 55 (23%) as Injury, and 26 (11%) as Failure. At the end of the study period, only 71 (46%) patients of all 153 AKI patients improved by at least one RIFLE category. With regression analysis, it was found that nitric oxide ventilation ($P = 0.04$) and younger age at the start of ECMO ($P = 0.004$) were significant predictors of AKI. Survival until intensive care unit discharge was significantly lower for patients in the Failure category (35%) as compared with the Non-AKI (78%), Risk (82%), and Injury category (76%), with all $P < 0.001$, whereas no significant differences were found between the three latter RIFLE categories.

Conclusions: Two thirds of neonates receiving ECMO had AKI, with a significantly increased mortality risk for patients in the Failure category. As AKI during childhood may predispose to chronic kidney disease in adulthood, long-term monitoring of kidney function after ECMO is warranted.

Keywords: Critical care, acute kidney injury, extracorporeal membrane oxygenation (ECMO), RIFLE, serum creatinine

Introduction

Extracorporeal membrane oxygenation (ECMO) is an advanced cardiopulmonary bypass (CPB) technique providing mechanical life support to critically ill patients with acute reversible respiratory or cardiovascular failure, not responding to conventional intensive care. Many neonatal ECMO candidates already have an inflammatory response before the start of ECMO because of asphyxia, hypoxia, infection, or shock. Unfortunately for these already critically ill patients, exposure to components of the ECMO circuit can aggravate this inflammatory response, resulting in a so-called capillary leakage syndrome [1]. High levels of circulating endotoxins, exotoxins, interleukins, and leukotrienes from activated leukocytes and thrombocytes, as well as complement

* Correspondence: a.zwiers@erasmusmc.nl
[1]Intensive Care and Department of Pediatric Surgery
Full list of author information is available at the end of the article

factors, bring harm to the capillary basement membranes [2]. This leads not only to water and small-molecule leakage through the capillary membrane, but also to leakage of relatively large molecules, including albumin, resulting in generalized edema. The blood pressure will decrease because of extravasation of water and proteins, necessitating administration of vasopressor drugs. Low blood pressure and tissue edema may cause deficient tissue perfusion and oxygenation, leading to further organ failure, of which aggravation of existent lung failure and oliguric kidney failure are most prominent.

Acute kidney injury (AKI) requires adjustment of treatment in the short-term; for example, dosages of renally eliminated drugs should be adjusted, and nephrotoxic drugs must be avoided. Reported incidences of AKI among critically ill neonates admitted to a pediatric Intensive Care Unit (ICU) vary widely, between 4.5% and 82.0% [3-8]. This large range is partly explained by the lack of a standard definition of AKI. For that reason, the Acute Dialysis Quality Initiative group proposed a classification system for use in critically ill adult patients, termed the RIFLE criteria [9]. The classification comprises three levels of severity - Risk, Injury, and Failure - and two outcomes: loss of renal function and end-stage renal disease. It is based on changes in serum creatinine (SCr) levels and duration of oliguria. Subsequently, Akcan-Arikan and colleagues [5] proposed a RIFLE classification adapted for pediatrics (pRIFLE). The RIFLE criteria demonstrated clinical relevance for diagnosing AKI, classifying its severity, monitoring the progression of AKI, and predicting mortality in hospitalized adult and pediatric patients [7,8,10].

Previous research showed that renal failure is common both in adults and children receiving ECMO and is associated with increased mortality [3,6,11-13]. By using the Extracorporeal Life Support Organization (ELSO) Registry, Askenazi and colleagues [14] performed a large cross-sectional study in ECMO-treated neonates and children. Of the 7,941 neonates studied, 27.4% died. AKI (SCr >1.5 mg/dl) occurred more often in nonsurvivors than in survivors (19.0% versus 3.9%; $P < 0.0001$), and more nonsurvivors were treated with renal-replacement therapy (RRT) than were survivors (39.7% versus 16.0%; $P < 0.0001$). This and earlier studies in ECMO-treated patients tend to be limited for several reasons. First, the used upper limit for the definition of AKI (SCr >1.5 mg/dl) is debatable, as it does not necessarily indicate kidney injury. In newborns, this cut-off value may include lower grades of AKI, whereas in older infants, this definition corresponds only to severe cases of the RIFLE category, Failure. Second, information is lacking on the time points when SCr levels peaked and on allocation of RRT, which may have prevented patients from ever reaching increased SCr levels. Therefore, the aim of this study was to define systematically the incidence and clinical course of AKI in critically ill neonates receiving ECMO support, by using SCr concentrations and consequent RIFLE categories in the time frame before we applied standard continuous hemofiltration (HF) [15].

As a secondary objective, we aimed to describe the relation between the severity of AKI and survival until ICU discharge.

Methods

Setting

The ICU at the Erasmus MC-Sophia Children's Hospital, Rotterdam, has been serving as an ECMO facility since 1992. This tertiary hospital is one of the two pediatric centers providing ECMO support in The Netherlands. Since 1992, more than 550 children (up to 18 years of age) have been treated with ECMO, presently at a rate of 30 ECMO runs annually. Two thirds of children receiving ECMO support are neonates. During the study period, the venoarterial bypass procedure was the common initial procedure. ECMO support was considered in patients with potentially reversible cardiac and/or respiratory failure unresponsive to optimal conventional therapy, including nitric oxide- and/or high-frequency oscillatory ventilation, maximal fluid resuscitation, and administration of inotropic and vasopressive drugs to maintain the mean arterial pressure within age-adjusted reference values.

Entry criteria for ECMO were a prolonged oxygenation index >25; prolonged alveolar-arterial oxygen difference >600 mm Hg; cardiorespiratory failure for more than 2 hours with pH <7.15 and PaO_2 <5.3 kPa. Contraindications for ECMO were gestational age <34 weeks; <2.0 kilograms; mechanical ventilation for more than 10 days; preexisting intracranial hemorrhage; coagulopathy; and/or other severe congenital anomalies. During the study period, these criteria did not change.

Patients

In this cohort study, we reviewed data of all full-term neonates (≤28 days of age) who received ECMO support within our institution between January 1992 and January 2006. Patients were not eligible for the study if ECMO support had been combined with standard continuous HF for intravascular volume management, which has been part of the clinical protocol since 2005. In contrast, patients who received HF secondary to AKI were enrolled. Other reasons for exclusion were preexisting structural renal anomalies. If a patient had undergone more than one ECMO run, only data related to the first run were included.

Variables

Data were retrieved from our electronic data registry and the hospital's Patient Data Management System (PDMS), which stores all prospectively collected physiological parameters, laboratory results, and therapeutic modalities. Demographic variables were retrieved from the patients' medical records: age and weight at the start of ECMO, gender, primary diagnosis leading to the initiation of ECMO, Apgar scores at 1, 5, and 10 minutes after birth, perinatal asphyxia, cardiac arrest, the use of nitric oxide (NO) ventilation, and the administration of vasopressor drugs before ECMO. The following data on the ECMO run were retrieved: type of ECMO (for example, venoarterial or venovenous) and ECMO course (for example, ECMO duration, need for major surgery, and progressive heart failure during ECMO). In addition, we used length of ICU stay and survival until ICU discharge. With regard to survival, we distinguished between early nonsurvivors and late nonsurvivors by using a cut-off point of 24 hours after ECMO.

AKI definition

SCr was assessed by enzymatic assay (Creatinine Plus; Roche Diagnostics, Branchburg, NJ, USA) on a Hitachi 912 analyzer, as described elsewhere [16]. SCr was measured daily as part of standard clinical care. When SCr was not available on a day of treatment, the absent measurement was reported as a missing value. When more than one SCr measurement had been performed on a single day of treatment, the mean of these values was used. When HF was provided, SCr measurements were disregarded.

To determine the clinical course and severity of AKI, patients were assigned SCr-based RIFLE scores on each day of ECMO treatment: R (risk for kidney injury), I (injury to the kidney), and F (failure of kidney function) [9]. RIFLE strata L (loss of renal function) and E (end-stage renal disease) were not scored, as the study period was restricted to the first 12 days of ECMO treatment. Because, in many cases, no pre-ECMO SCr concentrations were available, RIFLE categories Risk, Injury, and Failure were defined as, respectively, SCr above 150%, 200%, and 300%, of the median of locally collected SCr reference values, as recently published by our institution [17]. These SCr reference values were obtained from children without kidney disease, by using small age intervals ranging from 1 day in the first week after birth up to 3 months at the end of the first year of age. Patients requiring continuous HF for AKI were included in the RIFLE category Failure. Ultimately, patients were grouped according to the highest RIFLE score attained while receiving ECMO. Improvement of AKI was defined as a decline in SCr corresponding to at least one RIFLE category. Whereas inclusion of urine output in the RIFLE criteria has been demonstrated to be helpful to stage AKI in critically ill patients, we decided not to use our data on urine output. The reason for use of SCr exclusively for determining the RIFLE category was that diuresis varied widely, not only because of variation in kidney function, but, more important, because of changes in clinical guidelines for the use of diuretic drugs over the years of the study period [18,19].

Statistical analysis

Data were analyzed by using Statistical Package for the Social Sciences (SPSS) version 17 for windows (SPSS, Chicago, IL, USA). All data are expressed as median values with interquartile range (IQR) for continuous variables or numbers with percentages for categoric variables, unless otherwise indicated. To obtain RIFLE scores, SCr values were expressed in percentages of the median of age-specific reference values. Univariate overall comparisons between groups (Kruskal-Wallis test or Pearson χ^2 test, as appropriate) were performed to detect differences between groups (that is, Non-AKI versus Risk versus Injury versus Failure). The Mann-Whitney U test was used to compare RIFLE distributions per ECMO day according to whether the patients survived. Significant predictors of AKI in univariate analyses were entered in multivariate analysis (logistic regression) to identify independent predictors.

To evaluate the relation between AKI severity and survival until ICU discharge, a logistic regression analysis was used to determine independent predictors for death. Reported are odds ratios (ORs) with 95% confidence intervals (95% CIs). The survival after ECMO decannulation until ICU discharge for each RIFLE category was additionally evaluated graphically by using a Kaplan-Meier survival plot and log-rank tests. Two-sided P = 0.05 was considered the limit of significance in all analyses.

Informed consent

Because of the design of this cohort study, the need for ethics approval and informed consent was waived by the local Medical Research & Ethics Committee of Erasmus University Medical Center.

Results

Patients

Spanning a 14-year period from January 1992 until January 2006, 282 neonatal patients received ECMO support. Thirty-five patients were excluded because they received routine HF to prevent excessive fluid accumulation, despite normal pre-HF SCr levels. For three patients, we were unable to retrieve adequate clinical data, and two patients had congenital renal abnormalities on ultrasound. Hence in total, 242 ECMO-treated

neonates were included in the study, of whom 179 (74%) survived to ICU discharge. Of the 63 nonsurvivors, 30 (48%) patients died within 24 hours after ECMO decannulation, primarily because of rebound pulmonary hypertension (Figure 1). Table 1 represents detailed patient characteristics grouped according to the highest RIFLE score attained during ECMO.

For all patients, the median gestational age and weight on ICU admission was 40.0 weeks (IQR, 38.3 to 40.6) and 3.3 kg (IQR, 2.9 to 3.7), respectively. The most common primary diagnoses to initiate ECMO were meconium-aspiration syndrome (MAS) (42% of all patients) and congenital diaphragmatic hernia (CDH) (29% of all patients). The primary diagnoses, grouped as "other," included failure to wean from CPB after cardiac surgery, and concomitant respiratory syncytial virus and *Bordetella pertussis* infections, mostly in children with severe comorbidities. Median age at the start of ECMO support was 38 hours (IQR, 26 to 63). The median ECMO duration was 5.8 days (IQR, 3.9 to 9.4), and all patients had been treated with venoarterial ECMO. One, however, was initially given venovenous ECMO, but because of insufficient circulatory support, converted to venoarterial ECMO. Eighteen (7%) patients underwent major surgery during ECMO, including surgical repair of diaphragmatic hernia or congenital heart defect.

Renal function and AKI

The median number of SCr measurements while receiving ECMO was six (IQR, four to nine) per patient. Evidence of AKI while receiving ECMO had been documented for 153 patients (64%), with 72 in the Risk category, 55 in the Injury category, and 26 in the Failure category (30%, 23%, and 11% of all ECMO-treated patients, respectively). Of the 26 patients in the Failure group, 10 (38%) received continuous HF in addition to ECMO support for severe metabolic derangement and fluid excess unresponsive to diuretic therapy, as reflected by progressive edema, ongoing oliguria, and hypertension. The median ECMO day at which patients reached the highest RIFLE category for the first time was day 2 (IQR, 1 to 4) for Risk, day 2 (IQR, 1 to 5) for Injury, and day 1 (IQR, 1 to 3) for Failure. Of all 153 AKI patients, only 71 (46%) improved at least one RIFLE category, of whom 35 (49%), 30 (42%), and six (9%) initially were classified as Risk, Injury and Failure, respectively. An overview of the AKI evolution is provided in Figure 2. The median duration from the highest RIFLE category until the start of improvement was 2 days (IQR, 1 to 5) for Risk, 2 days (IQR, 1 to 3) for Injury, and 4 days (IQR, 3 to 6) for patients with Failure. At the end of the study period, only 126 (52%) patients of the total pool of 242 patients were classified as Non-AKI.

In univariate analysis, patients with evidence of AKI were younger at the start of ECMO treatment (P = 0.004). Patients who had had a cardiac arrest before ECMO were more prone to develop AKI ($P < 0.001$), whereas no correlation was found with perinatal asphyxia or diagnosis category. The pre-ECMO use of NO ventilation was associated with a lower incidence of AKI ($P < 0.001$). Major surgery or myocardial stun during ECMO, did not correlate with the occurrence of AKI. Thus, variables considered for the multivariate analysis included younger age at the start of ECMO, cardiac arrest, and NO ventilation before ECMO. By using multiple logistic regression, we found that only younger age at the start of ECMO treatment ($P = 0.004$) and lack of NO ventilation ($P = 0.04$) remained significant predictors of AKI. Patients with AKI had a longer ECMO duration ($P = 0.012$), whereas no significant increase was noted regarding the length of ICU stay.

The survival rate in patients without AKI was 78% and decreased to 35% in the Failure category (Table 1 and Figure 3). Figure 4 shows the distribution of RIFLE categories on each ECMO day, according to survival. Comparing survivors with nonsurvivors regarding the distributions of RIFLE categories on the different ECMO days, we found that survivors generally had a better (lower) RIFLE score. P values for day 1 to day 12 were significant (all $P < 0.05$) except for days 9, 10, and 12 (Figure 4). RIFLE was predictive for both early (<24 hours after ECMO) and late nonsurvivors (>24 hours after ECMO) ($P < 0.001$), but could not discriminate between these two outcomes ($P = 0.43$). Besides RIFLE score, ECMO duration, and age at the start of ECMO were significantly related to mortality in univariate analysis. Longer ECMO durations and younger age were generally associated with higher mortality (both $P < 0.005$). Diagnostic categories also were predictive for mortality ($P < 0.001$). The mortality rates for patients diagnosed with PPHN, MAS, CDH, and the remaining group, "other" were 4%, 5%, 63%, and 30%, respectively. Simultaneous evaluation by using multiple logistic regression showed that RIFLE score ($P = 0.003$), diagnostic category ($P < 0.001$), and ECMO duration ($P < 0.001$) were all independently related to mortality, whereas no significant effect of age remained. Survival until ICU discharge was significantly lower among Failure patients. As a result, the adjusted odds ratio of mortality for Failure in comparison with the other RIFLE categories combined was 12.7 (95% CI, 3.3 to 49.5; $P < 0.001$). No significant differences in survival were found between Non-AKI and the RIFLE categories Risk and Injury ($P = 0.58$).

Discussion

To our knowledge, this is the first study in a large cohort of ECMO-treated neonates evaluating the incidence rate of AKI, systematically classified by the SCr-based RIFLE criteria. On each day of ECMO treatment,

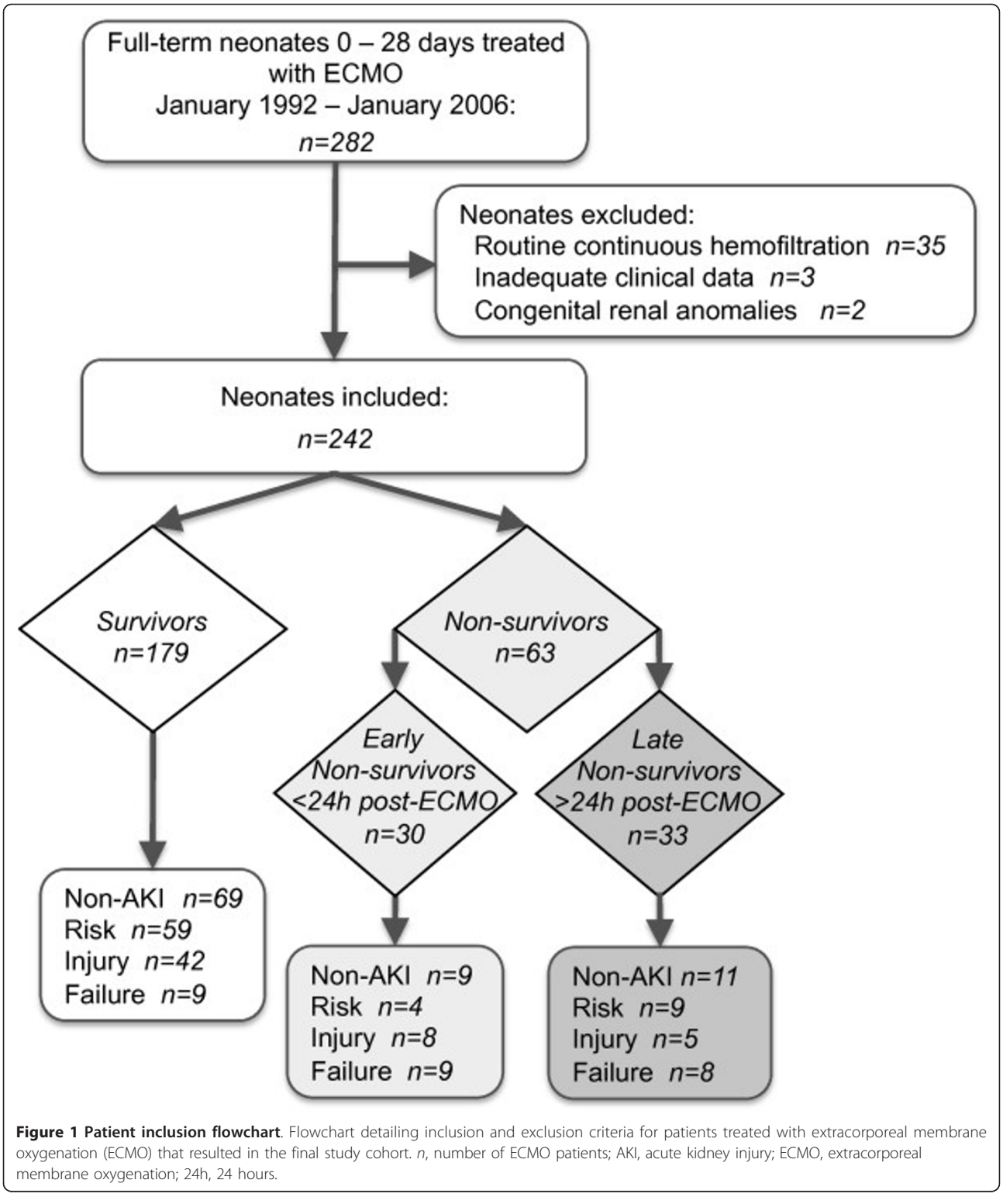

Figure 1 Patient inclusion flowchart. Flowchart detailing inclusion and exclusion criteria for patients treated with extracorporeal membrane oxygenation (ECMO) that resulted in the final study cohort. *n*, number of ECMO patients; AKI, acute kidney injury; ECMO, extracorporeal membrane oxygenation; 24h, 24 hours.

patients were assigned SCr-based RIFLE scores by using the actual SCr values in relation to the median of locally collected age-specific SCr reference values, as recently published by our institution [17]. These reference values allowed us to identify patients reliably as having various degrees of AKI, despite the considerable changes in SCr due to the influence of maternal SCr and the rapidly changing renal function throughout the first weeks of

Table 1 Patient characteristics grouped according to the highest RIFLE score attained

	RIFLE classification				
	Non-AKI	**Risk**	**Injury**	**Failure**	
	***n* = 89 (36%)**	***n* = 72 (30%)**	***n* = 55 (23%)**	***n* = 26 (11%)**	
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	***P* value***
Birth weight (kilograms)	3.3 (2.9-3.7)	3.4 (3.0-3.7)	3.3 (2.9-3.7)	3.0 (2.5-3.6)	0.242[a]
Apgar score					
1 minute after birth	6 (3-8)	5 (3-7)	5 (3-7)	4 (1-7)	0.616[a]
5 minutes after birth	7 (5-9)	7 (5-8)	7 (5-8)	6 (5-8)	0.815[a]
10 minutes after birth	7 (6-8)	7 (6-8)	7 (4-8)	7 (6-8)	0.904[a]
Age at start of ECMO (hours)	44 (27-104)	36 (21-45)	38 (26-59)	38 (28-64)	**0.004**[a]
ECMO duration (days)	4.9 (3.6-8.2)	6.4 (4.2-10.2)	5.7 (4.4-8.9)	7.8 (4.5-15.1)	**0.012**[a]
Length of ICU stay (days)	8 (6-8.2)	11 (7-20.8)	10 (6-18)	14.5 (5.8-22.3)	0.178[a]
	n (%)	*n* (%)	*n* (%)	*n* (%)	*P* value
Sex, female	41 (46%)	30 (42%)	25 (45%)	15 (58%)	0.576[b]
Diagnosis					0.155[b]
Meconium-aspiration syndrome^	40 (45%)	35 (49%)	22 (40%)	6 (23%)	
Congenital diaphragmatic hernia^	22 (25%)	22 (30%)	13 (24%)	13 (50%)	
Isolated PPHN	9 (10%)	8 (11%)	6 (11%)	3 (12%)	
Other	18 (20%)	7 (10%)	14 (25%)	4 (15%)	
Before ECMO					
Vasopressor drugs	81 (91%)	70 (97%)	50 (91%)	24 (92%)	0.535[b]
Nitric oxide ventilation	80 (90%)	53 (74%)	27 (49%)	14 (54%)	**<0.001**[b]
Perinatal asphyxia	48 (54%)	40 (56%)	39 (71%)	14 (54%)	0.142[b]
Cardiac arrest	5 (6%)	5 (7%)	14 (26%)	7 (27%)	**<0.001**[b]
During ECMO					
Major surgery	4 (4%)	4 (6%)	8 (15%)	2 (8%)	0.137[b]
Myocardial stunning	3 (3%)	4 (6%)	0 (0%)	1 (4%)	0.385[b]
Nonsurvivors	20 (22%)	13 (18%)	13 (24%)	17 (65%)	<0.001[b]
Early nonsurvivors	9 (45%)	4 (31%)	8 (62%)	9 (53%)	
<24 hours after ECMO					
Late nonsurvivors	11 (55%)	9 (69%)	5 (38%)	8 (47%)	
≥24 hours after ECMO					

RIFLE categories Risk, Injury, and Failure were defined as SCr above 150%, 200%, and 300%, respectively, of the median of age-specific SCr reference values. Continuous data are expressed as median (interquartile range (IQR)), and categoric data are expressed as number (%). AKI, acute kidney injury; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; PPHN, persistent pulmonary hypertension; RIFLE, Risk, Injury, Failure, Loss, End-stage renal disease; SCr, serum creatinine. *P* values indicate overall comparison of all groups (that is, Non-AKI versus Risk versus Injury versus Failure). Intergroup differences were assessed by using either [a]the Kruskal-Wallis test or [b]the Pearson χ^2 test, as appropriate. ^Majority of the patients had severe PPHN.

life, even irrespective of ECMO treatment. Furthermore, to collect a homogeneous study group, we excluded patients who were prophylactically treated with HF during ECMO for fluid management as part of standard clinical care. Moreover, we excluded patients with congenital renal malformations.

The incidence of AKI was 63% for the RIFLE scores Risk, Injury, and Failure; and 34% when exclusively evaluating the categories Injury and Failure. These results differ from those of other studies focusing on ECMO-treated patients [12,14].

One study reported, in a very large cohort of approximately 10,000 ECMO patients, a much lower AKI incidence rate, varying from 8.0% in neonatal patients to 20.5% in pediatric patients [14]. This discrepancy can be explained as follows. First, data were retrieved from the ELSO Registry database, which traditionally collects cross-sectional information, with the possibility that the AKI episode has been missed. Second, AKI was defined by using the renal complication code, as stated in the ELSO Registry (SCr >1.5 mg/dl). Although in newborns, this cut-off value may include lower grades of AKI, in older infants, this definition corresponds only to severe cases of the RIFLE category Failure. Finally, 27% of all patients received RRT according to hospital practice, of which further data on indication, timing, and dose are not provided. Standard HF may have prevented many patients from ever developing AKI, defined as SCr levels >1.5 mg/dl.

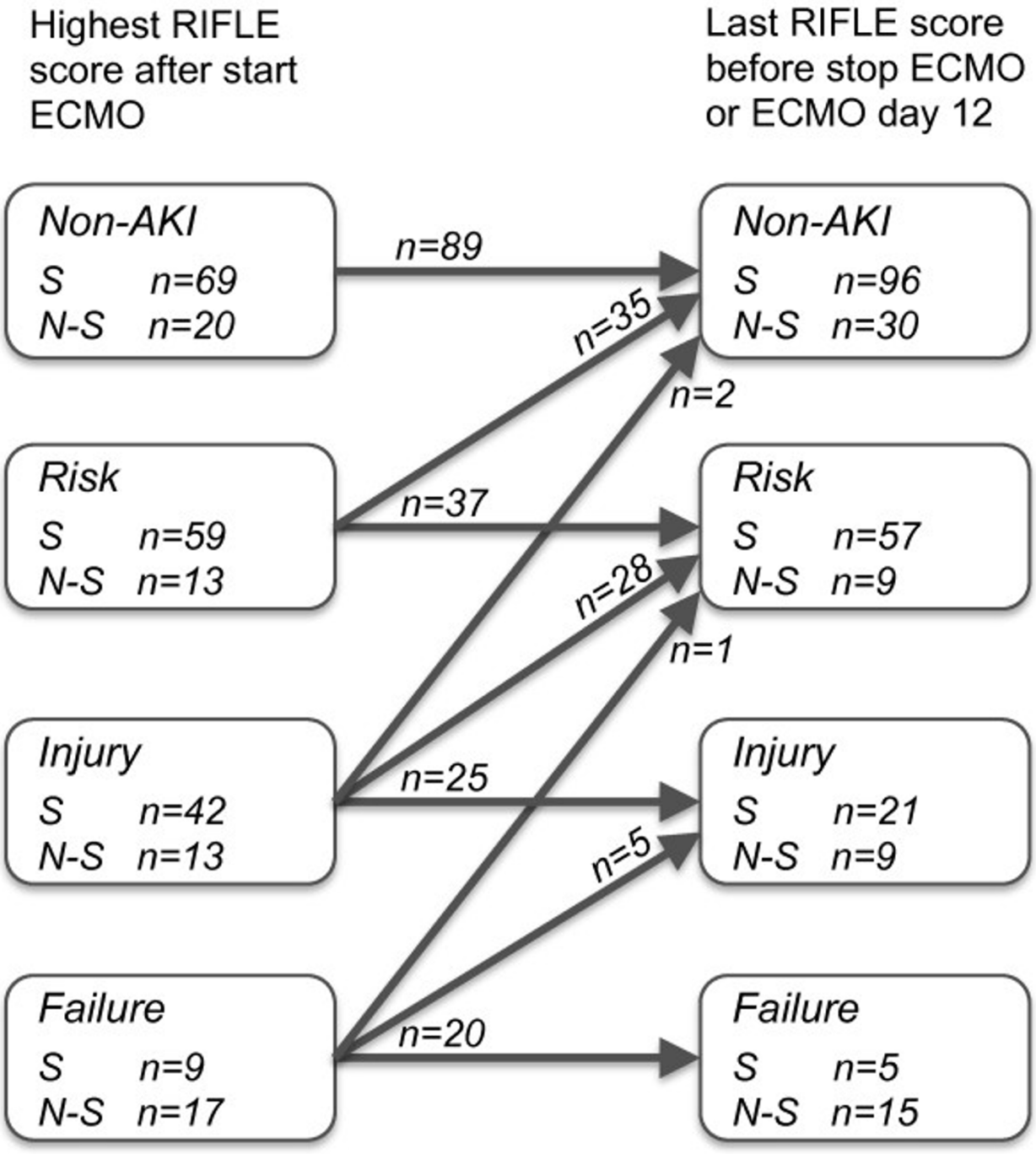

Figure 2 Evolution of acute kidney injury during extracorporeal membrane oxygenation (ECMO). Flow diagram showing the evolution of acute kidney injury (AKI) during treatment with ECMO. After the start of ECMO, all patients were stratified according to the highest RIFLE score attained. RIFLE categories Risk, Injury, and Failure were defined as, respectively, SCr above 150%, 200%, and 300%, of the median of age-specific SCr reference values. Subsequently the AKI evolution over time was evaluated by using the last RIFLE score before the cessation of ECMO or on ECMO day 12. All arrows indicate the direction of AKI evolution. Of all 153 AKI patients, only 71 (46%) patients improved at least one RIFLE category. *n*, number of ECMO patients (%); AKI, acute kidney injury; NS, nonsurvivor; RIFLE, Risk, Injury, Failure, Loss, End-stage renal disease; SCr, serum creatinine; S, survivor.

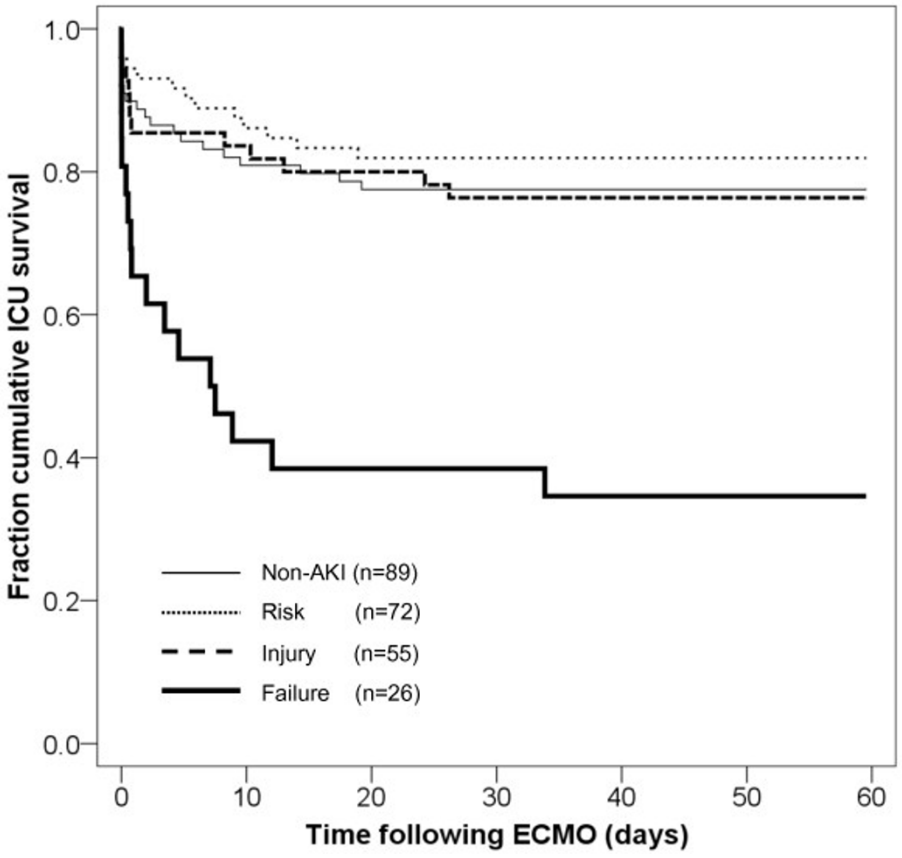

Figure 3 Kaplan-Meier survival curves stratified by RIFLE category. All patients are stratified according to the highest RIFLE score attained during ECMO. Kaplan-Meier analysis estimates, for each RIFLE category, the rate of survival until intensive care unit (ICU) discharge among all patients after the cessation of ECMO. RIFLE categories Risk, Injury, and Failure were defined as, respectively, SCr above 150%, 200%, and 300%, of the median of age-specific SCr reference values. The differences between the Failure category and each of the other RIFLE categories are significant (all $P < 0.001$; Log-Rank test). No significant differences were found between the Non-AKI, Risk, and Injury categories. ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; RIFLE, Risk, Injury, Failure, Loss, End-stage renal disease; SCr, serum creatinine.

A study by Smith and colleagues [20] demonstrated a higher incidence of 71.7% of acute renal failure in 45 pediatric cardiac patients requiring ECMO. AKI severity was classified with an adapted pRIFLE score, with criteria for fluid retention added. In this study, case selection is certainly an important selection bias, as only the most complicated cardiac cases received ECMO. Moreover, the incidence rate of AKI may have been overestimated, as the category Failure also included those patients treated with HF to reduce fluid retention and electrolyte disturbances.

Another study, in 68 neonates with CDH requiring ECMO, reported an AKI incidence of 70.6% [12]. The focus on solely CDH patients, with their compromised circulation, may explain this high incidence.

In our CDH patients, the AKI incidence was comparable at 69%. We identified two clinical factors associated with AKI. The favorable effect of NO ventilation before ECMO might suggest a protective role against AKI. One explanation is the systemic effect of inhaled NO, which includes modulation of the distribution of systemic blood flow and thereby potentially of renal perfusion. However, evidence on how changes in renal perfusion are related to the development of AKI is contradictory [21]. Another predictor for AKI is younger age at the start of ECMO. Patients who were younger at the start of ECMO may have been the sicker ones, as they were not responding to conventional therapy earlier in life.

Overall, the severity of AKI is maximal within the first 2 days after the start of ECMO. As a consequence, we cannot exclude pre-ECMO renal injury, as the majority of patients were in need of vasopressor drugs. The high SCr levels throughout the first ECMO days contrast the expected decrease in SCr due to dilution of the patients' blood by the extracorporeal volume. The clinical course of AKI is even more concerning, as only 46% of all patients initially classified as AKI show some degree of renal recovery during ECMO. In our study, survivors

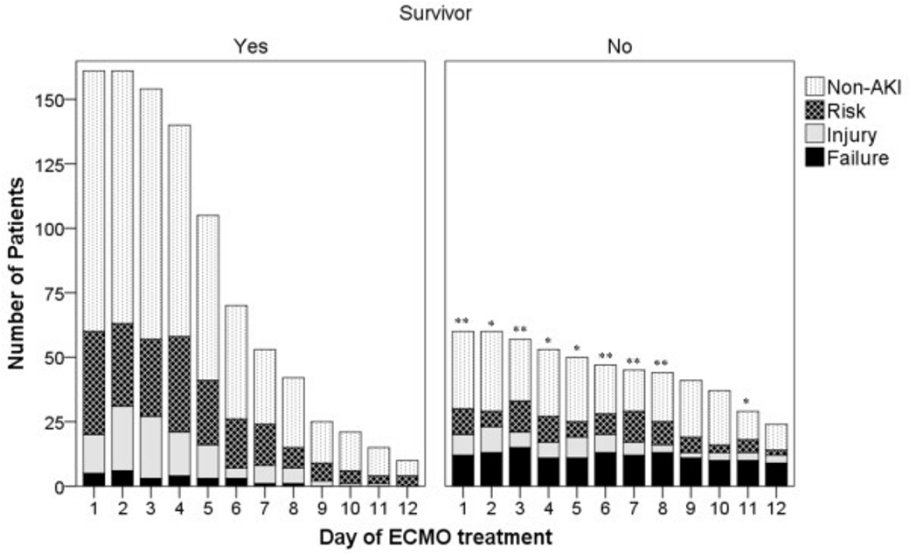

Figure 4 RIFLE distribution per day of ECMO treatment grouped according to survival. The distribution of RIFLE categories on each ECMO day for patients who survived until intensive care unit (ICU) discharge compared with patients who did not survive until ICU discharge. RIFLE categories Risk, Injury, and Failure were defined as, respectively, SCr above 150%, 200%, and 300%, of the median of age-specific SCr reference values. Differences in RIFLE distribution per ECMO day between survivors and nonsurvivors were assessed by using Mann-Whitney *U* tests; **P* < 0.05; ***P* < 0.01. Survivors generally had a better RIFLE category throughout ECMO. ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; RIFLE, Risk, Injury, Failure, Loss, End-stage renal disease; SCr, serum creatinine.

generally had a better RIFLE score than nonsurvivors. This is in agreement with a higher survival rate (78%) in patients without AKI compared with 35% in those with kidney failure. The adjusted odds ratio of mortality for Failure in comparison with the other RIFLE categories combined was 12.7 (95% CI, 3.3 to 49.5; $P < 0.001$). This high mortality risk confirms the previously reported association between AKI and mortality [6,11-14,20,22], and supports the idea that patients may benefit from early recognition of AKI and prevention of deterioration of renal function. With the high incidence of AKI in the present study, we should start worrying that many of these children could develop chronic kidney disease (CKD) in the long run [23-25].

Several limitations of this study should be addressed. First, SCr level is a delayed measure of decreased kidney function after AKI and is not very sensitive. Reference values vary widely during the first days of life, in particular with the risk of overestimation of AKI. Conversely, the ECMO circuit in neonates doubles the circulating volume, thereby diluting SCr levels. Hence, with SCr, the true incidence of AKI during the first days of ECMO treatment is hard to establish. A second limitation of our study is that we were not able to use urine output for grading AKI severity, which may have resulted in different incidences of Risk, Injury, and Failure.

The expected first sign of AKI associated with circulatory failure in ECMO candidates, tubular damage due to ischemia, may be detected early by the use of biomarkers in the urine, which are not affected by age or renal maturation, increased circulating volume, or the ECMO circuit itself. These biomarkers may prove to be more sensitive, to enable the early diagnosis of AKI, and may distinguish between potential AKI causes [26-29].

Conclusions

This study shows that the incidence of AKI in a large population of ECMO-treated neonates is remarkably high and that the severity of AKI is associated with mortality. Because AKI during childhood may predispose for CKD in adulthood, long-term follow-up of kidney function after ECMO is recommended.

Key messages

Two thirds of ECMO-treated patients had AKI.

The higher the severity of AKI, the higher the risk of death while being treated with ECMO.

Long-term monitoring of kidney function after ECMO treatment is recommended to screen for CKD.

Abbreviations

AKI: acute kidney injury; CDH: congenital diaphragmatic hernia; CI: confidence interval; CKD: chronic kidney disease; CPB: cardiopulmonary bypass; ECMO: extracorporeal membrane oxygenation; ELSO Registry: Extracorporeal Life Support Organization Registry; GFR: glomerular filtration rate; HF: hemofiltration; ICU: intensive care unit; IQR: interquartile range; MAS: meconium aspiration syndrome; NO: nitric oxide; NSs: nonsurvivors;

OR: odds ratio; PDMS: Patient Data Management System; PPHN: persistent pulmonary hypertension; RIFLE: risk injury failure loss end-stage renal disease; RRT: renal-replacement therapy; Ss: survivors; SCr: serum creatinine; SPSS: Statistical Package for the Social Sciences.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
AZ carried out the study and wrote the manuscript. WH performed statistical analysis and interpretation of data. ED and SG reviewed the manuscript and participated in data collection. SW, DT, and KC contributed to study design and writing of the manuscript. All authors read and approved the final manuscript.

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Authors' details
[1]Intensive Care and Department of Pediatric Surgery. [2]Department of Epidemiology & Biostatistics, Erasmus University, Rotterdam, The Netherlands. [3]Department of Pediatric Nephrology, Erasmus Medical Center-Sophia Children's Hospital, Dr Molewaterplein 60, 3015 GJ, Rotterdam, The Netherlands.

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References
1. Michel CC: **Transport of macromolecules through microvascular walls.** *Cardiovasc Res* 1996, **32**:644-653.
2. Stahl RF, Fisher CA, Kucich U, Weinbaum G, Warsaw DS, Stenach N, O'Connor C, Addonizio VP: **Effects of simulated extracorporeal circulation on human leukocyte elastase release, superoxide generation, and procoagulant activity.** *J Thorac Cardiovasc Surg* 1991, **101**:230-239.
3. Alkandari O, Eddington KA, Hyder A, Gauvin F, Ducruet T, Gottesman R, Phan V, Zappitelli M: **Acute kidney injury is an independent risk factor for pediatric intensive care unit mortality, longer length of stay and prolonged mechanical ventilation in critically ill children: a two-center retrospective cohort study.** *Crit Care* 2011, **15**:R146.
4. Bailey D, Phan V, Litalien C, Ducruet T, Merouani A, Lacroix J, Gauvin F: **Risk factors of acute renal failure in critically ill children: a prospective descriptive epidemiological study.** *Pediatr Crit Care Med* 2007, **8**:29-35.
5. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL: **Modified RIFLE criteria in critically ill children with acute kidney injury.** *Kidney Int* 2007, **71**:1028-1035.
6. Schneider J, Khemani R, Grushkin C, Bart R: **Serum creatinine as stratified in the RIFLE score for acute kidney injury is associated with mortality and length of stay for children in the pediatric intensive care unit.** *Crit Care Med* 2010, **38**:933-939.
7. Plotz FB, Bouma AB, van Wijk JA, Kneyber MC, Bokenkamp A: **Pediatric acute kidney injury in the ICU: an independent evaluation of pRIFLE criteria.** *Intensive Care Med* 2008, **34**:1713-1717.
8. Koralkar R, Ambalavanan N, Levitan EB, McGwin G, Goldstein S, Askenazi D: **Acute kidney injury reduces survival in very low birth weight infants.** *Pediatr Res* 2011, **69**:354-358.
9. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, Acute Dialysis Quality Initiative: **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-R212.
10. Lopes JA, Fernandes P, Jorge S, Goncalves S, Alvarez A, Costa e Silva Z, Franca C, Prata MM: **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.
11. Lin CY, Chen YC, Tsai FC, Tian YC, Jenq CC, Fang JT, Yang CW: **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**:2867-2873.
12. Gadepalli SK, Selewski DT, Drongowski RA, Mychaliska GB: **Acute kidney injury in congenital diaphragmatic hernia requiring extracorporeal life support: an insidious problem.** *J Pediatr Surg* 2011, **46**:630-635.
13. Thiagarajan RR, Laussen PC, Rycus PT, Bartlett RH, Bratton SL: **Extracorporeal membrane oxygenation to aid cardiopulmonary resuscitation in infants and children.** *Circulation* 2007, **116**:1693-1700.
14. Askenazi DJ, Ambalavanan N, Hamilton K, Cutter G, Laney D, Kaslow R, Georgeson K, Barnhart DC, Dimmitt RA: **Acute kidney injury and renal replacement therapy independently predict mortality in neonatal and pediatric noncardiac patients on extracorporeal membrane oxygenation.** *Pediatr Crit Care Med* 2011, **12**:e1-e6.
15. Blijdorp K, Cransberg K, Wildschut ED, Gischler SJ, Jan Houmes R, Wolff ED, Tibboel D: **Haemofiltration in newborns treated with extracorporeal membrane oxygenation: a case-comparison study.** *Crit Care* 2009, **13**:R48.
16. Junge W, Wilke B, Halabi A, Klein G: **Determination of reference intervals for serum creatinine, creatinine excretion and creatinine clearance with an enzymatic and a modified Jaffe method.** *Clin Chim Acta* 2004, **344**:137-148.
17. Boer DP, de Rijke YB, Hop WC, Cransberg K, Dorresteijn EM: **Reference values for serum creatinine in children younger than 1 year of age.** *Pediatr Nephrol* 2010, **25**:2107-2113.
18. van der Vorst MM, den Hartigh J, Wildschut E, Tibboel D, Burggraaf J: **An exploratory study with an adaptive continuous intravenous furosemide regimen in neonates treated with extracorporeal membrane oxygenation.** *Crit Care* 2007, **11**:R111.
19. van der Vorst MM, Wildschut E, Houmes RJ, Gischler SJ, Kist-van Holthe JE, Burggraaf J, van der Heijden AJ, Tibboel D: **Evaluation of furosemide regimens in neonates treated with extracorporeal membrane oxygenation.** *Crit Care* 2006, **10**:R168.
20. Smith AH, Hardison DC, Worden CR, Fleming GM, Taylor MB: **Acute renal failure during extracorporeal support in the pediatric cardiac patient.** *ASAIO J* 2009, **55**:412-416.
21. Prowle J, Bagshaw SM, Bellomo R: **Renal blood flow, fractional excretion of sodium and acute kidney injury: time for a new paradigm?** *Curr Opin Crit Care* 2012, **18**:585-592.
22. Hei F, Lou S, Li J, Yu K, Liu J, Feng Z, Zhao J, Hu S, Xu J, Chang Q, Liu Y, Wang X, Liu P, Long C: **Five-year results of 121 consecutive patients treated with extracorporeal membrane oxygenation at Fu Wai Hospital.** *Artif Organs* 2011, **35**:572-578.
23. Goldstein SL: **Acute kidney injury in children and its potential consequences in adulthood.** *Blood Purif* 2012, **33**:131-137.
24. Goldstein SL, Devarajan P: **Acute kidney injury in childhood: should we be worried about progression to CKD?** *Pediatr Nephrol* 2011, **26**:509-522.
25. Paden ML, Warshaw BL, Heard ML, Fortenberry JD: **Recovery of renal function and survival after continuous renal replacement therapy during extracorporeal membrane oxygenation.** *Pediatr Crit Care Med* 2011, **12**:153-158.
26. Han WK, Waikar SS, Johnson A, Betensky RA, Dent CL, Devarajan P, Bonventre JV: **Urinary biomarkers in the early diagnosis of acute kidney injury.** *Kidney Int* 2008, **73**:863-869.
27. Krawczeski CD, Goldstein SL, Woo JG, Wang Y, Piyaphanee N, Ma Q, Bennett M, Devarajan P: **Temporal relationship and predictive value of urinary acute kidney injury biomarkers after pediatric cardiopulmonary bypass.** *J Am Coll Cardiol* 2011, **58**:2301-2309.
28. Ricci Z, Morelli S, Favia I, Garisto C, Brancaccio G, Picardo S: **Neutrophil gelatinase-associated lipocalin levels during extracorporeal membrane oxygenation in critically ill children with congenital heart disease: preliminary experience.** *Pediatr Crit Care Med* 2012, **13**:e51-e54.
29. Soni SS, Ronco C, Katz N, Cruz DN: **Early diagnosis of acute kidney injury: the promise of novel biomarkers.** *Blood Purif* 2009, **28**:165-174.

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