Continuous Renal Replacement Therapy in Pediatric Severe Sepsis: A Propensity Score-Matched Prospective Multicenter Cohort Study in the PICU

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Objective: Continuous renal replacement therapy becomes available utilization for pediatric critically ill, but the impact of mortality rate in severe sepsis remains no consistent conclusion. The aim of the study is to assess the effect of continuous renal replacement therapy in pediatric patients with severe sepsis and the impact this therapy may have on their mortality.

Design: Propensity score-matched cohort study analyzing data prospectively collected by the PICUs over 2 years (2016–2018).

Measurements and Main Results: A total of 324 patients with severe sepsis were enrolled. The hospital mortality rate was 35.6% (64/180) in the continuous renal replacement therapy group and 47.9% (69/144) in the noncontinuous renal replacement therapy group. After propensity score adjustment, the hospital mortality rate was 21.3% (29/136) in the continuous renal replacement therapy group and 32.4% (44/136) in the noncontinuous renal replacement therapy group. In subgroup analysis, the relative risk of dying was 0.447 (95% CI, 0.208–0.961) only in patients complicated by acute respiratory distress syndrome (p = 0.037), but not in patients with shock, acute kidney injury, acute liver dysfunction, encephalopathy, and fluid overload greater than 10%. The mean duration of continuous renal replacement therapy was 45 hours (26–83 hr) with an ultrafiltration rate of 50 mL/kg/hr. The level of interleukin-6 was decreased, and the percent of natural killer cells (%) was improved in the continuous renal replacement therapy group compared with the noncontinuous renal replacement therapy group. Furthermore, continuous renal replacement therapy was an independently significant risk factor for hospital mortality in pediatric patients with severe sepsis, and the interval between continuous renal replacement therapy initiation and PICU admission was an independent risk factor for hospital mortality in patients receiving continuous renal replacement therapy.

Conclusions: Continuous renal replacement therapy with an ultrafiltration rate of 50 mL/kg/hr decreases hospital mortality rate in pediatric severe sepsis, especially in patients with acute respiratory distress syndrome. (Crit Care Med 2019; 47:e806–e813)

Key Words: acute respiratory distress syndrome; child; continuous renal replacement therapy; hospital mortality; severe sepsis
Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (1). Severe sepsis remains a burdensome health problem in infantile and children population. A worldwide study in 128 PICUs across 26 countries indicated that the hospital mortality rate was 25% in severe sepsis, and 17% of survivors had new moderate or worse disability at hospital discharge (2). Sepsis-induced acute kidney injury (AKI) comprises up to half of critical illness–associated AKI in adults (3, 4). The occurrence rate of AKI was reported 21% in pediatric severe sepsis, and septic AKI plays an independent risk factor for death and new disability (2, 5). Therefore, management of severe sepsis is still a most challenging issue in the PICU.

Accumulated evidences have strongly demonstrated that AKI and fluid overload (FO) were associated with high mortality in severe sepsis (5–7). Surviving Sepsis Campaign 2016 (1) suggests using continuous renal replacement therapy (CRRT) in patients with sepsis and AKI (weak recommendation, moderate quality of evidence), facilitating management of fluid balance in hemodynamically unstable septic patients (weak recommendation, very low quality of evidence). The benefits of CRRT in sepsis include kidney replacement, management of FO, clearance of toxic substances, alleviating of inflammatory reaction, or some combinational actions (6–9). Mortality ranges from 39% to 59% in children with sepsis receiving CRRT, likely reflecting severity of illness of patients election for CRRT application (10). However, well-designed clinical study regarding the role of CRRT in pediatric sepsis is limited in the PICU.

In the present study, we conducted a prospective multicenter cohort study to evaluate the effect of CRRT on the hospital mortality in pediatric severe sepsis.

MATERIALS AND METHODS

Study Design
We set up an observational multicenter prospective cohort of PICU patients with severe sepsis. The study was approved by the ethics committee of Children’s Hospital affiliated to Shanghai Jiao Tong University (Approval number: 2016R011-E02).

Setting and Patients
Patients were recruited in four university tertiary PICUs located in China mainland from July 2016 to June 2018. The clinical examination and data collection for enrolled patients were performed using standardized case report forms. The patients with severe sepsis were diagnosed based on the International Pediatric Sepsis Consensus Conference in 2005 (11) and Surviving Sepsis Campaign International Guidelines in 2012 (12). Sepsis-associated AKI was defined as infectious episode with AKI according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria (13). Sepsis-associated FO was defined as the FO greater than 10% (FO = [CRRT initial weight − PICU admission weight]/PICU admission weight × 100%) (14).

The inclusion criteria were as follows: 1) patients from 29 days to 18 years old; 2) patients with severe sepsis within 7 days; and 3) patients with one or more organ dysfunctions such as AKI, acute respiratory distress syndrome (ARDS), acute liver dysfunction, septic shock, or multiple organ dysfunction syndromes. Patients were excluded if they had the following condition: 1) patients with PICU stay less than 24 hours; 2) patients with primary immune function defect; 3) irreversible neurologic dysfunction; and 4) patients without the informed consent.

Patient’s Treatment
Patients were treated in accordance to current guidelines for treatment of sepsis. Initial management included fluid therapy, antibiotics, vasoactive drugs, nutrition, and other supportive therapy recommended by the International Pediatric Sepsis Consensus Conference in 2005 (11) and Surviving Sepsis Campaign International Guidelines in 2012 (12). The indications for CRRT include sepsis complicated by AKI, FO (> 10%), or hemodynamic instability, electrolyte disturbance, or moderate or severe ARDS (PaO2/FIO2 < 150 mm Hg). Electrolyte disturbance as a indication for CRRT was defined as the intractable electrolyte disturbance with poor response to conventional therapy. Sepsis complicated by moderate or severe ARDS (PaO2/FIO2 < 150 mm Hg) is an indication for CRRT initiation.

According to whether received CRRT, the patients were divided into CRRT group and non-CRRT group. Patients were excluded for CRRT and treated with conventional therapies if they met any of the following criteria: 1) complicated with severe coagulopathy disorder (international normalized ratio, > 3.0; or platelet count, < 10 × 109/L); 2) a history of biofilm or hemofilter allergy; 3) without consent for CRRT; 4) with difficult to set CRRT catheter access; and 5) acute leukemia or malignant tumor with a life expectancy of less than 2 years. In the non-CRRT group, besides of following current guidelines for treatment of sepsis, solution restriction and the application of diuretics should be considered if blood pressure could be stable with vasoactive drugs. All therapeutic decisions were independently made by the attending intensivists according to standard practice in each PICU.

CRRT Procedures
We performed CRRT with an ultrafiltration rate of 50 mL/kg/hr, performed using commercially available pump-driven machines (Prisma or Prismaflex; Gambro, Lund, Sweden) and HF20, M100, M60, or hemofilter of AN69 membrane (Gambro) dependent on body weights. For the patient complicated with AKI, hemofiltration and hemodialysis were performed. The blood flow rate was set on 4–6 mL/kg/min to achieve a filtration fraction of 25–35% in patients with FO. The filter circuit was prewashed with saline containing 5,000–10,000 IU/L unfractionated heparin (UFH). Vascular access was obtained with 6.5F–12F central venous catheters (Gambro; Colombes, France) in the right internal jugular or femoral vein, according to the patient body weight. Anticoagulation was achieved with UFH adjusted to a target activated partial thromboplastin time (APTT) of 40–55 seconds (1.5- to two-fold of normal value) or activated coagulation time (ACT) of 150–180
Clinical Data Collection
Data on demographics, clinical manifestations, comorbidities, illness severity, and outcome were collected prospectively. Underlying conditions on PICU admission were classified following the pediatric complex chronic conditions classification system (16). Illness severity was measured by the Pediatric Risk of Mortality (PRISM) score III (17). All subject records were encoded with a unique identifier that corresponded to the center and respective patient number.

Pre-CRRT initiation data collected were comprised of the following: age, gender, primary disease, comorbidity, and indications for CRRT initiation, the interval between CRRT initiation and PICU admission. The biochemical parameters in patients including lactate, the ratio of the PaO₂ to the FiO₂ (PaO₂/FiO₂), alanine transaminase (ALT), total bilirubin (TBIL), serum creatinine (sCr), blood urea nitrogen (BUN), inflammatory factors (tumor necrosis factor [TNF]-α and interleukin-6), and the percent of immune cells (natural killer [NK] cells, cluster of differentiation [CD]19+, CD4+, and CD8+) were prospectively collected.

Outcome Measures
The primary outcome was all-cause hospital mortality. Secondary outcomes included the length of PICU stay, 28-day mortality, changes of biochemical indexes, and the factors related to prognosis in patients received CRRT. The 28-day mortality was defined as the survival status after diagnosis with severe sepsis. All data were collected in well-designed case report forms. Monthly telephone conferences, biannual meetings, and clinical protocols including case definitions, data audits, and monitoring ensured uniform procedures among study sites.

Propensity Score Methods
In this prospective cohort study, propensity score matching analysis was performed to reduce the imbalance between the CRRT and non-CRRT groups. All the possible covariables (age, gender, shock, AKI, and FO) were included in the propensity score matching. Propensity scores were calculated using a logistic regression model. A one-to-one nearest neighbor matching was performed. Propensity scores were calculated using a logistic regression model. A one-to-one nearest neighbor matching was performed.

Statistical Analysis
Continuous variables were summarized as means ± sds for normal distribution data and as median (interquartile range) for abnormal distribution data. All variables were tested for normal distribution by using the Kolmogorov-Smirnov test.

RESULTS
Baseline Characteristics of Pediatric Patients With Severe Sepsis
Over the 2-year study period, a total of 407 patients were screened and 324 cases were enrolled. Among these patients, the mean age was 23.5 months (9–48 mo) and 182 patients (56.2%) were male. Of 324 patients with severe sepsis, 133 patients died and overall hospital mortality was 41.1%. Among 324 children with severe sepsis, 180 patients (55.6%) received CRRT (CRRT group) and 144 cases (44.4%) management in conventional strategy (non-CRRT group). After propensity score adjustment, there were 136 cases included in each group (Fig. 1).

The mainly primary infection was pneumonia in 116 cases (35.8%), followed by blood stream infection in 74 cases (22.8%), intestine in 66 cases (20.4%). The occurrence rate of comorbidities in enrolled patients was 52.8% (171/324) at admission. The most common comorbidity was congenital heart disease (20.7%; n = 67), followed by malignancies (22.5%; n = 73) and trauma (8.6%; n = 28). After propensity score adjustment, there were 136 cases in each group, and there was no significant difference in aspects of age, gender, PRISM III score, and comorbidities expect of congenital heart disease (all p > 0.05). The baseline characteristics of the patients with severe sepsis were presented in Table 1.
Changes of Biochemical Parameters in the Propensity-Matched Cohort

The changes in biochemical parameters for organ functions were showed in Supplemental Figure 1 (Supplemental Digital Content 2, http://links.lww.com/CCM/E734; and legend, Supplemental Digital Content 5, http://links.lww.com/CCM/E737) and Table 3. The plasma lactate levels were reduced gradually from 0 to 72 hours after CRRT (3 mmol/L [2–6.5 mmol/L] vs 2 mmol/L [1–3 mmol/L]; p < 0.001). The value of PaO2/FiO2 was significantly increased at 72 hours after CRRT (156 mm Hg [110–198 mm Hg] vs 166 mm Hg [121–210 mm Hg]; p < 0.001), and the clinical relevance of this effect needs further investigation. In addition, the levels of ALT were decreased after CRRT (p < 0.001) (Supplemental Fig. 1, Supplemental Digital Content 2, http://links.lww.com/CCM/E734; and legend, Supplemental Digital Content 5, http://links.lww.com/CCM/E737). Interleukin-6 level was significantly decreased at 72 hours after CRRT (1,480 ng/L [928.4–1,934 ng/L] vs 393.5 ng/L [234.1–685 ng/L]; p < 0.001). However, the levels of TNF-α were no difference before and after CRRT (p = 0.392). In addition, the percent of NK cells (NK%) was significantly increased at 72 hours after CRRT treatment (2.4% [1.3%–4.9%] vs 3.6% [2.1%–7.8%; p = 0.017] (Table 3). In the non-CRRT group, the levels of interleukin-6 showed a decreased trend after 72 hours treatment without statistical significance (957.5 ng/L [733–1,529 ng/L] vs 814.7 ng/L [172.7–1,338 ng/L]; p = 0.061), and there was no significant change in the level of TNF-α and the percent of NK%, CD19+, CD4+, and CD8+ (all p > 0.05) (Table 3).
The ratio of CRRT in survivors was 78.7% (107/199), which was higher than that in nonsurvivors (21.3%; 29/73) \( (p = 0.040) \). The levels of sCr, BUN, Pa\(_{co_2}\), lactate, ALT, TBIL, TNF-\(\alpha\), interleukin-6, as well as NK\%, CD19\+, CD4\+, and CD8\+ cells displayed no difference between nonsurvivors and survivors (all \( p > 0.05 \)) (Supplemental Table 1, Supplemental Digital Content 3, http://links.lww.com/CCM/E735). In the subgroup of patients receiving CRRT, the interval between CRRT initiation and PICU admission was significantly longer in nonsurvivors than in survivors (23 hr [19–37 hr] vs 14 hr [11–22 hr]; \( p < 0.001 \)). The basic value of Pa\(_o_2\)/Fi\(_o_2\) showed a lower tendency in nonsurvivors than in survivors (121 [99–154] vs 143 [112–202]; \( p = 0.044 \)) (Supplemental Table 1, Supplemental Digital Content 3, http://links.lww.com/CCM/E735).

### TABLE 1. Demographic and Clinical Characteristics of Pediatric Severe Sepsis Receiving Continuous Renal Replacement Therapy and Without Continuous Renal Replacement Therapy

| Characteristics | Before Propensity Score Adjustment | After Propensity Score Adjustment |
|-----------------|------------------------------------|-----------------------------------|
|                 | CRRT \((n = 180)\) | Non-CRRT \((n = 144)\) | \( p \) | CRRT \((n = 136)\) | Non-CRRT \((n = 136)\) | \( p \) |
| Age, mo, median (IQR) | 40 (12–80) | 33 (19–61) | 0.423 | 33 (12–65) | 35 (19–64) | 0.581 |
| Male, n (\%) | 104 (57.7) | 78 (54.1) | 0.482 | 77 (56.6) | 63 (46.3) | 0.089 |
| Pediatric Risk of Mortality III, median (IQR) | 17 (16–19) | 16 (15–19) | 0.049 | 17 (16–19) | 16 (15–19) | 0.081 |
| Primary infection, n (\%) | | | | | | |
| Respiratory system | 62 (34.4) | 54 (37.5) | 0.569 | 43 (31.6) | 48 (35.3) | 0.521 |
| Intestine | 39 (21.7) | 27 (18.8) | 0.517 | 31 (22.8) | 26 (19.1) | 0.456 |
| Liver and bile tract | 23 (12.8) | 10 (6.9) | 0.147 | 17 (12.5) | 10 (7.4) | 0.156 |
| Urinary system | 3 (1.7) | 3 (2.1) | 0.782 | 2 (1.5) | 3 (2.2) | 0.652 |
| Skin and soft tissue | 3 (1.7) | 6 (4.2) | 0.174 | 2 (1.5) | 6 (4.4) | 0.151 |
| Blood stream infection | 40 (22.2) | 34 (23.6) | 0.767 | 29 (21.3) | 33 (24.3) | 0.563 |
| CNS | 10 (5.6) | 12 (8.3) | 0.323 | 9 (6.6) | 12 (8.8) | 0.496 |
| Comorbidities, n (\%) | | | | | | |
| Congenital heart disease | 31 (17.2) | 36 (25.0) | 0.086 | 19 (14.0) | 33 (24.3) | 0.031 |
| Tumor or leukemia | 46 (25.6) | 27 (18.8) | 0.145 | 28 (20.6) | 24 (17.6) | 0.537 |
| Trauma | 17 (9.4) | 11 (7.6) | 0.565 | 13 (9.6) | 11 (8.1) | 0.669 |
| Nephrotic syndrome | 2 (1.1) | 1 (0.7) | 0.697 | 2 (1.5) | 1 (0.7) | 0.562 |
| No. of organ dysfunction, n (\%) | | | | | | |
| 1 | 10 (5.6) | 12 (8.3) | 0.337 | 7 (5.1) | 12 (8.8) | 0.234 |
| 2 | 13 (7.2) | 20 (13.9) | 0.053 | 11 (8.1) | 18 (13.2) | 0.169 |
| 3 | 30 (16.7) | 32 (22.2) | 0.224 | 22 (16.2) | 32 (23.5) | 0.128 |
| 4 | 58 (32.2) | 38 (26.4) | 0.227 | 43 (31.6) | 35 (25.7) | 0.283 |
| ≥ 5 | 59 (32.8) | 42 (29.2) | 0.444 | 44 (32.4) | 37 (27.2) | 0.353 |
| MODS, n (\%) | 117 (65.0) | 80 (55.6) | 0.062 | 86 (63.2) | 76 (55.9) | 0.217 |
| PICU stay, d, median (IQR) | 16 (8–24) | 7 (5–15) | < 0.001 | 16 (8–24) | 7 (5–14) | < 0.001 |
| 28-d mortality, n (\%) | 73 (40.6) | 74 (51.39) | 0.052 | 58 (42.6) | 66 (48.5) | 0.330 |
| Hospital mortality, n (\%) | 64 (35.6) | 69 (47.9) | 0.004 | 29 (21.3) | 44 (32.4) | 0.040 |

CRRT = continuous renal replacement therapy, IQR = interquartile range, MODS = multiple organ dysfunction syndromes.
Values are expressed as the median (IQR) or n (%).
Additionally, multivariate logistic analysis indicated that CRRT application was an independently protective factor for hospital mortality in pediatric severe sepsis (odds ratio [OR], 0.567 [0.328–0.978]; *p* = 0.041). Furthermore, the interval between CRRT initiation and PICU admission was an independently risk factor for hospital morbidity in patients with severe sepsis receiving CRRT (OR, 1.067 [1.029–1.106]; *p < 0.001) adjusted by *Pao*2/*Fio*2 value (Table 4). Supplemental Worksheet for this study is available online (Supplemental Digital Content 4, http://links.lww.com/CCM/E736).

**DISCUSSION**
In this multicenter, propensity score-matched, observational prospective cohort study, we demonstrated that CRRT decreases the hospital mortality rate in pediatric severe sepsis, especially in sepsis-associated ARDS. In addition, hospital mortality rate showed a reduced tendency without statistic significance in the CRRT group compared with the non-CRRT group in the subgroups of AKI, shock, acute liver dysfunction, or encephalopathy. Furthermore, CRRT application was a protective factor in pediatric severe sepsis, and the interval

| Variable | Pre-CRRT | CRRT After 3 d | *p* |
|----------|----------|----------------|-----|
| CRRT group, median (IQR) | | | |
| TNF-α, ng/L | 104 (54–129) | 91 (61.2–112) | 0.392 |
| Interleukin-6, ng/L | 1,480 (928.4–1,934) | 393.5 (234.1–685) | < 0.001 |
| NK cells, % | 2.4 (1.3–4.9) | 3.6 (2.1–7.8) | 0.017 |
| CD19*, % | 22.4 (10–39) | 21.3 (10.6–30) | 0.308 |
| CD4*, % | 29 (21.3–38) | 35.2 (23.6–43.1) | 0.058 |
| CD8*, % | 25 (18.9–38) | 29.0 (23–36.3) | 0.423 |
| Non-CRRT group, median (IQR) | | | |
| TNF-α, ng/L | 123 (98–165) | 110.5 (76–210) | 0.253 |
| Interleukin-6, ng/L | 957.5 (733–1,529) | 814.7 (1727–1,338) | 0.061 |
| NK cells, % | 3.2 (2.1–4.5) | 2.9 (1–7.8) | 0.110 |
| CD19*, % | 21 (75–45) | 24 (12–45.9) | 0.477 |
| CD4*, % | 29 (20.7–33) | 27 (18–41) | 0.199 |
| CD8*, % | 26.4 (22–39) | 34 (18–48) | 0.435 |

CD = cluster of differentiation, CRRT = continuous renal replacement therapy, IQR = interquartile range, NK = natural killer, TNF = tumor necrosis factor. Values are expressed as median (IQR).
Sepsis in the Propensity-Matched Cohort
Mortality in Pediatric Patients With Severe
Independently Associated With Hospital
the difference among four centers, we set the dose of hemofiltration did not improve 28-day mortality in patient with sepsis
high dose (80 mL/kg/hr) of continuous venovenous hemodiafiltration did not significantly reduce 28-day mortality compared with
jury (IVOIRE) study, high-volume hemofiltration (70 mL/kg/hr) reached a consensus. In high-volume versus standard-volume
sepsis under CRRT.

Effect of Different Ultrafiltration Dose of CRRT in Pediatric Sepsis

We previously indicated that CRRT significantly reduced interleukin-6 in patients with severe sepsis (21) and secondary hemophagocytic lymphohistiocytosis (15). Furthermore, the percentage of NK cells at day 1 significantly increased with non-CRRT group without statistic significance, partially due to relatively small sample size. We speculated that the decreased interleukin-6 level and increased NK% contributed to the impact of CRRT in severe sepsis, which needs pay attention to confirm in the future.

Our study has several limitations. First, the observational design precludes accurate conclusions due to lacking of randomization for CRRT. Second, we only enrolled the patients from the four PICUs located in China mainland. This may reduce generalization of our results. Third, for safety, we exclude patients with severe coagulopathy. Fourth, we did not systematically monitor the extravascular lung water (EVLW) in children with severe ARDS because EVLW monitoring is difficult to perform in pediatric population. It may impact the observed outcomes in ARDS received CRRT. Fifth, we only performed the CRRT with the ultrafiltration dose of 50 mL/kg/hr. The effects of different ultrafiltration dose of CRRT in pediatric sepsis need further investigation.

CONCLUSIONS
In our prospective, propensity score-matched, multicenter cohort study, we demonstrated that CRRT therapy decreases the hospital mortality in pediatric severe sepsis, especially in pediatric septic ARDS in China. All these results suggested that CRRT could be potential therapy for patients with ARDS.

Fluid management is associated with clinical outcome including ventilator-free days and oxygenation, especially in patients with ARDS complicated by FO (31). Non-survivors receiving CRRT with higher FO demonstrated less improvement in mechanical ventilation during CRRT (32). In addition, FO impairs gas exchange and reduces lung compliance in ARDS (33). In our study, the PaO2/FIO2 was improved after 72 hours of CRRT, indicating that improved oxygenation is partially contributed by CRRT. Consistently, a previous study reported that PaO2/FIO2 after 24 hours of CRRT was higher in ARDS patients with extrapulmonary etiology than in those with pulmonary etiology (34). Furthermore, early initiation (within 12 hr after ARDS onset) of CRRT significant improves oxygenation and significantly decreased bronchoalveolar lavage fluid after CRRT (26). In our study, we found that the interval between CRRT initiation and PICU admission was independently associated with the outcome of pediatric severe sepsis received CRRT. So, we speculated that the improved oxygenation of CRRT in septic ARDS was partially reduction of FO and bronchoalveolar lavage fluid.

We previously indicated that CRRT significantly reduced the inflammatory factors interleukin-6 in patients with severe sepsis (21) and secondary hemophagocytic lymphohistiocytosis (15). Furthermore, the percentage of NK cells at day 1 was associated with mortality in patients with severe sepsis (35). We speculated that the decreased interleukin-6 level and increased NK% contributed to the impact of CRRT in severe sepsis, which needs pay attention to confirm in the future.

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CONCLUSIONS
In our prospective, propensity score-matched, multicenter cohort study, we demonstrated that CRRT therapy decreases the hospital mortality in pediatric severe sepsis, especially in

**TABLE 4. Logistic Analysis of Variables Independently Associated With Hospital Mortality in Pediatric Patients With Severe Sepsis in the Propensity-Matched Cohort**

| Variable                          | OR (95% CI)   | p     |
|-----------------------------------|---------------|-------|
| In total patients                 |               |       |
| CRRT, yes or no                   | 0.567         | 0.041 |
|                                   | (0.328–0.978) |       |
| In patients with CRRT             |               |       |
| Interval between CRRT             | 1.067         | < 0.001 |
| initiation and PICU admission     | (1.029–1.106) |       |

CRRT = continuous renal replacement therapy, OR = odds ratio.
patients with severe sepsis complicated by ARDS. CRRT application is protective for pediatric patients with severe sepsis. Of pediatric patients supported by CRRT, the interval between CRRT initiation and PICU admission is significantly correlated with the prognosis.

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