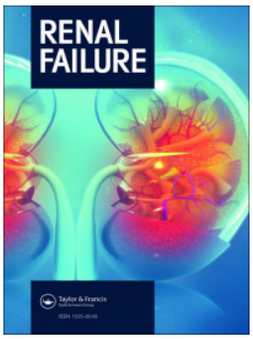

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CLINICAL STUDY

Risk factors associated with hospital mortality in non-surgical patients receiving extracorporeal membrane oxygenation and continuous renal replacement treatment: a retrospective analysis

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ABSTRACT

Objectives: The prognosis-predicting factors for non-surgical patients receiving continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO) remains limited. In this study, we aim to analyze prognosis-predicting factors in the non-surgical patients receiving these two therapies.

Methods: We retrospectively analyzed data from non-surgical patients with ECMO treatment from December 2013 until April 2023. Hospital mortality was primary endpoint of this study. The area under the curve and receiver operating characteristic curves were used to assess the sensitivity and specificity of mortality. The independent risk factors were identified by multivariate logistic regression. The prediction model was a nomogram, and decision curve analysis and the calibration plot were used to assess it. Using restricted cubic spline curves and Spearman correlation, the correlation analysis was performed.

Results: The model that incorporated CRRT duration and age surpassed the two variables alone in predicting hospital mortality in non-surgical patients with ECMO therapy (AUC value = 0.868, 95% CI = 0.779–0.956). Older age, CRRT implantation, and duration were independent risk factors for hospital mortality (all $p < 0.05$). The nomogram predicting outcomes model containing on CRRT implantation and duration was developed, and the consistency between the predicted probability and observed probability and clinical utility of the models were good. CRRT duration was negatively associated with hemoglobin concentration and positively associated with urea nitrogen and serum creatinine levels.

Conclusion: Hospital mortality in non-surgical ECMO patients was found to be independently associated with older age, longer CRRT duration, and CRRT implantation.

Abbreviations: AKI: Acute kidney injury; ALB: Albumin; AUC: Under the curve; BUN: Blood urea nitrogen; CI: Confidence interval; CRRT: Continuous renal replacement therapy; DCA: Decision curve analysis; ECMO: Extracorporeal membrane oxygenation; GFR: Glomerular filtration rate; Hb: Hemoglobin; KDIGO: Kidney Disease: Improving Global Outcomes; NYHA: New York Heart Association; OR: Odds ratio; ROC: Receiver operating characteristic; RCS: Restricted cubic spline; SD: Standard deviation; VA-ECMO: Veno-arterial ECMO

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Acute renal injury; continuous renal replacement therapy; extracorporeal membrane oxygenation; mortality; non-surgical patient; risk factors

Introduction

A potentially reversible treatment for patients with the most seriously life-threatening cardiorespiratory failure is extracorporeal membrane oxygenation (ECMO), which temporarily circumvents the functioning of these organs [1]. Patients receiving ECMO therapy are at high higher risk of experiencing multiple organ failures, resulting in high mortality, including acute brain injurey, fluid overload, and acute kidney injury (AKI) [2–5]. Consequently, patients undergoing ECMO treatment are increasingly receiving

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continuous renal replacement therapy (CRRT) for the prevention and treatment of fluid overload and management of AKI [6].

More and more investigations were reported about the factors predicting prognosis in patients receiving ECMO combined with CRRT. About 42–85% of adult patients on ECMO developed AKI [7–10], with approximately 45% of these patients ultimately requiring CRRT [11]. Dado et al. [12] found that mortality was up to 80%, which was associated with the combination of CRRT and ECMO. In a multivariate analysis, older age and positive net fluid balance were independently associated with mortality [12]. The investigations of Deatrick et al. [11] and Devasagayaraj et al. [13, 14] had similar findings: ECMO survival with CRRT was significantly lower than the ECMO-only group, though the risk factors they reported were not consistent. Our previous research found that in the group of surgical patients requiring ECMO-which mostly comprised patients having cardiovascular surgery and needing veno-arterial ECMO (VA-ECMO)—the requirement for CRRT was an independent risk factor for death [15]. Older age, absence of valvular heart disease, and decreased serum albumin (ALB) concentration were independent risk factors for mortality in the subset of patients undergoing concurrent CRRT and ECMO [15]. The heterogeneity of mortality risk factors among patients undergoing ECMO in combination with CRRT may be attributed to the multifactorial nature of these conditions, which includes both variables inherent to ECMO and AKI and those resulting from the underlying diseases. Thus, it is still necessary to investigate the combined use of ECMO and CRRT in patients with different underlying diseases.

We continue to examine prognostic markers in non-surgical patients who have undergone CRRT and ECMO within the last approximately nine years in the current study. The risk factors for mortality in patients undergoing combination CRRT and ECMO for both surgical and non-surgical illnesses were investigated.

Materials and methods

Participants in the study and data gathering

By selecting patient records of The Affiliated Panyu Central Hospital of Guangzhou Medical University and the First Affiliated Hospital of Sun Yat-sen University, we were able to identify patients who received ECMO implantation between 2013 and 2023. The exclusion criteria were as follows: age <18; incomplete data; pregnancy; and surgery while hospitalized. The patient's medical records were used to obtain clinical data, including demographic information, medical history, clinical features, and auxiliary testing. In compliance with the 1975 Helsinki Declaration, the study was reviewed and approved by the institutional review boards of The Affiliated Panyu Central Hospital of Guangzhou Medical University (approval number: PYRC-2023-378; title: Clinical study on IABP and ECMO; Protocol: 2023-06-01; approval data: November 29, 2023).

Study definitions and outcome

Hospital mortality was primary endpoint of this study. The endpoint of death was monitored either during the hospital stay or within 30 days of the patient's discharge. A degree of overlap exists between the durations of CRRT and ECMO use. The outcome thereafter transpired following the concurrent use of CRRT and ECMO. VA-ECMO implantation was permitted for patients with an Interagency Registry for Mechanically Assisted Circulatory Support profile I or II [16]. The Extracorporeal Life Support Organization's indications are identical to those for venovenous-ECMO [17]. The Kidney Disease: Improving Global Outcomes (KDIGO) criteria [18] categorized chronic kidney disease as Glomerular filtration rate (GFR) categories G3a-G5. The KDIGO guidelines serve as the basis for the diagnosis and staging of AKI [19]. At the time of enrollment, current heart failure was classified as New York Heart Association (NYHA) class III/IV. Based on the results of the initial test at admission, the blood test result was determined. Unless otherwise indicated, the International Classification of Diseases, Ninth Revision, and Clinical Modification codes were used to define additional variables and cutoffs.

Statistical analysis

The Mann-Whitney *U* test or unpaired Student *t*-test were used to compare continuous variables, depending on the normality of the data. The continuous variables were presented as mean ± standard deviation (SD) or medians (interquartile range). Categorical variables were compared using the Fisher exact test or the chi-squared test. The multivariate and univariate logistic regression analyses were used to screen for the risk variables. Four different models were used for potential confounder adjustment: model 1 for age and gender; model 2 for age, gender, NYHA functional classes and serum ALB concentration; model 3 for age, gender, NYHA functional classes, serum ALB concentration, hemoglobin (Hb) concentration, creatinine concentration, and BUN level; model 4 for age, gender, NYHA functional classes, serum ALB concentration, Hb concentration, serum creatinine level, BUN level, severe myocarditis, and monocytes. The receiver operating characteristic (ROC) curve values and area under the curve (AUC) values were used to assess the prediction capacity. A nomogram for the prediction of hospital mortality based on the variables containing CRRT implantation or CRRT duration was developed. Decision curve analysis (DCA) and calibration plots were used to assess the model further. Correlation analysis between CRRT duration and the variables was characterized using Spearman's rank correlation test. Using restricted cubic spline (RCS) curves, the relationship between age and hospital mortality was shown and evaluated. $p < 0.05$ was used to determine statistical significance. The R statistical tool (The R Foundation; http://www.r-project.org; version 4.1.3), SPSS 22 (IBM, Chicago, IL), and STATA version 14.0 were used for performing all statistical analyses (StataCorp, College Station, TX).

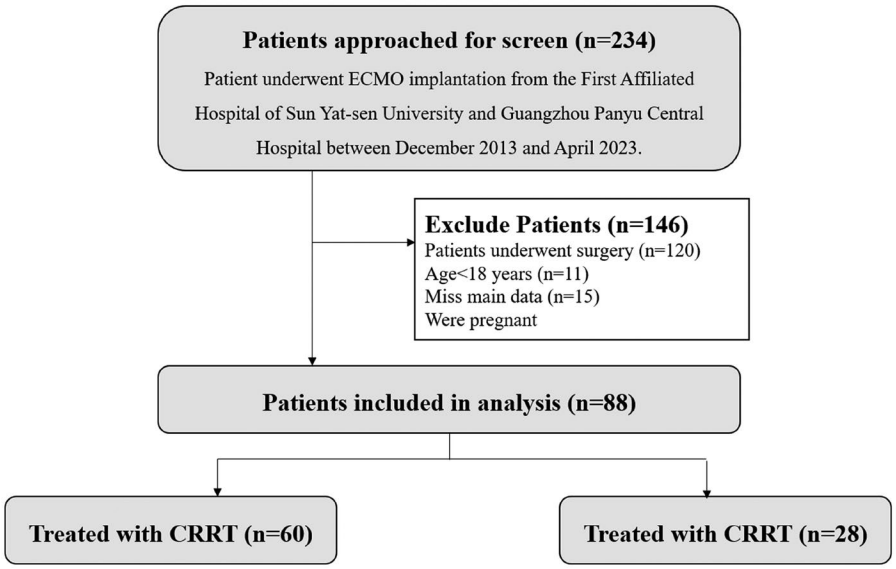

Figure 1. Flow chart for study inclusion/exclusion of patients with ECMO implication. ECMO: extracorporeal membrane oxygenation; CRRT: continuous renal replacement therapy

Results

Baseline characteristics

The patient inclusion flowchart is depicted in Figure 1. Table 1 presents the demographic information of the patients participating in the study. A total of 88 patients who met the inclusion criteria were included in this study; of these, 65 (73.86%) died recently while in the hospital. As shown in Table 1, non-survivors had older age, lower levels of Hb, higher levels of creatinine, more CRRT, and less severe myocarditis. Other clinical indicators showed no significant change. For ECMO model, 43 patients underwent VA-model and 45 patients for VV-model. The ECMO indication of this cohort contained severe heart failure, severe pneumonia, severe myocarditis, myocardial infarction (MI), and interstitial lung disease (Table 1).

Hospital mortality prognosis among non-surgical patients undergoing ECMO implantation as predicted by CRRT implantation and other clinical indicators

This study employs ROC curve analysis to identify the prognostic indicators for hospital mortality among non-surgical patients undergoing ECMO implantation. Table 2 shows that the diagnostic performance of clinical indexes containing age, BUN level, serum creatinine level, and CRRT duration for hospital mortality was satisfactory (AUC value for age = 0.717, 95% confidence interval [CI] = 0.597–0.837; AUC value for BUN level = 0.600, 95% CI = 0.477–0.723; AUC value for serum creatinine level = 0.620, 95% CI = 0.497–0.743; AUC value for CRRT duration = 0.850, 95% CI = 0.777–0.924). Furthermore, the predictive model combining the CRRT duration and age showed significantly improved accuracy of themselves alone in predicting hospital mortality of non-surgical patients undergoing ECMO implantation (Figure 2, AUC value for CRRT duration and age = 0.868, 95% CI = 0.779–0.956).

The hospital mortality prognostic significance of CRRT implantation in non-surgical patients undergoing ECMO implantation

Using univariate and multivariate regression analysis, the predictive relevance of CRRT for hospital mortality in non-surgical patients following ECMO implantation was investigated. The outcomes of the univariate logistic regression analysis are presented in Table 3. Hospital mortality in non-surgical patients who underwent ECMO implantation was associated with CRRT implantation, CRRT duration, age, Hb concentration, and serum creatinine level (CRRT implantation: odds ratio [OR] = 5.667, 95% CI = 2.033–15.796, $p = 0.001$; CRRT duration: OR = 1.912, 95% CI = 1.424–2.567, $p = 0.000$; age: OR = 1.050, 95% CI =1.016–1.084, $p = 0.003$; Hb concentration: OR = 0.982, 95% CI = 0.965–0.999, $p = 0.041$; serum creatinine level: OR = 1.009, 95% CI = 1.000–1.018, $p = 0.042$). Further multivariate analysis was performed to examine the predictive value of CRRT concerning hospital mortality among non-surgical patients undergoing ECMO implantation. Model 1 was corrected for age and gender in multivariate analyses, whereas model 2 was adjusted for age, gender, NYHA functional classes, and serum ALB concentration. Age, gender, NYHA functional classes, serum ALB concentration, Hb concentration, serum creatinine level, and BUN level were adjusted for in Model 3. Model 4 was adjusted for age, gender, NYHA functional classes, serum ALB concentration, Hb concentration, serum creatinine level, BUN level, severe myocarditis, and monocytes. In all models, there was a significant association between hospital mortality and CRRT implantation and duration (for CRRT implantation, model 1:

Table 1. Baseline characteristics of the study population with different survival status in hospital.

	Survival ($n=23$)	Death ($n=65$)	p value
Demographics			
Age	44.096 ± 3.26	56.86 ± 1.85	**0.0016***
Male, *n* (%)	9 (39.13%)	47(72.31%)	0.307
Laboratory events			
WBC,10^9/L	7.81 (5.78–12.23)	9.51 (5.89–15.3)	0.325
Neutrophils, 10^9/L	6.45 (4.15–8.96)	7.71 (4.44–13.76)	0.386
Lymphocytes, 10^9/L	0.86 (0.34–1.38)	0.97 (0.45–1.7)	0.558
Monocytes, 10^9/L	0.37 (0.13–0.79)	0.47 (0.31–0.84)	0.078
Hb, g/L	124 (100–139)	113 (86–129)	**0.0365***
Platelets, 10^9/L	187 (102–216)	176 (86–229)	0.653
BUN, μmol/L	6.5 (4.6–8.3)	7.7 (5–12.8)	0.083
Creatinine, μmol/L	81 (62–108)	94 (70–178)	**0.0289***
ALB, g/L	33 (29–38)	34 (28.2–37.8)	0.656
ALT, U/L	52 (23–98)	52 (31–77)	0.752
AST, U/L	92 (32–312)	76 (41–166)	0.714
Total bilirubin, μmol/L	15.4 (8.9–21.7)	17.2 (11.5–38.2)	0.199
CRP, mg/L	42.2 (4.95–202.74)	48.43 (8.18–112)	0.362
NTproBNP, pg/ML	505.5 (268.6–4477)	1327 (242.5–7494)	0.249
cTNT, ng/ML	0.09 (0.016–2.13)	0.064 (0.019–0.358)	0.702
Medical history			
heart failure	19 (82.61%)	47 (72.31%)	0.327
Coronary heart disease	4 (17.39%)	15 (23.08%)	0.569
Valvular disease	0 (0%)	2 (3.08%)	0.395
Hypertension	5 (21.74%)	26 (40.00%)	0.115
Hyperlipidemia	1 (4.35%)	3 (4.62%)	0.958
Previous MI	1 (4.35%)	2 (3.08%)	0.773
Cerebrovascular disease	0 (0.0%)	9 (13.85%)	0.060
COPD	0 (0.0%)	3 (4.62%)	0.294
Previous kidney disease	2 (8.70%)	13 (20.00%)	0.215
Tumor history	3 (13.04%)	11 (16.92%)	0.662
Peripheral vascular disease	0 (0.0%)	2 (3.08%)	0.395
Atrial fibrillation/flutter	2 (8.70%)	8 (12.31%)	0.639
Diabetes	3 (13.04%)	18 (27.69%)	0.157
Surgery history	6 (26.08%)	29 (44.62%)	0.119
Smoke	5 (21.74%)	17 (26.15%)	0.674
Mechanical support			
CRRT implantation	9 (39.14%)	51 (78.46%)	**0.001***
ECMO model			
VA Model	11 (47.83%)	32 (49.23%)	0.908
VV Model	12 (52.17%)	33 (50.77%)	
ECMO indication			
Severe heart failure	10 (43.48%)	27 (41.54%)	0.871
Severe pneumonia	13 (56.52%)	39 (60.00%)	0.771
Severe myocarditis	3 (13.04%)	1 (1.54%)	**0.023***
MI	0 (0.0%)	4 (6.15%)	0.223
Interstitial lung disease	0 (0.0%)	2 (3.08%)	0.395
Mechanical ventilation	17 (73.91%)	52 (80.0%)	0.542

Values are presented as the mean ± standard error, median (interquartile range), or number of patients (%).
ALB, blood albumin; ALT, blood alanine transaminase; AST, blood aspartate transaminase; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; Hb, Hemoglobin; MI, myocardial infarction; VA ECMO, veno-arterial extracorporeal membrane oxygenation; VV ECMO, veno-venous extracorporeal membrane oxygenation; WBC, white blood cell.
*Statistically significant. Bold values in the table indicate $p < 0.05$.

Table 2. ROC Curve analysis for predicting mortality in non-surgical patients undergoing ECMO implantation.

	ROC area	95% CI
Age	0.717	0.597–0.837
Hb, g/L	0.358	0.234–0.481
ALB, g/L	0.472	0.334–0.609
BUN, μmol/L	0.600	0.477–0.723
Creatinine, μmol/L	0.620	0.497–0.743
CRRT duration, day	0.850	0.777–0.924

ECMO, extracorporeal membrane oxygenation; ALB, blood albumin; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; Hb, Hemoglobin; ROC, receiver operating characteristic.

OR = 7.646, 95% CI = 2.308–25.330, $p=0.001$; model 2: OR = 8.682, 95% CI = 2.443–30.855, $p=0.001$; model 3: OR = 5.995, 95% CI = 1.624–22.129, $p=0.007$; model 4: OR = 4.931, 95% CI = 1.216–19.991, $p=0.025$. For CRRT duration, model 1: OR = 2.218, 95% CI = 1.511–3.267, $p<0.001$; model 2: OR = 2.386, 95% CI = 1.553–3.666, $p=0.000$; model 3: OR = 2.193, 95% CI = 1.406–3.420, $p=0.001$; model 4: OR = 2.054, 95% CI = 1.299–3.246, $p=0.002$) (Table 4). Age was also significantly associated with hospital mortality in all models including whether CRRT implantation or CRRT duration (in the models including CRRT implantation, model 1: OR = 1.064, 95% CI = 1.024–1.107, $p=0.002$; model 2: OR = 1.072, 95% CI = 1.027–1.119, $p=0.001$; model 3: OR = 1.080, 95% CI = 1.029–1.134, $p=0.002$; model 4: OR = 1.100, 95% CI = 1.037–1.164, $p=0.001$; in the models including CRRT duration, model 1: OR = 1.077, 95% CI = 1.028–1.129, $p=0.002$; model 2: OR = 1.090, 95% CI = 1.034–1.150, $p=0.001$; model 3: OR = 1.010,

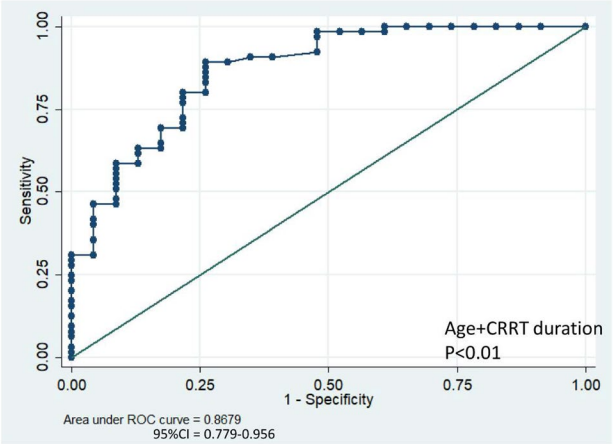

Figure 2. ROC curves for CRRT during and age in-hospital mortality of the non-surgical patients undergoing ECMO implantation. ECMO: extracorporeal membrane oxygenation; CRRT: continuous renal replacement therapy; ROC: receiver operating characteristic.

Table 3. Univariate analysis of risk factors for mortality in non-surgical patients undergoing ECMO implantation.

Variables	OR (95% CI)	*p* value
CRRT implantation	5.667 (2.033–15.796)	**0.001***
CRRT duration, day	1.912 (1.424–2.567)	**0.000***
Age	1.050 (1.016–1.084)	**0.003***
Gender	1.679 (0.618–4.555)	0.309
NYHA	0.901 (0.655–1.240)	0.523
ALB, g/L	0.984 (0.919–1.054)	0.652
Hb, g/L	0.982 (0.965–0.999)	**0.041***
BUN, μmol/L	1.098 (0.986–1.222)	0.089
Creatinine, μmol/L	1.009 (1.000–1.018)	**0.042***
Severe myocarditis	0.104 (0.010–1.058)	0.056
Monocytes, 10^9/L	3.409 (0.847–13.725)	0.084

*Statistically significant. Bold values in the table indicate $p < 0.05$.
ECMO, extracorporeal membrane oxygenation; ALB, blood albumin; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; Hb, Hemoglobin; NYHA, New York Heart Association; OR, odds ratio; CI, confidence interval.

Table 4. Multivariable analysis of CRRT implantation and CRRT duration for mortality in non-surgical patients undergoing ECMO implantation.

	CRRT implantation		CRRT duration	
Variables	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Model 1	7.646 (2.308–25.330)	**0.001***	2.218 (1.511–3.267)	**0.000***
Model 2	8.682 (2.443–30.855)	**0.001***	2.386 (1.553–3.666)	**0.000***
Model 3	5.995 (1.624–22.129)	**0.007***	2.193 (1.406–3.420)	**0.001***
Model 4	4.931 (1.216–19.991)	**0.025***	2.054 (1.299–3.246)	**0.002***

Model 1 adjusted for age and gender.
Model 2 adjusted for age, gender, NYHA and ALB.
Model 3 adjusted for age, gender, NYHA, ALB, Hb, creatinine and BUN.
Model 4 adjusted for age, gender, NYHA, ALB, Hb, creatinine, BUN, severe myocarditis and monocytes.
*Statistically significant. Bold values in the table indicate $p < 0.05$.
ECMO, extracorporeal membrane oxygenation; ALB, blood albumin; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; Hb, Hemoglobin; NYHA, New York Heart Association; OR, odds ratio; CI, confidence interval.

95% CI = 1.034–1.161, $p = 0.002$; model 4: OR = 1.113, 95% CI = 1.041–1.190, $p = 0.002$) (Table 5). Furthermore, the relationship between age and the risk of hospital mortality was analyzed using RCS. The result showed that a significant association was observed between older age with the higher risk of hospital mortality (Figure 3, p = 0.015, P-non-linear = 0.423).

Clinical application of the prediction model combining CRRT implantation in non-surgical patients undergoing ECMO implantation

Since CRRT implantation/CRRT duration, age, NYHA functional classes, serum ALB concentration, serum creatinine level, and BUN level significantly affected the prognosis of ECMO patients, we evaluated the model by combining these factors using a calibration plot and DCA in our study. A nomogram was created to predict outcomes based on the model, including whether CRRT implantation or CRRT duration, and a score was assigned to each variable. The total score was then calculated by summing all of the individual scores to improve the model's use in clinical practice (Figures 4A, 5A). The models' calibration plots demonstrated a strong correlation between the observed and anticipated probabilities (Figures 4B, 5B). The clinical value of the models was also evaluated using DCA, and the outcomes showed the models' strong clinical utility (Figures 4C, 5C).

Correlation of CRRT duration with clinical variables in non-surgical patients undergoing ECMO implantation

Non-surgical patients undergoing ECMO implantation exhibited a correlation between CRRT duration and clinical factors, as seen in Table 6. The duration of the CRRT was shown to be favorably correlated with serum creatinine level (Spearman's Rho = 0.289, $p = 0.006$) and BUN level (Spearman's Rho = 0.333, $p = 0.002$) but negatively correlated with Hb concentration (Spearman's Rho = −0.341, $p = 0.001$).

Discussion

In the present study, the diagnostic performance of age, BUN level, serum creatinine level, and CRRT duration for hospital mortality of non-surgical patients undergoing ECMO implantation was satisfactory, and the predictive model combining the CRRT duration and age displayed significantly improved accuracy. Although hospital mortality was linked to Hb concentration, serum creatinine level, CRRT, CRRT duration, and age in non-surgical patients undergoing ECMO implantation, only CRRT, CRRT duration, and age were identified as independent risk factors. For clinical applications, the models combining CRRT, CRRT duration, and age were evaluated using a calibration plot and DCA. CRRT duration was negatively associated with Hb concentration and positively associated with BUN level as well as serum creatinine level in non-surgical patients undergoing ECMO implantation.

The use of ECMO in the operating room, intensive care unit, emergency department, interhospital transport, and cardiac resuscitation has increased dramatically during the past decade [3]. AKI, thrombosis, infection, and bleeding were among the common adverse effects of ECMO treatment, despite recent improvements in patient survival [20]. AKI, as

Table 5. Multivariable analysis of clinical variables for mortality in non-surgical patients undergoing ECMO implantation.

Variables		CRRT implantation		CRRT duration	
		OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age, year	Model 1	1.064 (1.024–1.107)	**0.002**	1.077 (1.028–1.129)	**0.002***
	Model 2	1.072 (1.027–1.119)	**0.001**	1.090 (1.034–1.150)	**0.001***
	Model 3	1.080 (1.029–1.134)	**0.002**	1.010 (1.034–1.161)	**0.002***
	Model 4	1.100 (1.037–1.164)	**0.001**	1.113 (1.041–1.190)	**0.002***
ALB, g/L	Model 2	0.941 (0.864–1.026)	0.168	0.927 (0.842–1.020)	0.122
	Model 3	0.962 (0.876–1.056)	0.417	0.947 (0.851–1.055)	0.323
	Model 4	0.934 (0.848–1.030)	0.170	0.930 (0.836–1.034)	0.180
Hb, g/L	Model 3	0.974 (0.944–1.005)	0.104	0.975 (0.942–1.010)	0.164
	Model 4	0.970 (0.937–1.005)	0.091	0.969 (0.931–1.008)	0.118
Creatinine,	Model 3	1.006 (0.990–1.023)	0.451	1.007 (0.988–1.027)	0.451
μmol/L	Model 4	1.001 (0.984–1.018)	0.938	1.002 (0.983–1.022)	0.846
BUN, μmol/L	Model 3	1.006 (0.831–1.218)	0.953	0.971 (0.786–1.199)	0.783
	Model 4	1.061 (0.868–1.297)	0.561	1.026 (0.820–1.284)	0.821

Model 1 including CRRT implantation or CRRT duration, age and gender.
Model 2 including CRRT implantation or CRRT duration, age, gender, NYHA and ALB.
Model 3 including CRRT implantation or CRRT duration, age, gender, NYHA, ALB, Hb, creatinine and BUN.
Model 4 including CRRT implantation or CRRT duration, age, gender, NYHA, ALB, Hb, creatinine, BUN, severe myocarditis and monocytes.
*Statistically significant. Bold values in the table indicate $p < 0.05$.
ECMO, extracorporeal membrane oxygenation; ALB, blood albumin; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; Hb, Hemoglobin; NYHA, New York Heart Association; OR, odds ratio; CI, confidence interval.

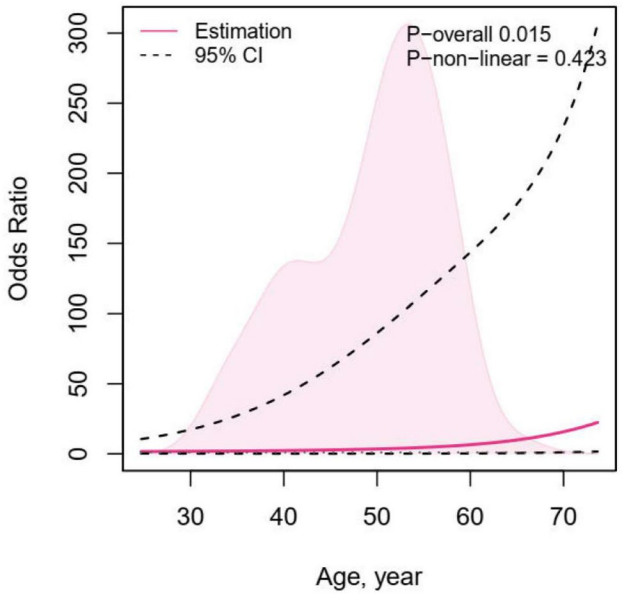

Figure 3. The restricted cubic spline analysis on the association between age and hospital mortality.

a frequent complication of ECMO treatment, was significantly worthy of in-depth understanding, because research on its influencing factors and RRT could clinically prevent and manage this high-risk group, thereby reducing mortality [21]. The underlying mechanisms of AKI in patients receiving ECMO therapy were complicated. The patient's physical condition and major illness might be one of the most important factors that can lead to AKI. Before initiating ECMO, hemodynamic instability, high intrathoracic pressure, systemic inflammatory/immune-mediated effects, low cardiac output, severe hypoxemia, neurohormonal imbalance, hypercapnia, and exposure to nephrotoxic drugs could lead to AKI [22]. Furthermore, AKI can be caused by cardiac dysfunction, elevated intra-abdominal pressure, renal congestion, and other critical illness-related consequences such as limb ischemia, hemorrhage, infection, and coagulopathy, which are all present in patients with heart failure [22, 23]. Prevention and treatment of fluid overload, in addition to AKI, were the primary causes of RRT starting during ECMO [24]. Patients with hemodynamic instability were a good candidate for CRRT, which also provides more accurate fluid and electrolyte control [25]. Numerous studies have reported elevated mortality rates among ECMO patients undergoing CRRT; however, the extent to which these rates directly contribute to mortality or just reflect the severity of the disease remains unknown [26, 27]. Our previous and present investigations found that 73.3% (77/105) of surgical patients receiving ECMO and 68.1% (60/88) of non-surgical patients receiving ECMO needed CRRT (Table 1) [15]. Additionally, the research demonstrated that among surgical patients undergoing ECMO and CRRT, older age, absence of valvular heart disease, and lower blood ALB concentration were independent risk factors for death [15]. However, in the present investigation, it was discovered that among non-surgical patients undergoing ECMO implantation, the combination of CRRT implantation, CRRT duration, and older age constituted an independent risk factor for hospital mortality (Tables 4 and 5), regardless of the ECMO models (Supplement Table 1). This combination also contributed to a significantly improved accuracy for hospital mortality in the predictive model (Table 2, Figure 2). This difference in results may be due to differences in patient populations. Given that the majority of patients in our prior investigation underwent cardiac surgery, we postulated that patients with valvular disease would exhibit superior postoperative recovery and an improved underlying condition in comparison to those undergoing alternative cardiac procedures like aortic surgery, heart transplantation, and coronary artery bypass surgery. Although in this study, most patients were treated medically, thus, in the absence of surgical factors, the importance of AKI and age was even more prominent. In each of our investigations, older age was a consistent risk factor for hospital mortality (Figure 3, Table 5), which was consistent with existing reported results, that older age

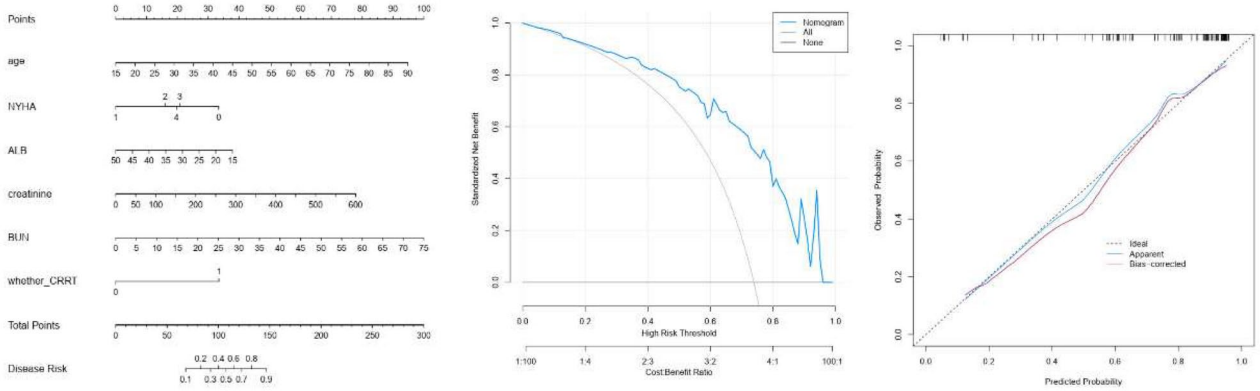

Figure 4. Nomogram, calibration plot, and DCA of the model consisting of whether CRRT, age, NYHA functional classes, serum ALB concentration, serum creatinine level, and BUN level in the prediction of hospital mortality of the non-surgical patients undergoing ECMO implantation. (A) A nomogram for the model was developed. (B) Calibration curves of the model. (C) DCA was performed to validate the clinical applicability of the prediction model. ECMO: extracorporeal membrane oxygenation; CRRT: continuous renal replacement therapy; DCA: Decision curve analysis; ALB: albumin; NYHA: New York Heart Association; BUN: blood urea nitrogen

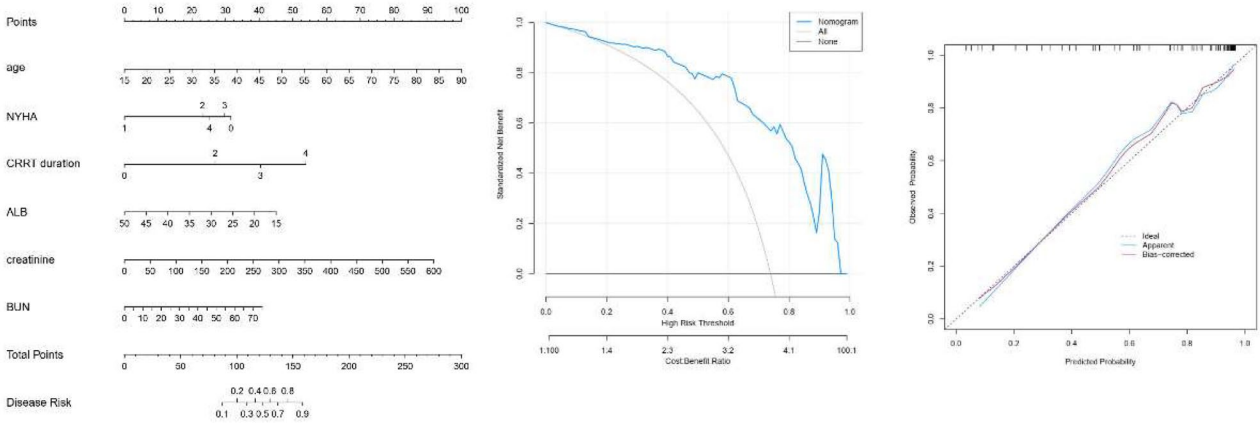

Figure 5. Nomogram, calibration plot, and DCA of the model consisting of CRRT duration, age, NYHA functional classes, serum ALB concentration, serum creatinine level, and BUN level in the prediction of hospital mortality of the non-surgical patients undergoing ECMO implantation. (A) A nomogram for the model was developed. (B) Calibration curves of the model. (C) DCA was performed to validate the clinical applicability of the prediction model. ECMO: extracorporeal membrane oxygenation; CRRT: continuous renal replacement therapy; DCA: Decision curve analysis; ALB: albumin; NYHA: New York Heart Association; BUN: blood urea nitrogen

Table 6. Correlation of CRRT duration with clinical variables in non-surgical patients undergoing ECMO implantation.

Variables	Spearman's Rho	*p* value
Age	0.055	0.611
NYHA	−0.122	0.256
ALB, g/L	0.040	0.713
Hb, g/L	−0.341	**0.001***
BUN, μmol/L	0.333	**0.002***
Creatinine, μmol/L	0.289	**0.006***
Monocytes, 10^9/L	0.139	01985
Neutrophils, 10^9/L	0.188	0.078
WBC, 10^9/L	0.193	0.071

*Statistically significant. Bold values in the table indicate $p < 0.05$.
ECMO, extracorporeal membrane oxygenation; ALB, blood albumin; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; Hb, Hemoglobin; NYHA, New York Heart Association; WBC, white blood cell.

was one of the reported risk factors for AKI during ECMO [28]. Additionally, it was previously observed that surgical patients undergoing ECMO and CRRT had a reduced concentration of serum ALB. This finding established CRRT as an independent risk factor. In contrast, hospital mortality was associated with Hb concentration and serum creatinine level, but not serum ALB concentration, in non-surgical patients undergoing ECMO and CRRT (Table 3). We speculated that this may be related to the severity of AKI in the non-surgical patients receiving ECMO and CRRT (Table 6). It has been observed that high plasma free Hb concentration, serum creatinine concentration, red blood cell distribution width > 14.1%, and intraoperative transfusion were shown to be related to an elevated risk of severe AKI [28, 29]. Thus, different disease backgrounds and treatment methods may lead to different prognoses for patients who use ECMO and CRRT in combination. The establishment of prognostic models for different groups of people can greatly help clinicians determine the prognosis of patients.

Nomogram is a prognostic tool that has been extensively utilized for the prognosis of tumors and heart diseases. It integrates possible risk variables to anticipate clinical outcomes [30, 31]. Recently, the nomogram was used to develop the potential model-based clinical characteristics for ECMO

patients. Wang et al. [32] used the nomogram, which included serum creatinine, uric acid, and lactate levels at the 2-h time point during ECMO, to create an AKI risk prediction model for patients. Cui et al. [33] created a 30-day survival prediction model for adult ECMO patients based on factors such as sex, DIC, and APACHE II scores, as well as the average daily norepinephrine dosage. An early warning system was developed by Li et al. [34] for clinical practice, which integrated multiple variables such as length of mechanical ventilation, ECMO environment in the intensive care unit, white blood cell count abnormalities, and older age to identify patients receiving VA-ECMO treatment after heart surgery who had high-risk nosocomial infections. Meropenem in patients undergoing VA-ECMO was characterized by a population pharmacokinetic model generated by a prospective cohort trial; without CRRT, a higher dose was necessary [35]. In the present study, we also used a nomogram to predict outcomes based on the model combining CRRT/CRRT duration, age, NYHA functional classes, serum ALB concentration, serum creatinine concentration, and BUN level (Figures 4A, 5A). The consistency between the predicted probability and observed probability and clinical utility of the models were good (Figures 4B, C, 5B, C). However, most models were constructed using retrospective research and failed to account for new biomarkers, such as neutrophil gelatinase-associated lipocalin, due to the absence of blood sample detection. To build a more accurate early prognostic model for patients undergoing ECMO treatment, therefore, a comprehensive, meticulously planned study is required.

Limitations

There are several limitations to this study. First, since this was retrospective research, confounding variables might have an impact on the findings. Some important information was lacking, such as acute brain injury, hemolysis, and gastrointestinal hemorrhage. Second, there were no dynamic, ongoing observational analysis data on indicators in our study. Third, the sample size was still limited, even though our study was a two-center investigation. Larger sample sizes and multicenter research can be performed in the future.

Conclusions

In summary, we found a significant association and satisfactory diagnostic performance of age, BUN level, serum creatinine concentration, and CRRT/CRRT duration for hospital mortality of non-surgical patients undergoing ECMO implantation. The predictive model combining the CRRT duration and age displayed significantly improved accuracy. CRRT implantation, CRRT duration, and older age were independent risk factors. CRRT duration was negatively associated with Hb concentration and positively associated with BUN level as well as serum creatinine concentration in non-surgical patients undergoing ECMO implantation. For clinical application, the nomogram models combining CRRT implantation, CRRT duration, and age were evaluated using a calibration plot and DCA.

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Authors' contributions

Jian Hou, Suiqing Huang, Dayu Wang and Jianhao Li conceptualized the study, analyzed the data, wrote and finalized manuscript. Cuiping Wang, Dayu Wang and Ruibin Wei provided funding. Cuiping Wang, Jianhao Li, Zhen Liu, Junteng Zheng provided support in data collection. All authors read and approved the final version of manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

Ethical standards

The study was reviewed and approved by the Institutional Review Board of The Affiliated Panyu Central Hospital of Guangzhou Medical University (approval number: PYRC-2023-378).

Informed consent

All subjects involved in the research project provided their written informed consent.

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