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ORIGINAL RESEARCH

# Decreased urine output is associated with increased in-hospital mortality from sepsis-associated acute respiratory distress syndrome

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## Abstract

The relationship between urine output (UO) and in-hospital mortality in patients with sepsis-associated acute respiratory distress syndrome (ARDS) has not been elucidated. The demographic and clinical characteristics of patients from the intensive care unit with sepsis-associated ARDS in the Medical Information Mart for Intensive Care-IV database were collected, and binomial logistic regression was performed to determine whether UO was an independent risk factor for in-hospital death. Using the Logistic Organ Dysfunction System (LODS) and Sequential Organ Failure Assessment (SOFA) as a reference, receiver operating characteristic (ROC) curves were drawn to analyze the efficacy of UO in predicting in-hospital mortality, and the Kaplan-Meier curve was drawn with the optimal cut-off value of the ROC curve. Decision curve analysis (DCA) was performed to assess the clinical net benefit of UO in predicting in-hospital mortality. UO was an independent risk factor for in-hospital mortality in patients with sepsis-associated ARDS. The area under the ROC (AUC) for UO in predicting in-hospital mortality was 0.712, which was comparable to LODS and SOFA. The patients were grouped by the optimal UO cut-off value (1515 mL/day) identified by the ROC curve. The results showed that the median in-hospital survival time for the low-UO group was 20.565 days, and that of the high-UO group was 84.670 days. The risk of in-hospital death of the low-UO group was 3.0792 times that of the high-UO group. DCA showed that when using UO to predict in-hospital mortality, the clinical net benefit was higher than LODS or SOFA at almost all available threshold probabilities, particularly when the threshold probability was between 0.2 and 0.4. As a result, UO showed moderate efficacy in predicting in-hospital mortality, and when used to predict the in-hospital mortality of patients with sepsis-related ARDS, its clinical net benefit was higher than that of LODS or SOFA.

## Keywords

Urine output; Sepsis; Acute respiratory distress syndrome; In-hospital mortality; MIMIC-IV

## 1. Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Acute respiratory distress syndrome (ARDS) is a serious complication of sepsis, characterized by acute, diffuse and inflammatory lung injury, which can lead to severe hypoxemia, bilateral lung infiltration and decreased lung compliance [2]. The annual incidence of ARDS ranges from 5 to 80 cases per 100,000 individuals, with an overall in-hospital mortality of approximately 40% [3]. ARDS is reported in up to 50% of sepsis patients admitted to the intensive care unit (ICU). Sepsis-associated ARDS has been associated with significant mortality, higher than in patients with sepsis alone or ARDS alone [4–6]. Therefore, it is imperative to determine the clinical characteristics of septic patients who develop ARDS after ICU admission and propose effective strategies for predicting in-hospital mortality.

Urine output (UO) is a low-cost and easy-to-record measurement in clinical practice, which has shown great application value in mortality prediction in intensive care patients. Zhang *et al.* [7] demonstrated an independent association between increased UO and decreased mortality in unselected critically ill patients. Heffernan *et al.* [8] found that a UO threshold $<0.5$ mL/kg/h could moderately predict mortality in patients admitted to the ICU, which was consistent with the current definition of acute kidney injury (AKI), although the relative importance of UO in predicting survival varied with admission diagnosis. In addition, UO has been shown to be an independent risk factor for in-hospital mortality in


  

intensive care septic shock patients, with its performance in predicting in-hospital mortality even comparable to the Sequential Organ Failure Assessment (SOFA) score [9]. As for ARDS, Hsiao *et al.* [10] found that UO measured on the first day of receiving extracorporeal membrane oxygenation (ECMO) supportive therapy had good prognostic power in predicting in-hospital mortality. Another study found that increased UO was significantly associated with lower mortality in ARDS, and when the association between UO and mortality was determined by UO/fluid intake (UO/FI), patients with low UO/FI ratios and higher UO were found to have greater survival benefit [11].

However, no studies have thoroughly investigated the value of UO in sepsis-associated ARDS patients. Thus, this study intended to characterize the UO on the first day of admission in sepsis-associated ARDS and attempted to determine the association between their UO and in-hospital mortality.

## 2. Methods

### 2.1 Database and study population

This retrospective study enrolled patients diagnosed with sepsis-associated ARDS from the Medical Information Mart for Intensive Care-IV (MIMIC-IV, version 1.0, https://mimic.mit.edu/) database. The MIMIC-IV database is an open database on intensive care patients jointly developed by the Massachusetts Institute of Technology, Beth Israel Deaconess Medical Center, and Philips Medical under the funding of the National Institutes of Health, which collected tens of thousands of real patient hospitalization information in the Boston area of the United States from 2008 to 2019. Author Tianyang Hu signed the database use agreement after passing the "Protect Human Research Participants" exam (Record ID: 37474354) and was allowed to access the database. All patients in this database were anonymous, and their private information, such as names and addresses, were deidentified [12]; thus, this study requires neither informed consent from the patients nor ethical review. This study complied with the Declaration of Helsinki.

ARDS in this study was defined using the Berlin definition, with the International Classification of Diseases-10 (ICD-10) code J80. In the MIMIC-IV database, 261 patients were diagnosed with ARDS, and after excluding repeated admission to the ICU, 214 patients were identified. Further, after excluding patients who stayed in the ICU for less than 24 hours, 188 patients were identified as eligible for this study. Among them, a total of 168 patients were diagnosed with sepsis. Here, sepsis was defined according to the Sepsis-3 criteria [1].

The following information on the enrolled cases was collected: age, gender, length of hospital stay, length of stay in ICU, Charlson Comorbidity Index (index for quantifying comorbidities [13], including myocardial infarct, chronic pulmonary disease, diabetes, cancer, *etc.*), combined treatment with AKI on the first day of admission, laboratory tests on the first day (including hemoglobin, white blood cell, platelets, blood urea nitrogen, creatinine, international normalized ratio/INR, total bilirubin and anion gap), blood gas analysis on the first day (including lactate, pH, and oxygenation index, *i.e.*, $PaO_2/FiO_2$), vital signs on the first day (including mean artery pressure, respiratory rate, and saturation of peripheral oxygen, *i.e.*, $SpO_2$), UO on the first day, Logistic Organ Dysfunction System (LODS) score on the first day, SOFA score on the first day, and treatments during the ICU stay (including mechanical ventilation, ECMO and diuretic use). The average was taken if a variable was measured multiple times during the day. The term mechanical ventilation in this study indicates that the ventilation methods during the ICU stay included at least tracheal intubation or other types of invasive ventilation, and non-mechanical ventilation indicates that only high-flow oxygen, other non-mechanical ventilation or no ventilation treatment. Diuretics included furosemide, hydrochlorothiazide, spironolactone, bumetanide, chlorothiazide, metolazone, *etc.*

### 2.2 Statistical analysis

After determining normality by the Kolmogorov-Smirnov test, continuous variables that obeyed the normal distribution are expressed as mean $\pm$ standard deviation (M $\pm$ SD) and were compared using the independent sample t-test; if not, they are expressed as the median with interquartile range (IQR) and were compared using the Wilcoxon rank-sum test. Categorical variables were expressed as numbers (percentage) and compared using the Chi-square test. Binomial logistic regression was performed to determine whether potential variables associated with in-hospital mortality were independent risk factors for in-hospital mortality (variables with $p$ values $< 0.1$ in the univariate analysis were included in the multivariate analysis). The receiver operating characteristic (ROC) curves of UO, LODS and SOFA score were drawn separately, and the area under the ROC curve (AUC) was compared using the Z test following the method of Delong *et al.* [14] to determine their predictive value.

In-hospital mortality is a time-to-event variable, and its failure event is death during hospitalization. Data were censored if the patients were alive at discharge. All patients were followed during their hospital stay [7]. We also performed an in-hospital survival analysis using the log-rank test, after which UO was divided into two groups (high-UO and low-UO) according to the optimal cut-off value indicated by the ROC curve, and Kaplan-Meier survival curves were drawn.

Decision curve analysis (DCA) is a simple method to evaluate clinical predictive models, diagnostic tests and molecular markers [15]. The AUC only measures the diagnostic accuracy of the predictive model and fails to take into account the clinical utility of a particular model. In contrast, the strength of DCA is that it can integrate patient or decision-maker preferences into the analysis. Judging by a certain indicator whether a patient will suffer from a certain disease or will have a certain outcome, no matter which value is selected as the cut-off value, there will be the possibility of false positives and false negatives, both of which cannot be avoided at the same time. Thus, the DCA curve was used to assess the model that could achieve the greatest clinical net benefit. "Net benefit" was calculated by the difference between the proportion of relative harms of false positives and false negatives weighted by the odds of the selected threshold for high-risk designation, that is,

the difference between the expected benefit and the expected harm [16]. We plotted DCA curves of UO, LODA and SOFA scores to assess the clinical net benefit of using UO to predict in-hospital mortality for patients with sepsis-associated ARDS.

Analyses were performed using the R (version 4.1.2, R Foundation for Statistical Computing, Vienna, Austria) or MedCalc statistical (version 19.6.1, MedCalc Software Ltd, Ostend, Belgium) software, and a $p$-value $< 0.05$ was considered as having statistical significance.

## 3. Results

### 3.1 Demographic and clinical characteristics

Of the eligible 168 patients, 61 died and 107 survived during hospitalization, resulting in an in-hospital mortality rate of 36.3%. There were no significant differences in age, gender, Charlson Comorbidity Index (CCI), AKI and treatment (mechanical ventilation, ECMO and diuretic use) between patients who died (non-survival group) and survived (survival group). The length of hospital and ICU stay in the non-survival group was significantly shorter than in the survival group. The UO of the non-survival group was significantly lower than the survival group, and the LODS and SOFA scores were significantly higher than the survival group. Details of the other laboratory tests, blood gas analysis and other variables are shown in Table 1.

### 3.2 Logistic regression analysis

For the binomial logistic regression analysis, we performed univariate regression analyses of potential variables and those with a $p$-value $< 0.1$ (including whether combined AKI, INR, anion gap, lactate, pH, mean artery pressure, $SpO_2$ and UO) were included in the multivariate regression analysis. After adjustment for potential confounders, UO was identified as an independent risk factor for in-hospital mortality in patients with sepsis-associated ARDS (Odds Ratio (OR) = 1.000, 95% Confidence Interval (CI): 0.999–1.000, $p = 0.046$) (Table 2).

### 3.3 Comparison of ROC curves

As shown in Table 3 and Fig. 1, the AUCs of UO, LODS and SOFA were 0.712, 0.632 and 0.636, respectively, with UO demonstrating the highest sensitivity and Youden index. Pairwise comparison of these three predictors showed that the Z value of UO versus LODS was 1.773 ($p = 0.0762$), UO versus SOFA was 1.661 ($p = 0.0968$) and LODS versus SOFA was 0.117 ($p = 0.9072$). All $p$ values $> 0.05$, indicated no statistical difference in the predictive power of the three indicators.

### 3.4 Comparison of Kaplan-Meier curves

Next, we grouped UO by the optimal cut-off value obtained from the ROC curve into a low-UO group ($\leq$1515 mL/day) or a high-UO group ($>$1515 mL/day). Kaplan-Meier curve showed that the in-hospital survival time of the low-UO group was significantly shorter than the high-UO group (Fig. 2). Survival analysis showed that the median in-hospital survival time of the low-UO group was 20.6 days, while that of the high-UO group was 84.7 days. Further, we also found that the risk of in-hospital death in the low-UO group was 3.0792 times (95% CI: 1.8403–5.1520, log-rank $p < 0.0001$) that of the high-UO group.

### 3.5 Comparison of DCA curves

The interpretation of the DCA curve was similar to the ROC curve, whereby a larger area under the curve indicated that the corresponding predictor could have the greatest net benefit in clinical practice. Fig. 3 illustrates the DCA results. The abscissa represents the threshold probability, and the ordinate represents the net benefit. The UO represented by the red curve is above the other two scoring systems (blue curve, LODS score represented; black curve, SOFA score) at nearly all available threshold probabilities, especially for probabilities between 0.2 and 0.4, indicating a significant net benefit. When the threshold probability was about 0.3, the ordinate corresponding to the red curve was about 0.4, and the ordinate corresponding to the other two curves was about 0.3. These could be interpreted as selecting 0.3 for threshold probability if a patient is judged to be at risk of in-hospital death, following which active intervention would be needed. Out of 100 patients, the use of UO as a predictor of in-hospital mortality was estimated to benefit approximately 40 patients, while the other two scoring systems benefited only approximately 30 patients. These results suggest that UO had the highest relative clinical net benefit when used to predict in-hospital mortality for patients with sepsis-associated ARDS.

## 4. Discussion

This is the first study to investigate the relationship between UO on the first day of admission and sepsis-related ARDS in patients admitted to the ICU. After adjustment for AKI, ECMO and diuretic use, the results showed that UO was independently associated with in-hospital mortality and demonstrated a moderate value in predicting in-hospital mortality (AUC = 0.712, comparable to the LODS and SOFA scores). Survival analysis indicated that the risk of in-hospital death in the low-UO group ($\leq$1515 mL/day) was approximately 3 times that of the high-UO group ($>$1515 mL/day). For the risk management of high-severity diseases such as sepsis and ARDS, a previous study suggested that multiple organ dysfunction or failure models could be used and that the LODS and SOFA scores were representative scoring systems [17]. However, our study shows that UO had a higher Youden index than LODS and SOFA scores. DCA also suggested that the clinical net benefit of UO in predicting in-hospital mortality in these patients was higher than with LODS and SOFA scores. These findings indicate the potential importance of UO in the clinical management of patients with sepsis-related ARDS.

Decreased UO characterizes renal hypoperfusion due to low cardiac output or systemic vasodilation. Patients with sepsis have abnormal vasoconstriction and vasodilation functions, increased vascular permeability and reduced blood volume at an early stage, eventually causing hypoperfusion in tissues and organs. If renal insufficiency is not detected early and corrected in time, it could further evolve into intrinsic AKI or even irreversible renal damage. Decreased UO can also lead to fluid

**TABLE 1. Demographic and clinical characteristics.**

| Characteristics | Non-survival group (n = 61) | Survival group (n = 107) | *p* |
|---|---|---|---|
| Age, year | 58.3 ± 17.2 | 55.3 ± 16.6 | 0.267 |
| Gender (male) | 33 (54.1) | 57 (53.3) | 0.918 |
| Length of Hos stay, day | 9.0 (3.6–17.7) | 21.8 (12.5–33.0) | <0.001 |
| Length of ICU stay, day | 6.7 (2.9–14.2) | 11.6 (5.9–18.5) | <0.001 |
| CCI | 5.0 (3.0–6.5) | 5.0 (2.0–7.0) | 0.344 |
| AKI | 18 (29.5) | 18 (16.8) | 0.054 |
| Laboratory test | | | |
| Hemoglobin, g/dL | 9.6 (8.1–11.3) | 9.7 (8.5–11.8) | 0.540 |
| White blood cell, $10^9$/L | 14.6 (10.5–19.7) | 14.5 (9.2–19.6) | 0.518 |
| Platelets, $10^9$/L | 147 (87–225) | 189 (119–260) | 0.076 |
| BUN, mmoL/L | 30.0 (17.8–45.0) | 20.3 (13.8–40.3) | 0.078 |
| Creatinine, mg/dL | 1.55 (1.30–2.33) | 1.25 (0.80–2.02) | 0.035 |
| INR | 1.75 (1.40–2.42) | 1.35 (1.20–1.65) | 0.001 |
| Total bilirubin, mg/dL | 1.65 (0.58–4.08) | 0.70 (0.42–1.35) | 0.021 |
| Anion gap, mmoL/L | 19.5 (15.5–21.0) | 16.5 (13.0–19.8) | 0.030 |
| Blood gas analysis | | | |
| Lactate, mmoL/L | 4.00 (2.28–6.55) | 2.22 (1.50–3.75) | 0.001 |
| pH | 7.28 ± 0.11 | 7.32 ± 0.09 | 0.038 |
| $PaO_2/FiO_2$, mmHg | 145.8 (89.9–218.5) | 151.2 (112.2–197.2) | 0.324 |
| Vital signs | | | |
| MAP, mmHg | 72.6 (66.9–78.4) | 75.3 (71.8–80.3) | 0.024 |
| Respiratory rate, cpm | 23.6 ± 4.5 | 23.4 ± 4.9 | 0.796 |
| $SpO_2$, % | 94.8 (92.5–96.8) | 95.5 (93.6–97.4) | 0.149 |
| Urine output, mL/day | 765 (185–1405) | 1675 (924–2595) | <0.001 |
| Scoring systems | | | |
| LODS | 10.3 ± 3.5 | 8.9 ± 3.5 | 0.013 |
| SOFA | 12.2 ± 4.3 | 10.4 ± 4.0 | 0.008 |
| Treatment method | | | |
| Mechanical ventilation | 49 (80.3) | 85 (79.4) | 0.890 |
| ECMO | 3 (4.9) | 3 (2.8) | 0.669 |
| Diuretic | 17 (27.9) | 26 (24.3) | 0.610 |

*Values are expressed as M ± SD / median (IQR) or n (%).*
*Abbreviations: Hos = hospital, ICU = Intensive Care Unit, CCI = Charlson Comorbidity Index, AKI = Acute Kidney Injury; BUN = Blood Urea Nitrogen, INR = International Normalized Ratio, $PaO_2/FiO_2$ = Oxygenation index, MAP = Mean Artery Pressure, cpm = count per minute, $SpO_2$=Saturation of Peripheral Oxygen, LODS = Logistic Organ Dysfunction System, SOFA = Sequential Organ Failure Assessment, ECMO = Extracorporeal Membrane Oxygenation.*

**TABLE 2. Binomial Logistic regression analysis of variables potentially associated with in-hospital mortality.**

| | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| Variables | OR (95% CI) | *p* | OR (95% CI) | *p* |
| Age | 1.011 (0.992–1.030) | 0.266 | | |
| Gender | 1.034 (0.550–1.943) | 0.918 | | |
| CCI | 1.040 (0.936–1.155) | 0.470 | | |
| AKI | 2.070 (0.980–4.372) | 0.057 | 1.271 (0.511–3.160) | 0.607 |
| Hemoglobin | 0.928 (0.808–1.065) | 0.288 | | |
| WBC | 1.004 (0.968–1.041) | 0.837 | | |
| Platelets | 0.998 (0.995–1.001) | 0.161 | | |
| BUN | 1.008 (0.995–1.022) | 0.245 | | |
| Creatinine | 1.050 (0.864–1.275) | 0.623 | | |
| INR | 1.937 (1.163–3.228) | 0.011 | 1.420 (0.798–2.529) | 0.233 |
| Total bilirubin | 1.048 (0.987–1.113) | 0.125 | | |
| Anion gap | 1.068 (1.003–1.137) | 0.040 | 0.995 (0.900–1.100) | 0.926 |
| Lactate | 1.205 (1.058–1.373) | 0.005 | 1.148 (0.934–1.411) | 0.19 |
| pH | 0.028 (0.001–0.851) | 0.040 | 7.001 (0.042–1159.8) | 0.455 |
| $PaO_2/FiO_2$ | 1.000 (0.996–1.003) | 0.829 | | |
| MAP | 0.962 (0.923–1.002) | 0.061 | 0.972 (0.922–1.025) | 0.291 |
| RR | 1.009 (0.944–1.078) | 0.795 | | |
| SpO2 | 0.905 (0.828–0.990) | 0.029 | 0.956 (0.855–1.069) | 0.432 |
| Urine output | 0.999 (0.999–1.000) | 0.001 | 1.000 (0.999–1.000) | 0.046 |
| MV | 1.057 (0.481–2.320) | 0.890 | | |
| ECMO | 1.793 (0.351–9.172) | 0.483 | | |
| Diuretic | 1.204 (0.590–2.456) | 0.610 | | |

*Abbreviations: OR = Odds Ratio, CI = Confidence Interval, CCI = Charlson Comorbidity Index, AKI = Acute Kidney Injury; WBC = White Blood Cell, BUN = Blood Urea Nitrogen, INR = International Normalized Ratio, $PaO_2/FiO_2$ = Oxygenation index, MAP = Mean Artery Pressure, RR = Respiratory rate, $SpO_2$ = Saturation of Peripheral Oxygen, MV = Mechanical Ventilation, ECMO = Extracorporeal Membrane Oxygenation.*

**TABLE 3. Comparison of ROC curves.**

| Factors | AUC | 95% CI | Optimal cut-off | Sensitivity | Specificity | Youden index |
|---|---|---|---|---|---|---|
| UO | 0.712 | 0.635–0.780 | ≤1515 | 83.05 | 53.4 | 0.3645 |
| LODS | 0.632 | 0.553–0.706 | >10 | 52.46 | 68.22 | 0.2068 |
| SOFA | 0.636 | 0.557–0.710 | >10 | 72.13 | 50.47 | 0.2260 |

*Abbreviations: ROC = Receiver the Operating Characteristic, AUC = Area Under the ROC Curve, CI = Confidence Interval, UO = Urine Output, LODS = Logistic Organ Dysfunction System, SOFA = Sequential Organ Failure Assessment.*

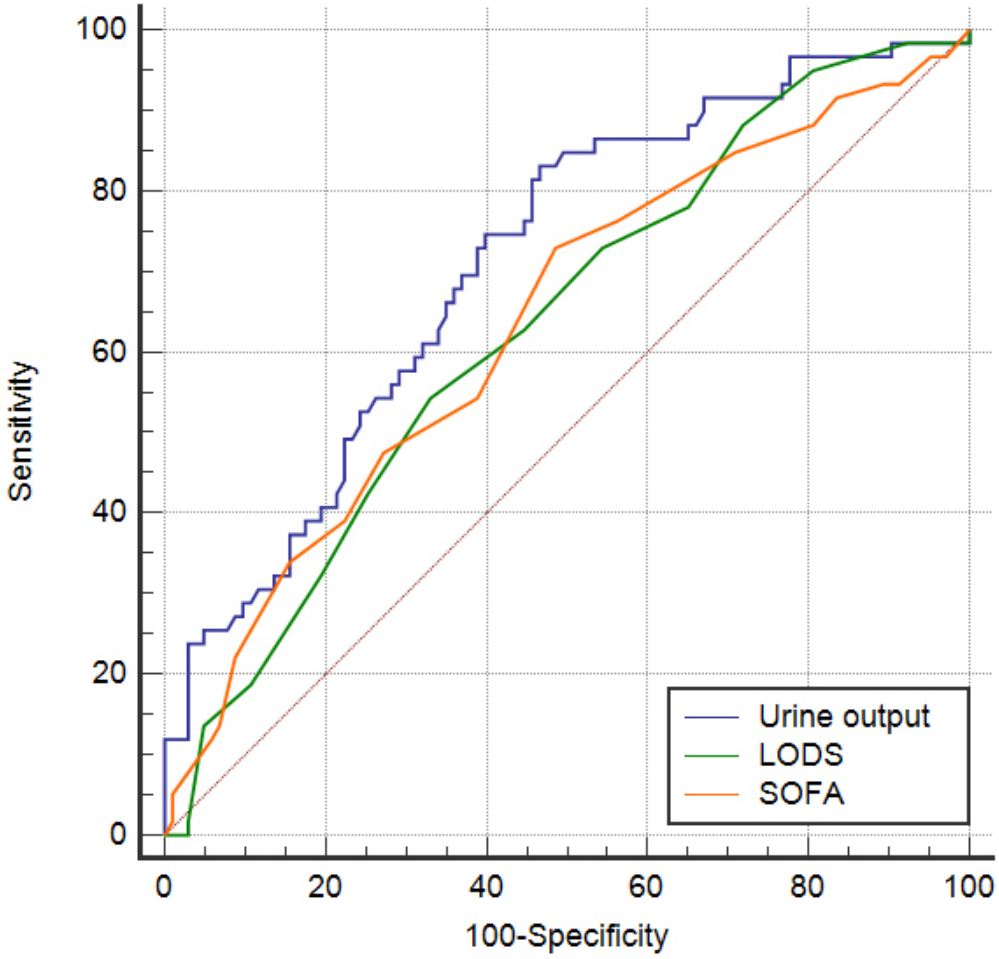


**FIGURE 1. ROC curves of urine output, LODS and SOFA.** Abbreviations: ROC = Receiver the Operating Characteristic, LODS = Logistic Organ Dysfunction System, SOFA = Sequential Organ Failure Assessment.

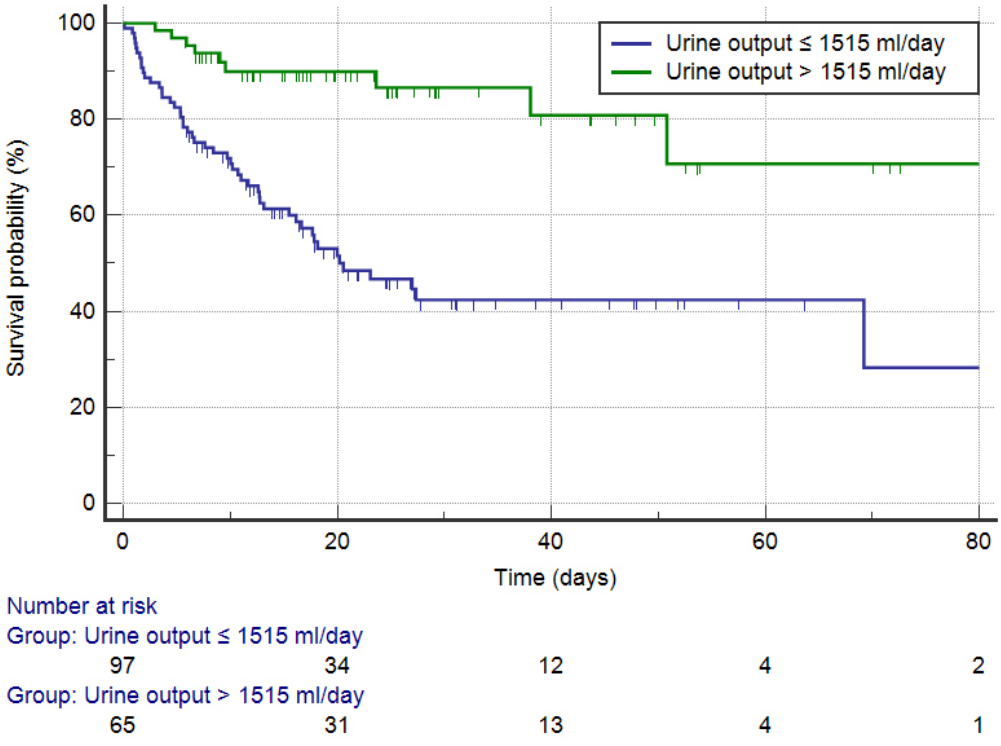


**FIGURE 2. Kaplan-Meier survival curves by urine output category (log-rank $p < 0.0001$).**

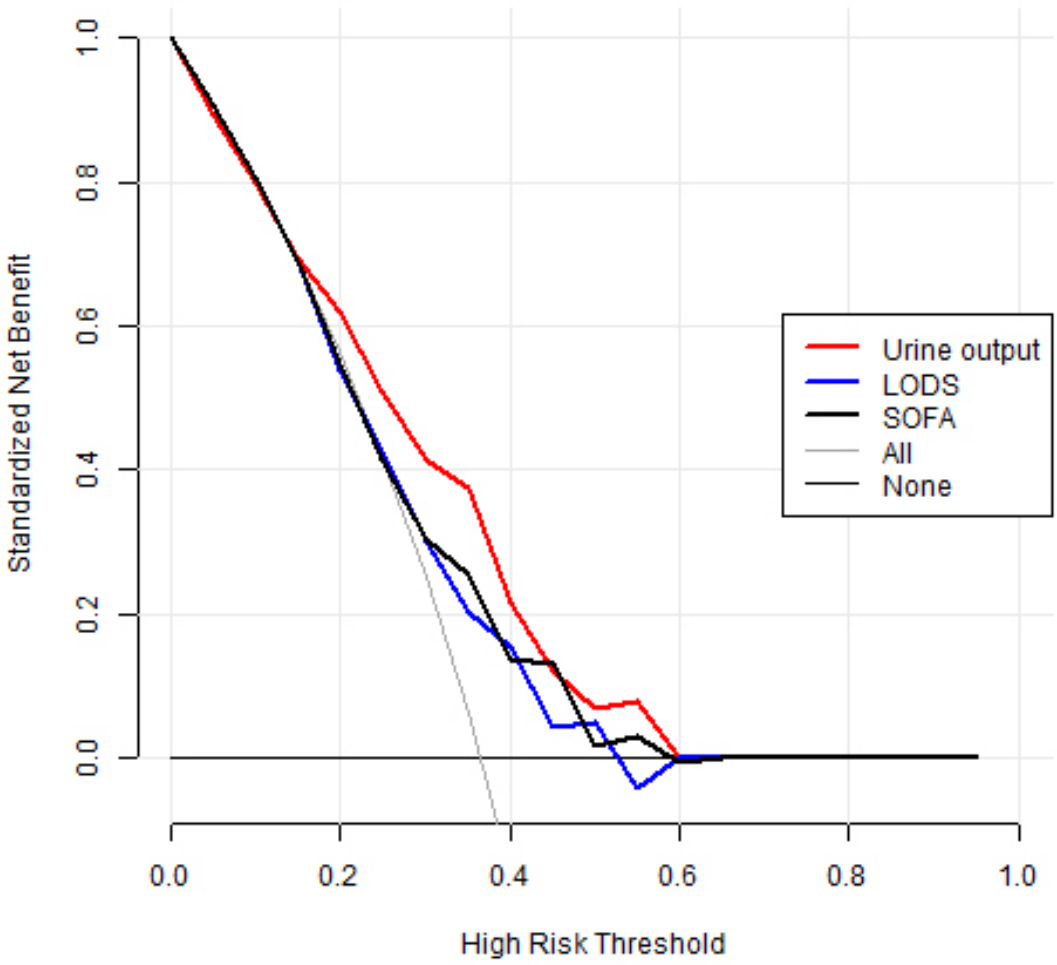


**FIGURE 3. DCA curves of urine output, LODS and SOFA.** Abbreviations: DCA = Decision Curve Analysis, LODS = Logistic Organ Dysfunction System, SOFA = Sequential Organ Failure Assessment.

overload, further impairing oxygenation and oxygen transport in lung tissues, inducing and aggravating ARDS, and resulting in organ dysfunction such as the heart and brain. Fluid overload inevitably increases preload, leading to circulatory failure and further increasing in-hospital mortality [10, 18]. The above factors might be the underlying reasons for the higher in-hospital mortality in patients with sepsis-related ARDS due to decreased UO. Shen *et al*. [11] reported that the ability to excrete higher volumes of urine could indicate relatively better organ function and less fluid accumulation, which in turn reduced fluid overload in patients and corresponded to lower mortality.

Although the predictive value and clinical net benefit of UO in predicting in-hospital mortality in sepsis-associated ARDS patients were similar or even superior to the two well-known scoring systems, the use of LODS and SOFA still have some limitations for the actual clinical application of UO. It is generally believed that UO appears to be more closely related to renal function, causing clinicians to focus more on renal impairment in patients with decreased UO while ignoring increased mortality. However, previous studies showed that a decrease in urine output might not necessarily represent the damage to renal function but rather the protective mechanism of the kidney itself in achieving successful compensation [18, 19]. We found no difference in the combined AKI, ECMO treatment and diuretic use between the non-survival group and the survival group, which confirms the rationality of this renal self-protection mechanism. Therefore, for the sepsis-associated ARDS patients in this study, we emphasize that the increased mortality associated with decreased UO should be independent of renal function. Blood pressure is also closely related to UO. A prolonged hypotensive state can lead to lactic acidosis, which further deteriorates cardiac function and aggravates the hypotensive state, forming a vicious circle that, if not managed in time, could lead to multiple organ failure and death [10]. Among the patients in this study, the mean arterial pressure in the non-survival group was lower than in the survival group. However, after adjusting for mean arterial pressure in multivariate regression analysis, UO was still an independent risk factor for in-hospital mortality. In contrast, mean arterial pressure was no longer associated with in-hospital mortality, suggesting that the contribution of low UO to death could be much greater than that of low blood pressure.

The measurement of UO is convenient and economical. Currently, advanced life support technologies such as ECMO have not been popularized in some areas where medical resources are lacking. In this case, early identification of patients

with a high risk of death is particularly important because early intervention could reduce mortality. Since pulmonary edema due to increased vascular permeability is a hallmark of ARDS [20], sepsis-associated ARDS also requires stringent fluid management. Optimizing fluid status is a fundamental issue in critical care practice, and improving pulmonary edema in ARDS patients through active fluid management has important clinical implications. Thus, reliable indicators to assist fluid management are urgently needed in this situation. UO is an important modifiable parameter in fluid management and an excellent indicator for judging peripheral organ perfusion and body fluid load. Given the importance of UO in early goal-directed therapy (EGDT) [21] for sepsis/septic shock, especially for UO $\geq$0.5 mL/kg/h within 6 hours of early fluid resuscitation, we advocate that the role of UO in fluid management in sepsis-associated ARDS patients should be revisited. It must be pointed out that we do not recommend using UO alone to predict the mortality of these patients because the prediction efficiency of a single indicator could be low and less reliable. Thus, UO could be considered when building new prediction models.

Although this present study benefits from the rigorous design of the MIMIC-IV database when collecting patient information and ensuring the authenticity of the data, this study still had certain limitations. First, UO can be easily affected by fluid intake, and in this study, the exact fluid intake data (including water intake and diet) were unavailable, which might have affected the stability of the results. Second, this study only examined the UO on the first day and did not assess the impact of dynamic changes in UO on mortality, which might have underestimated its value. Furthermore, the diagnosis data collected in this study were all at discharge, which did not mean that the patients developed sepsis and ARDS on the day of admission, so the predictive value of UO could also be overestimated. Lastly, this study was based on the U.S. population data, and whether the results apply to patients in other countries or regions, or patients of other races, remain to be clarified. Therefore, it is necessary to design rigorous prospective clinical randomized controlled trials to determine the real-world effects of UO on in-hospital mortality in sepsis-associated ARDS patients.

## 5. Conclusions

Decreased UO was identified as an independent risk factor for in-hospital mortality in patients with sepsis-associated ARDS, and UO demonstrated moderate efficacy (AUC = 0.712) in predicting in-hospital mortality. When UO was used to predict in-hospital mortality in patients with sepsis-related ARDS, the clinical net benefit was higher than that of LODS or SOFA. Due to the limitations of this retrospective study, rigorously designed prospective clinical randomized controlled trials are still needed to confirm these findings.

### AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

### AUTHOR CONTRIBUTIONS

FLC and YTL—designed the research study. FLC and YTL—performed the research. YKL—analyzed the data. FLC and TYH—wrote the manuscript. All authors read and approved the final manuscript.

### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study required neither informed consent from the patients nor ethical review and complied with the Declaration of Helsinki.

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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