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Prognostic value of the extravascular lung water and pulmonary vascular permeability indices in severe adult respiratory distress syndrome managed with extracorporeal membrane oxygenation

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Severe acute respiratory distress syndrome (ARDS) is commonly seen in intensive care units (ICUs). It is characterized by capillary endothelium and alveolar epithelium damage that results in significant increases in capillary permeability and extravascular lung water. It is difficult to quantify pulmonary edema accurately using conventional imaging. Pulse index continuous cardiac output (PiCCO) is a parameter based on transpulmonary thermodilution that overcomes these shortcomings. Several measurements derived from PiCCO can be determined continuously and accurately, including extravascular lung water index (ELWI), and pulmonary vascular permeability index (PVPI). Several prospective studies have demonstrated that early goal-directed treatment (EGDT) according to these measurements can help with volume management and ultimately reduce the in-hospital mortality rate in critically-ill patients.[1]

For patients with severe ARDS with oxygenation indexes less than 100 mmHg, extracorporeal membrane oxygenation (ECMO) can improve oxygenation without adding average alveolar pressure. Because of the existence of pulmonary edema in these patients, it is necessary to accurately measure ELWI and PVPI in a timely manner during treatment, and to tailor treatment to improve outcomes. Nevertheless, blood volumes and circulation patterns change during ECMO, and the reliability and prognostic value of the parameters obtained using PiCCO are controversial and lack evidence-based support. Therefore, the aim of the present study was to comprehensively analyze the clinical value of hemodynamics obtained by PiCCO in adults with severe ARDS assisted by ECMO at our center.

The ethics committee of Tianjin Third Central Hospital approved the study protocol (No. IRB2020-012-01) and all patients or their family members provided informed consent forms for participation in the study. The inclusion and exclusion criteria were described previously.[2,3] When measuring PiCCO parameters, we paused the running of ECMO. Ten milliliters of cold saline (0–6°C) were then injected quickly (less than 5 s) from the right internal jugular vein catheter. The thermistor tip of the femoral artery catheter was to measure temperature changes downstream. Every measurement was repeated three times and the average was taken as the final result. The measurement was taken at least twice a day. Quantitative data were expressed as mean ± standard deviation or median (interquartile range), and categorical data were expressed as numbers and proportions. The independent sample's *t*-test and Chi-square test were applied for comparison of data between groups. For multiple longitudinal comparisons of data, one-way analysis of variance with repeated measures and the least significant difference *post-hoc* analysis were used. Correlations between PVPI and ELWI and between ELWI and survival outcome were evaluated with Spearman correlation analysis. Receiver operating characteristic (ROC) curve was used to assess a variable's capacity to predict the outcome of survival. Kaplan-Meier survival analysis was

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utilized to measure differences in cumulative survival rates. SPSS 23.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. All two-sided P values were considered to be statistically significant if $P < 0.05$.

The data from 30 adults with ARDS managed with ECMO in our hospital from January 2008 to December 2018 were comprehensively reviewed. The age range was 20 to 74 years and the mean age was 44.7 ± 20.3 years. Twenty-six were male. There were no significant differences between survival (18 patients) and non-survival groups (12 patients) with respect to age, gender, comorbidities, Acute Physiology and Chronic Health Evaluation II/sequential organ failure assessment score, treatment strategies, volume of blood product transfusion, ECMO-related complications, lengths of ICU stay, or in-hospital stay (all $P > 0.05$) [Supplementary Table 1, http://links.lww.com/CM9/A333]. However, the maximum dosage of norepinephrine before ECMO establishment in the non-survival group was significantly higher than that of the survival group (0.6 [0.4, 5.0] $\mu g \cdot kg^{-1} \cdot min^{-1}$ *vs.* 0.5 [0.3, 2.8] $\mu g \cdot kg^{-1} \cdot min^{-1}$, $Z = -2.198$, $P = 0.026$). There was a tendency for longer length of mechanical ventilation before ECMO support in the non-survival group than in the survival group (24.0 [4.0, 120.0] h *vs.* 9.0 [3.0, 47.5] h, $P = 0.088$).

The time points of data acquisition included immediately (T_0), 24 h ($T_{24\,h}$), 48 h ($T_{48\,h}$), 72 h ($T_{72\,h}$), and 1 week ($T_{1\,w}$) after catheterization. The evolution characteristics showed that the ELWI value of the survival group decreased significantly after treatment (P-trend < 0.001). The comparison of the data at various time points within the survival group demonstrated that the ELWI values at 24 h, 72 h, and 1 week after catheterization were significantly lower when compared to that of the initial time point (T_0) after treatment [Supplementary Table 2, http://links.lww.com/CM9/A333]; this was not observed in the non-survival group. The results of inter-group comparisons showed that the ELWI values at 72 h (10.7 ± 3.7 mL/kg *vs.* 17.3 ± 4.5 mL/kg, $P = 0.006$) and 1 week (9.1 ± 2.9 mL/kg *vs.* 14.3 ± 4.0 mL/kg, $P = 0.027$) in the survival group were significantly lower than those of the non-survival group. The PVPI in the survival group also demonstrated a downward trend after treatment despite no statistical significance (P-trend $= 0.122$). There was no such decline in the non-survival group (P-trend $= 0.725$). The results of intergroup comparisons showed that the PVPI values at 72 h (2.3 ± 0.6 *vs.* 3.4 ± 1.2, $P = 0.008$) and 1-week (2.0 ± 0.6 *vs.* 2.6 ± 0.8, $P = 0.041$) in the survival group were significantly lower than those of the non-survival group. The ELWI and PVPI values showed a significant linear correlation at both 72 h ($r = 0.950$, $P < 0.0001$) and 1 week ($r = 0.834$, $P < 0.0001$). No significant differences were found in terms of other PiCCO parameters on intra-group or inter-group comparisons at each time point.

ROC curve analysis was conducted for ELWI at various time points to measure the discriminative performance for survival to discharge. ELWI at $T_{72\,h}$ had the best discriminating performance for survival to discharge, and the area under curve was 0.900 (95% confidence interval [CI]: 0.699–1.101; $P = 0.043$). The cutoff value was 12.5 mL/kg with 100% sensitivity and 70% specificity [Supplementary Table 3, http://links.lww.com/CM9/A333]. Spearman correlation analysis showed that ELWI at $T_{72\,h}$ significantly correlated with survival to discharge ($r = 0.632$, $P = 0.015$). The patients were reclassified based on the cutoff of ELWI (12.5 mL/kg) and Kaplan-Meier survival analysis was performed in patients with the value of ELWI at $T_{72\,h}$ less than 12.5 mL/kg ($n = 16$) and no less than 12.5 mL/kg ($n = 14$). A significant difference in cumulative survival rates was observed between the two groups (log-rank test: $\chi^2 = 5.241$, $P = 0.022$; hazard ratio, 5.82, 95% CI: 1.90–17.86).

Implementation of ECMO requires highly specialized teams, and consumes a great deal of human and medical resources. One of the key points to improve success rate is to assess the individualized characteristics of pulmonary edema and to adopt EGDT. It is crucial to identify safe and effective monitoring indexes to assist with accurate fluid management. Compared to the conventional chest imaging, the ELWI and PVPI obtained from PiCCO directly reflect the amount of extravascular lung water and permeability of pulmonary capillaries, providing the possibility to quantify the physiological changes in the patients in a timely and dynamic manner. In this study, we found that the ELWI values at each time point in the non-survival group were all significantly higher than those of the survival group, especially at 72 h and one week. This is consistent with our early treatment experience of adults with ARDS who were not managed with ECMO.[4] The value of ELWI in the survival group decreased significantly as the treatment progressed, and this was not seen in the non-survival group. The inflection point where the ELWI began to decrease in the survival group was earlier than that of the non-survival group (48 h *vs.* 72 h). This finding suggests that it may be valuable to predict outcome by comprehensively analyzing the dynamic evolution of ELWI value within one week.

For ECMO-assisted patients with severe ARDS, blood volume and circulation patterns change during extracorporeal cardiopulmonary bypass. The reliability of using PiCCO to monitor hemodynamics in the scenario was once questioned and its prognostic value remains without evidence-based support. Previous studies have shown that measurements of ELWI obtained by PiCCO in ARDS patients seem not to be significantly affected by an extracorporeal bypass under the premise that the flow of a pumpless lung-assist system does not exceed 20% of cardiac output.[5] For our patients, we paused extracorporeal circulation when we collected the PiCCO measurements and limited the total time of the parameter acquisition to five minutes. We found no significant hemodynamic fluctuations in any patient during the acquisition of PiCCO data, and the variability of data by triple-repeated measurement was comparable to that of our ARDS adults without ECMO assistance.

PVPI demonstrated similar dynamic evolution, and also had certain value to predict the prognosis. Nevertheless, no statistical significance was found in respect of the overall change trend of PVPI in the survival group. This may be due to the following reasons: First, although PVPI is derived from ELWI, the correlation between them was not shown strong in some studies, suggesting that they may have different pathophysiologic significance. Second, PVPI may be influenced by factors such as lymphatic drainage and the alveolar fluid clearance rate. Third, all patients in our study received various types of anti-inflammatory treatments (such as corticosteroids) that may reduce the degree of endothelial cell injury to some extent. Finally, there were limitations of sample size on statistical power.

In conclusion, PiCCO can be used for volume monitoring during ECMO assistance in severe ARDS patients. ELWI and PVPI at 72 h after PiCCO establishment may facilitate to predict their intra-hospital survival.

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Conflicts of interest

None.

References

1. Sánchez-Sánchez M, Garcia-de-Lorenzo A, Asensio MJ, Herrero E, Cachafeiro L, Agrifoglio A. Effectiveness of treatment based on transpulmonary thermodilution in critically ill patients. Intensive Care Med 2015;41:1154–1155. doi: 10.1007/s00134-015-3761-x.
2. Huang L, Li T, Xu L, Hu XM, Duan DW, Li ZB, *et al*. Performance of multiple risk assessment tools to predict mortality for adult respiratory distress syndrome with extracorporeal membrane oxygenation therapy: an external validation study based on Chinese single-center data. Chin Med J 2016;129:1688–1695. doi: 10.4103/0366-6999.185871.
3. Huang L, Li T, Xu L, Hu XM, Duan DW, Li ZB, *et al*. Extracorporeal membrane oxygenation outcomes in acute respiratory distress treatment: case study in a Chinese referral center. Med Sci Monit 2017;23:741–750. doi: 10.12659/msm.900005.
4. Sun L, Gao X, Li Z, Feng Q, Wang Z, Wang W, *et al*. The prognostic value of extravascular lung water index in patients with acute respiratory distress syndrome. Chin Crit Care Med 2014;26:101–105. doi: 10.3760/cma.j.issn.2095-4352.2014.02.009.
5. Mross M, Sakka SG. Influence of different blood flows through a pumpless lung assist system on transpulmonary thermodilution-derived variables. Intensive Care Med 2010;36:369–370. doi: 10.1007/s00134-009-1670-6.

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