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Respiratory compliance related to prognostic of lung transplant patients with veno-venous extracorporeal membrane oxygenation support

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Veno-venous extracorporeal membrane oxygenation (VV-ECMO) plays an important role in the perioperative care of critically ill lung transplant patients. However, the factors predicting prognosis are unclear. This study assessed the association between static respiratory compliance (Crs) and outcomes of lung transplant patients receiving VV-ECMO in terms of 90-day mortality. Data were retrospectively collected for patients that underwent lung transplantation with VV-ECMO support during 2022–2023. Patients were divided into two groups according to the early postoperative Crs: lower Crs (Crs < 25 ml/cmH_2O) and higher Crs (Crs ≥ 25 ml/cmH_2O). Differences in patient characteristics and prognosis were then compared between the two groups. Receiver operating characteristic (ROC) curve analysis was used to evaluate the value of Crs for predicting 90-day mortality and univariate Cox proportional hazard model analysis was performed to estimate risk of Crs. Data were available for a total of 85 patients, including 50 (58.8%) patients in the higher Crs group and 35 (41.2%) patients in the lower Crs group. A lower Crs was significantly associated with a longer postoperative ECMO duration (hours, 42 vs. 24; *P* = 0.022), longer postoperative ventilator time (days, 3.7 vs. 2.0; *P* = 0.003), higher application of continuous renal replacement therapy (CRRT) (20.0% vs. 6.0%; *P* = 0.049), higher incidence of pneumonia (42.9% vs. 20.0%; *P* = 0.023), and higher 90-day mortality (22.9% vs. 6.0%; *P* = 0.023). The area under the curve of Crs for predicting 90-day mortality was 0.661 (*P* = 0.034). A higher Crs was a protective factor (hazard ratio = 0.925 [0.870–0.984)] *P* = 0.014). For lung transplant patients receiving VV-ECMO support, Crs < 25 ml/cmH_2O is associated with more complications and higher 90-day mortality. As Crs is easily obtained at the bedside, it may be useful for predicting prognosis and guiding patient management.

Keywords Respiratory compliance, Extracorporeal membrane oxygenation, Lung transplant, Prognostic: intensive care unit

Lung transplantation is an effective procedure for benign end-stage lung disease. However, patients with poor underlying condition are prone to insufficient cardiopulmonary function to maintain the necessary oxygenation and circulatory stability during surgery. Thus, veno-venous extracorporeal membrane oxygenation (VV-ECMO) is a reliable and effective form of support that can expand the patient population suitable for lung transplantation and support the transition to the perioperative period[1]. According to the International Society of Heart and Lung Transplantation, ECMO is performed in 29% of all lung transplants; however, ECMO does not reduce the risk of death[2]. Thus, predictors are needed to indicate prognosis at an early stage to guide clinical practice. Static respiratory compliance (Crs) is a measure that can be easily determined at the bedside. Prior studies have reported a significant correlation between Crs and prognosis in patients with acute respiratory distress syndrome (ARDS) undergoing VV-ECMO[3]. Primary graft dysfunction (PGD) occurs 72 h after lung transplantation and has many clinical features in common with ARDS[4]. Notably, both PGD and ARDS can affect lung compliance.

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In this study, we aimed to investigate the relationship between Crs and the prognosis of lung transplant patients with VV-ECMO.

Methods

Study design

This retrospective study investigated patients who underwent lung transplantation with VV-ECMO between 2022 and 2023 at the Affiliated Wuxi People's Hospital of Nanjing Medical University. The inclusion criteria were (1) age > 18 years and (2) underwent lung transplantation with VV-ECMO. The exclusion criteria were (1) lung retransplantation; (2) incomplete Crs records. Figure 1 shows the flow diagram of patients in this study.

This retrospective study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Commission of the Affiliated Wuxi People's Hospital of Nanjing Medical University (No. KY24059). Due to the retrospective nature of this study, the need for informed consent was waived by the Committee.

ECMO strategy

The pre-ECMO evaluation is performed by both surgeons and anesthesiologists according to the Extracorporeal Life Support Organization (ELSO) guidelines[5]. In cases requiring one-lung ventilation, if the hemodynamics were stable and the percutaneous oxygen saturation (SpO_2) was maintained > 90%, ECMO treatment was not considered; if the hemodynamics were stable and SpO_2 was continuously < 90%, VV-ECMO support was used. VV-ECMO support was established intraoperatively in all cases that met the indications for ECMO.

Peripheral cannulation was the preferred method of support with VV-ECMO. The most common cannulation sites were femoral-internal jugular, with the tip of a femoral drainage cannula at the inferior vena cava-right atrium junction and an internal jugular return cannula with the top either at the superior vena cava-right atrium junction or the right atrium. ECMO management and weaning were performed following the ELSO guidelines[6].

Measurement of Crs

Within 2 h of admission to the ICU, patients were in a supine position without spontaneous respiration; otherwise, safe doses of sedative, analgesic, and muscle relaxants were used to prevent spontaneous breathing. Patients received volume-controlled ventilation delivered using a square waveform flow. The initial parameter settings were: tidal volume (VT) at 6 mL/kg of predicted body weight (PBW), PBW was calculated as 50 + 0.91 × (height [cm] – 152.4) for men and 45.5 + 0.91× (height [cm] – 152.4) for women, positive end-expiratory

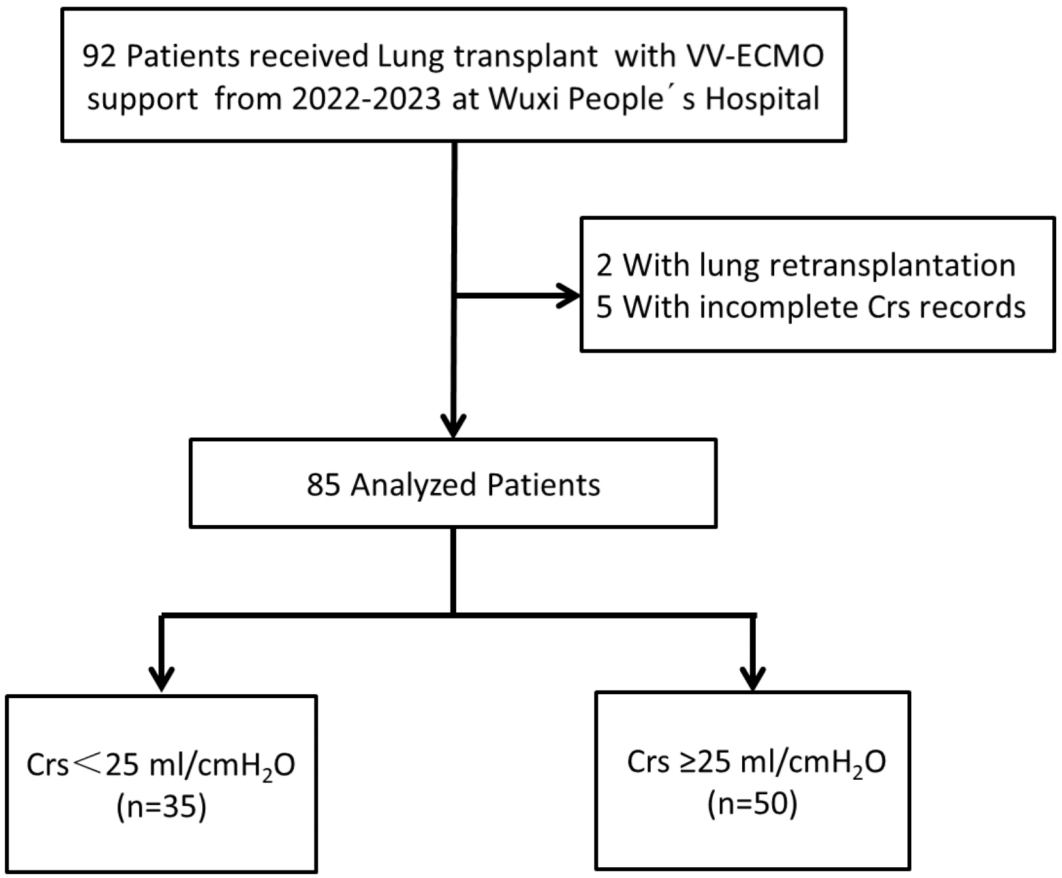

Fig. 1. The flow diagram.

pressure (PEEP) at 5 cmH_2O, respiratory rate (RR) at 12/min. Next, we recorded the plateau pressure (Pplat); Crs was calculated as VT/(Pplat-PEEP). The ventilator parameters during the non-measurement period were set by clinicians according to the lung-protective ventilation strategy and each patient's condition[7].

PGD definition

PGD was diagnosed according to the latest recommendation of the ISHLT working group[4]. Patients were graded on the basis of the ratio of the partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) (P/F ratio) and chest radiographs. The PGD grade at index ICU admission (0 h), 24 h, 48 h, and 72 h was assessed. Patients with a chest x-ray indicating pulmonary infiltrates and P/F ratio < 200 were defined as PGD3, while patients on ECMO were defined as PGD3 with any P/F ratio.

Data collection

The following data were collected from the medical records of lung transplant patients: age, body mass index (BMI), gender, primary disease, chronic disease, preoperative cardiopulmonary function and laboratory parameters, Acute Physiology and Chronic Health Evaluation II (APACHEII) score, Sequential Organ Failure Assessment (SOFA) score, cold ischemia time, surgical condition, ventilator parameters and ECMO settings, lac, P/F, and $PaCO_2$ within 2 h after surgery. The primary outcome was 90-day survival after lung transplantation. The secondary outcomes were postoperative ECMO time, postoperative ventilator time, ICU stay, hospital stay, PGD3, continuous renal replacement therapy (CRRT), and pneumonia.

Statistical analysis

Normally distributed continuous variables are presented as the mean ± standard deviations and Student's t test was used for group comparisons. Non-normally distributed continuous variables are presented as the median (interquartile range) and the Mann-Whitney U test was used for group comparisons. Categorical variables are expressed as numbers (percentages) and analyzed using the Chi-square test or Fisher's exact test. Receiver operating characteristic (ROC) curve analysis was used to calculate the area under the curve (AUC) values to assess the predictive ability of Crs for 90-day mortality. Cutoff points were calculated by obtaining the best Youden index (sensitivity + specificity − 1). The Kaplan-Meier method was used to plot the cumulative curves of ECMO and mechanical ventilation times between the two groups. For the survival analysis, the effect of a lower Crs was assessed using the log-rank test. Univariate Cox regression was used to examine the correlation between Crs and 90-day mortality. Statistical analysis was performed using SPSS 25.0, GraphPad Prism 6.0, and R version 4.3.0 with the KMsurv, survival, and survminer packages. Results with a two-tailed P value < 0.05 were considered to be statistically significant.

Results

Clinical characteristics

Data were available for a total of 85 lung transplant patients who received VV-ECMO. In the ROC analysis, the AUC of Crs for predicting 90-day mortality was 0.661 ($P = 0.034$). The best Youden index was obtained when Crs = 25 ml/cmH_2O. Based on Crs values, patients were assigned to the higher Crs group ($n = 50$, 58.8%) or lower Crs group ($n = 35$, 41.2%). As shown in Table 1, there were no significant group differences in the baseline data ($P > 0.05$)。.

Postoperative outcomes

Compared to the higher Crs group, the lower Crs group had a higher driving pressure (14 ± 1.2 vs. 12 ± 0.8 cmH_2O, $P<0.001$) and Pplat (20 ± 1.3 vs. 18 ± 1.1 cmH_2O, $P = 0.015$). There were no significant group differences in terms of ventilator parameter settings or VV-ECMO flow rates at the initial postoperative procedure (Table 2). Figure 2A shows the change in P/F over time. The P/F at 24 h was higher than that at 0 h, while the 48 h and 72 h P/F values tended to be stable. Compared to the lower Crs group, the higher Crs group had a higher 0 h P/F (274 ± 39.3 vs. 197 ± 33.1, $P = 0.006$) and 24 h P/F (348 ± 28.2 vs. 259 ± 23.9, $P<0.001$). Moreover, the higher Crs group had a lower 0 h $PaCO_2$ (32.5 ± 1.9 vs. 38.2 ± 3.6 mmHg, $P = 0.003$) and 24 h $PaCO_2$ (35.9 ± 2.1 vs. 39.7 ± 2.6 mmHg, $P = 0.020$) compared to the lower Crs group, as shown in Fig. 2B.

For all patients, the 24 h, 48 h, and 72 h PGD proportions were 51.8%, 35.3%, and 31.8%, respectively. The incidence of grade 3 PGD at 48 h was significantly lower than that at 24 h ($P = 0.030$); however, there was no significant difference between 72 h and 48 h (Fig. 3). The lower Crs group tended to include more patients with 24 h PGD3 ($P = 0.087$). Compared with the higher Crs group, the lower Crs group had increased pneumonia (42.9% vs. 20.0%, $P = 0.023$), CRRT (20.0% vs. 6.0%, $P = 0.049$), postoperative ECMO time (42 h vs. 24 h, $P = 0.022$), and postoperative MV time (3.7 days vs. 2.0 days, $P = 0.003$) and decreased 90-day survival (77.1% vs. 94.0%, $P = 0.023$).

The cumulative curve of ECMO weaning and MV showed a significant difference between the two groups (Fig. 4). The difference in K-M survival curves between the lower and higher Crs groups was statistically significant ($P = 0.023$, Fig. 5).

The effect of Crs remained significant in the univariate Cox regression model [HR 0.925 (0.870–0.984), $P = 0.014$], indicating that higher Crs was a protective factor for 90-day mortality.

Discussion

VV-ECMO during lung transplantation is considered a safe and effective form of life support that is increasingly used[8]. Critically ill patients often require ECMO support due to preoperative respiratory failure, pulmonary hypertension, or cardiac dysfunction during lung transplantation[9]. The V-V mode offers a main

Variables	Higher Crs ($n=50$)	Lower Crs ($n=35$)	*P* value
Age (years), mean (SD)	52 ± 3.0	53 ± 4.1	0.806
BMI, mean (SD)	21.2 ± 1.0	21.6 ± 1.5	0.625
Male sex, n (%)	42(84.0)	23(65.7)	0.090
Primary disease, n (%)			0.944
IPF	33(66.0)	23(65.7)	
Silicosis	8(16.0)	7(20.0)	
COPD	4(8.0)	2(5.7)	
Others	5(10.0)	3(8.6)	
Hypertension, n (%)	4(8.0)	6(17.1)	0.198
Diabetes, n (%)	11(22.0)	7(20.0)	0.824
Coronary atherosclerosis, n (%)	8(16.0)	4(11.4)	0.551
MPAP(mmHg), mean (SD)	37.2 ± 11.2	36.7 ± 10.5	0.817
LVEF (%), mean (SD)	61.7 ± 3.6	62.5 ± 3.3	0.625
APACHEIIscore (points), mean (SD)	21.2 ± 2.36	20.8 ± 3.01	0.593
SOFA (points), mean (SD)	12.98 ± 2.13	12.96 ± 2.14	0.881
FEV1 (L), mean (SD)	1.08 ± 0.15	0.94 ± 0.11	0.180
FVC (L), mean (SD)	1.60 ± 0.14	1.48 ± 0.13	0.421
6MWT (m), mean (SD)	224 ± 22.3	224 ± 27.3	0.959
Hb (g/L), mean (SD)	129 ± 5.1	128 ± 6.6	0.658
ALB (g/L), mean (SD)	36 ± 1.2	37 ± 1.4	0.635
AST (U/L), mean (SD)	26.8 ± 3.9	28.2 ± 5.0	0.649
Serum creatinine (umol/L), mean (SD)	59.4 ± 3.5	58.7 ± 5.4	0.836
Cold-ischemia time (h), mean (SD)	7.62 ± 2.01	7.71 ± 1.99	0.711
Operation time (min), mean (SD)	355.2 ± 88.3	349.5 ± 92.6	0.467
Surgical type, n (%)			0.157
SLT	18(36.0)	18(51.4)	
BLT	32(64.0)	17(48.6)	

Table 1. Cohort characteristics. Abbreviations: BMI, body mass index ; IPF, idiopathic pulmonary fibrosis; COPD, Chronic obstructive pulmonary disease; FEV1, Forced Expiratory Volume in the first second; MPAP, mean pulmonary arterial pressure; LVEF, left ventricular ejection fraction; APACHE, acutephysiology and chronic health evaluation; SOFA, sepsis related organ failure assessment; FVC, forced vital capacity; 6MWT,6 min walk test; Hb, hemoglobin ; ALB, albumin; AST, Aspartate transaminase ; ECMO, extracorporeal membrane oxygenation; SLT, single lung transplantation; BLT, bilateral lung transplantation.

pulmonary support effect[10]. ECLS has reported survival rates of 56–100% for ECMO support as a bridge to lung transplantation[11–13]. The use of ECMO for intraoperative support management varies considerably across centers across the world. Its use in the perioperative setting of lung transplantation is associated with favorable outcomes[14]. Christian et al. reported that ECMO as a bridge to lung transplantation is associated with higher perioperative mortality, but acceptable mid-term survival, in carefully selected patients[15]. In another larger study, Ius et al. found no differences in long-term complications or outcomes in ECMO recipients[16]. Sef et al. reported a similar 30-day mortality between bridge to transplantation and non-bridge to transplantation patients (4.6% vs. 6.6%, $p=0.083$) despite a higher incidence of early postoperative complications (e.g., need for ECMO, delayed chest closure, and acute kidney injury)[17]. In their study, the 90-day survival rate of patients treated with VV-ECMO lung transplantation was 87%. Takahashi et al. retrospectively analyzed clinical data of 204 patients with PGD3 after lung transplantation from 2010 to 2020, finding no significant survival difference between patients with and without perioperative ECMO. Thus, the authors concluded that perioperative ECMO did not increase the risk of mortality[18]. Zhao et al. reported that the use of intraoperative ECMO support reduced ischemia-reperfusion injury due to the avoidance of hyperperfusion in double sequential or lobar lung transplantation, improved surgical exposure and reduced operative time[19]. Notably, the donor lung is prone to the development of pulmonary edema by ischemia reperfusion injury. Prolonging the use of VV-ECMO thus enables "lung rest" and restoration of lung function. ECMO respiratory support reduces lung injury by ultraprotective lung ventilation strategies and the potential harm of high FiO_2 to lungs in PGD3 patients. During the postoperative period, ECMO may also affect right ventricular afterload by reducing pulmonary resistance. ECMO may reduce the pulmonary edema on lung injury to lower the PGD grade. A previous controlled study at our center found that delayed VV-ECMO weaning was associated with lower complications and shorter hospital stay[20]. However, delayed ECMO weaning will impact the incidence of PGD3 at 0 h. Thus, further research is needed to analyze ECMO strategies in lung transplantation patients.

The main findings of the present study are that, using Crs = 25 ml/cmH_2O as the cut-off point, the lower Crs group had a longer ECMO time, longer MV time, higher incidence of complications, and decreased 90-

Variables	Higher Crs ($n=50$)	Lower Crs ($n=35$)	*P* value
Pinsp(cmH_2O), mean (SD)	20 ± 0.7	20 ± 0.9	0.955
PEEP(cmH_2O), mean (SD)	6 ± 0.4	6 ± 0.5	0.619
Plat(cmH_2O), mean (SD)	18 ± 1.1	20 ± 1.3	0.015
DP(cmH_2O), mean (SD)	12 ± 0.8	14 ± 1.2	<0.001
RR(/min), mean (SD)	13 ± 0.6	13 ± 0.8	0.925
FiO_2(%), mean (SD)	48 ± 1.7	46 ± 2.1	0.227
ECMO bloodflow(L/min), mean (SD)	1.9 ± 0.2	2.0 ± 0.3	0.322
ECMO rpm (r/min), mean (SD)	2000 ± 300	2100 ± 200	0.415
Lac(umol/L), mean (SD)	3.9 ± 0.6	4.7 ± 1.4	0.280
Crs(ml/cmH_2O), mean (SD)	35.5 ± 2.7	20.2 ± 1.1	<0.001
0hP/F, mean (SD)	274 ± 39.3	197 ± 33.1	0.006
24hP/F, mean (SD)	348 ± 28.2	259 ± 23.9	<0.001
48hP/F, mean (SD)	329 ± 25.1	317 ± 40.4	0.579
72hP/F, mean (SD)	313 ± 28.0	292 ± 29.7	0.303
0h$PaCO_2$(mmHg), mean (SD)	32.5 ± 1.9	38.2 ± 3.6	0.003
24h$PaCO_2$(mmHg), mean (SD)	35.9 ± 2.1	39.7 ± 2.6	0.020
48h$PaCO_2$(mmHg), mean (SD)	42.0 ± 2.2	41.1 ± 1.4	0.601
72h$PaCO_2$(mmHg), mean (SD)	44.7 ± 2.3	43.6 ± 3.0	0.543
24hPGD3, n(%)	22(44.0)	22(62.9)	0.087
48hPGD3, n(%)	16(32.0)	14(40.1)	0.448
72hPGD3, n(%)	13(26.0)	14(40.0)	0.172
Pulmonary infection, n(%)	10(20.0)	15(42.9)	0.023
CRRT, n(%)	3(6.0)	7(20.0)	0.049
Postoperative ECMO time (h), median (IQR)	24(18,50)	42(22,117)	0.022
Postoperative ECMO time ≤ 24 h, n(%)	27(54.0)	16(45.7)	
24 h< Postoperative ECMO time ≤ 48 h, n(%)	10(20.0)	5(14.3)	
48 h< Postoperative ECMO time ≤ 72 h, n(%)	7(14.0)	1(2.9)	
Postoperative ECMO time >72 h, n(%)	6(12.0)	13(37.1)	0.024
Successfully weaning from ECMO, n(%)	49(98.0)	30(85.7)	0.030
Postoperative MV time, (d), median (IQR)	2.0(1.6,3.6)	3.7(1.9,8.9)	0.003
Successfully weaning from MV, n(%)	48(96.0)	28(80.0)	0.018
ICU stay (d), mean (SD)	6 ± 1.9	8 ± 2.0	0.155
Hospital stay(d), mean (SD)	48 ± 10.0	55 ± 18.2	0.512
90-day survival, n(%)	47(94.0)	27(77.1)	0.023

Table 2. Postoperative data and observed outcomes. Abbreviations: Pinsp, peak inspiratory pressure; PEEP, positive end expiratory pressure; Plat, plateau pressure; DP, driving pressure; RR, respiratory rate; Crs, static respiratory compliance; P/F, PaO_2 / FiO_2;PGD, primary graft dysfunction; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; MV, mechanical ventilation; ICU, intensive care unit.

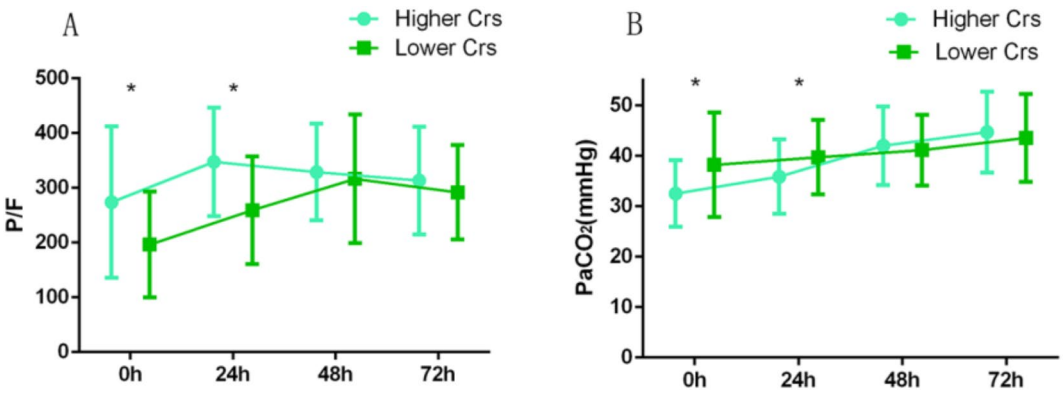

Fig. 2. **A** P/F recorded from 0 h to 72 h in two groups; **B** $PaCO_2$ recorded from 0 h to 72 h in two groups.

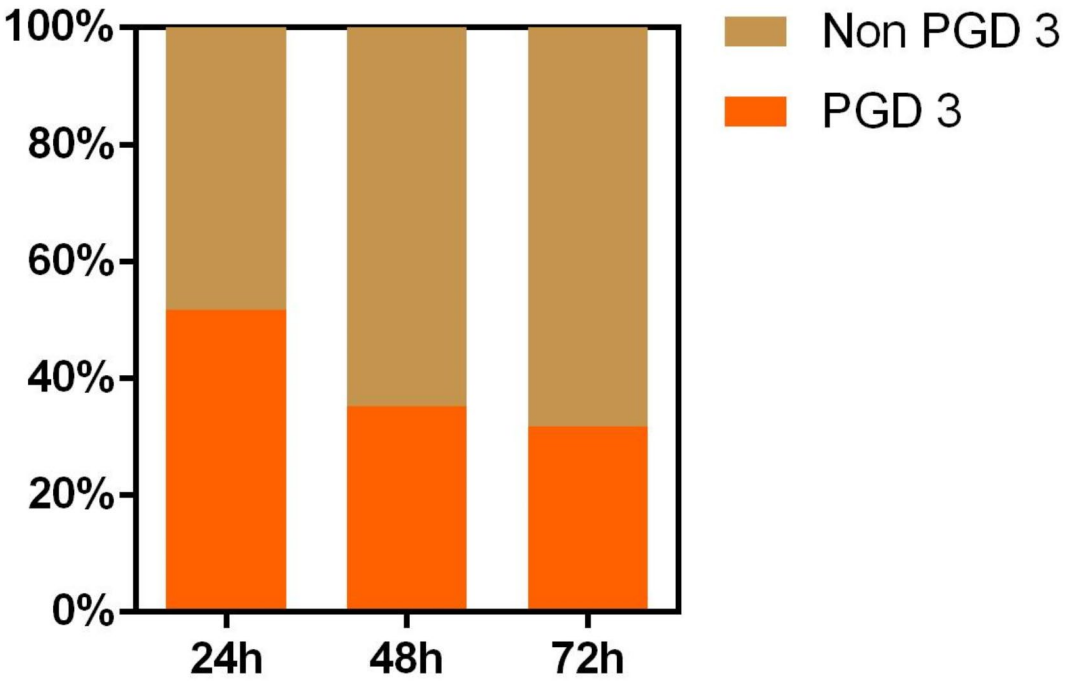

Fig. 3. Proportion of postoperative PGD3 occurrence at 24 h, 48 h and 72 h.

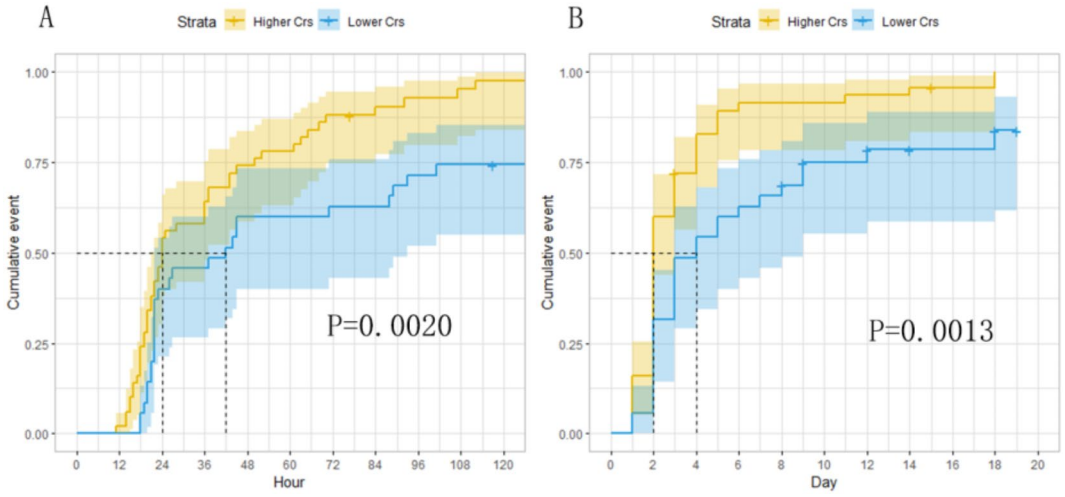

Fig. 4. **A** Postoperative ECMO time curves in two groups ; **B** Ventilator time curves in two groups.

day survival rate, suggesting that Crs might be a prognostic factor. Notably, there are relatively few known prognostic factors for lung transplantation patients with VV-ECMO support[21]. As Crs is easily measured at the bedside, increased clinical attention and management of patients with lower Crs may improve outcomes. In a study of COVID-19 patients with VV-ECMO divided into three groups based on Crs (Crs ≤ 11 cmH_2O, Crs 11–20 cmH_2O, and Crs >20 cmH_2O), Crs was associated with 180-day survival[3]. PGD is an acute lung injury due to ischemia-reperfusion during lung transplantation. The incidence of patients with ECMO was further increased, with 57% of patients developing PGD3 within 72 h after surgery[22]. PGD shares many clinical features and radiographic findings with ARDS, including decreased lung function, increased elastic resistance, and ventilation/flow imbalance[23]. Decreased lung compliance results in low PaO_2 and decreased excretion of CO_2, which delay the weaning of ECMO and MV and increase the incidence of ventilator-associated pneumonia and other complications[24]. Patients with lower Crs are more susceptible to ventilator-associated lung injury, even when low-tidal volume lung protective ventilation is used[25]. Ischemia reperfusion injury is not only a risk factor for PGD, but can also lead to inflammatory damage in other organs, and the kidney, one of the affected organs, is prone to acute kidney injury. In addition, the use of nephrotoxic drugs also increases the incidence of acute kidney injury in lung transplantation. These high-risk factors will require increased use of CRRT[26]. These

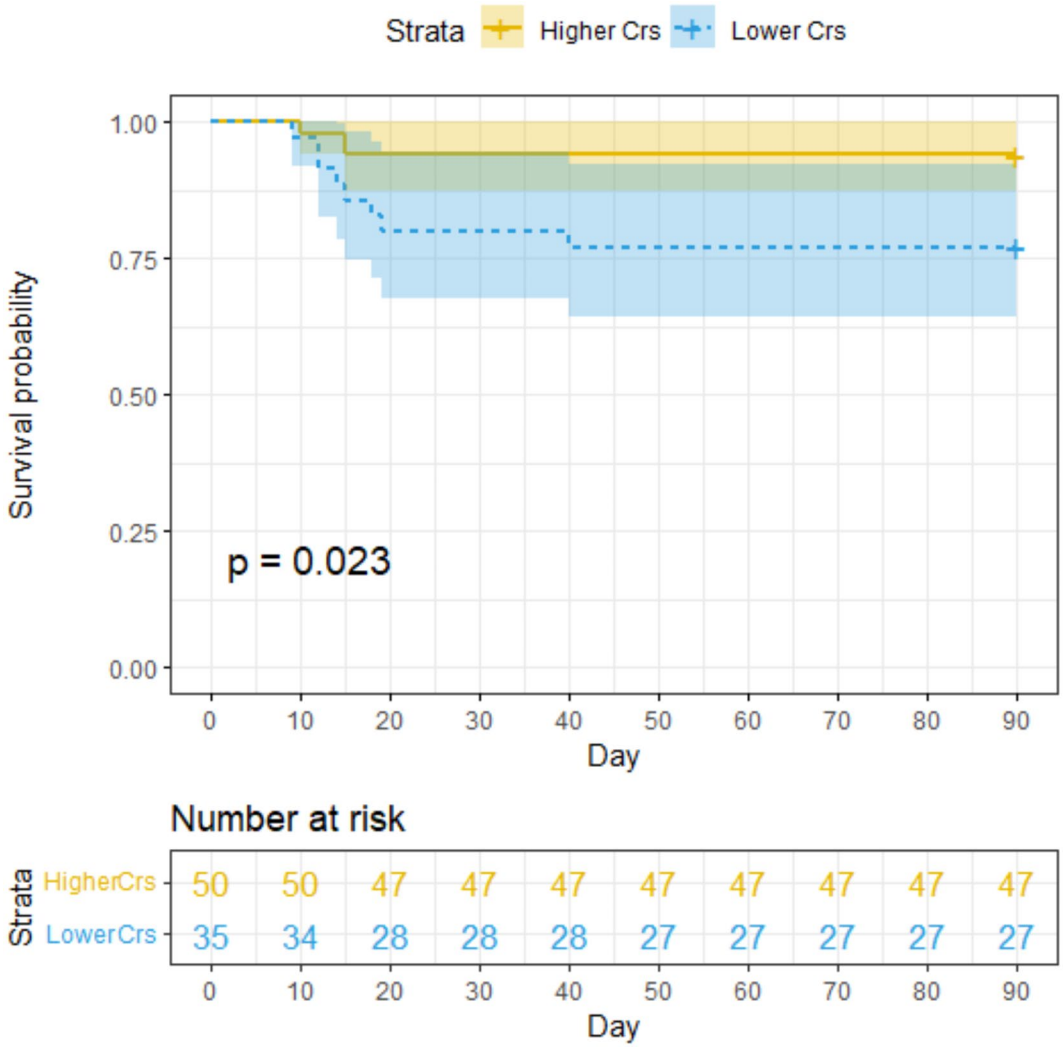

Fig. 5. Kaplan–Meier survival curves in patients.

risk factors can interact, further affecting prognosis. In the present study, there was no significant difference between groups in the incidence of PGD3 at 24 h, 48 h, and 72 h. There are several possible explanations for this finding. Different PGD phenotypes may have had different effects on lung compliance. Alternatively, it may relate to the sample size. The incidence of PGD3 in the two groups gradually approached similar levels over time, which might relate to PGD treatment and progression. The lower Crs group showed a delayed rise in P/F and a high initial carbon dioxide content. Although there were differences between P/F and carbon dioxide, the overall trend was similar. Future studies should explore whether different PGD phenotypes can be distinguished according to Crs in order to provide individualized clinical management, and the relationship between changes in Crs and PGD warrants further research.

Our study is subject to several limitations. First, it is a retrospective single-center study. Although the lung transplantation capacity of our center is relatively high, multi-center validation is needed. Second, the dynamic change in lung compliance was not monitored. The relationship between dynamic change and prognosis should be further studied. Third, as data on donor lungs were not collected, we cannot exclude the influence of donor lungs on prognostic confounding factors. Fourth, as ventilatory management of lung transplantation patients was relatively individualized, this may have influenced outcomes.

Conclusions

In lung transplant patients with VV-ECMO support, Crs < 25 ml/cmH_2O is associated with higher complications and 90-day mortality. Furthermore, the lower Crs group tended to have an increased incidence of PGD3. The use of Crs, which is easily accessible at the bedside, may help predict prognosis and guide patient management. The relationship between Crs and the prognosis of lung transplantation patients with VV-ECMO needs to be confirmed through multi-center prospective studies in the future.

Data availability

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Received: 25 April 2024; Accepted: 6 March 2025
Published online: 11 March 2025

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Author contributions

Hongyang Xu, Jingyu Chen, and Chenhao Xuan participated in the design of the study. Chenhao Xuan wrote the application for the ethical approval. Chenhao Xuan collected the data. Chenhao Xuan and Jingxiao Gu analyzed the data. Chenhao Xuan drafted the manuscript. Chenhao Xuan prepared Figs. 1, 2, 3, 4 and 5; Table 1, and 2. All authors read and approved the final manuscript.

Funding

No funding was received to assist with the preparation of this manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

This retrospective study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and

approved by Ethics Commission of the Affiliated Wuxi People's Hospital of Nanjing Medical University (No. KY24059), and the need for informed consent was waived by the Committee due to the retrospective nature of this study.

Additional information

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