Aspartate transaminase/alanine transaminase ratio as a significant prognostic factor in patients with sepsis: a retrospective analysis

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Research

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Abstract

Background: The study was performed to investigate the relationship between aspartate transaminase/alanine transaminase ratio (DRR) and long-term mortality among patients diagnosed with sepsis or septic shock.

Methods: We conducted a retrospective study among adult septic patients who were admitted to surgical intensive care unit (ICU) of the Chinese People's Liberation Army (PLA) General Hospital from January 2014 to December 2018. Baseline characteristics were compared between survivors and non-survivors. We applied univariate as well as multivariate Cox regression analyses to evaluate DRR in relation to 180-day mortality. The potential prognostic value of DRR in predicting mortality rate was assessed by receiver operating curve (ROC) analysis. Besides, we conducted subgroup analysis by stratifying patients via optimal DRR cut-off value.

Results: We included a total number of 183 patients in the current study, 44 (24%) patients died within 180-day hospitalization. Univariate and multivariate Cox analysis revealed that DRR was an independent predictor of 180-day mortality (hazard ratio [HR] 1.421, 95% confidence interval [CI] 1.073-1.883, P = 0.014). The predicting accuracy of 180-day mortality for DRR was presented as ROC with an area under the curve (AUC) of 0.708 (95% CI 0.629–0.786, P < 0.001). As we stratified all enrolled patients into two groups by using the optimal cut-off value of 1.29, we observed a significantly higher mortality in patients with relatively high DRR.

Conclusions: An elevated DRR was associated with higher 180-day mortality among septic patients, and DRR might be an optimal marker for predicting the long-term mortality of sepsis. More prospective and randomized trials are needed to confirm the prognostic value of DRR.

1 Introduction

Sepsis is a life-threatening syndrome caused by dysregulated host response to infection, which leads to multiple organ dysfunction and even death [1, 2]. With the increase of the elderly population and greater recognition, the morbidity and mortality of sepsis show a trend of gradual increase, the Intensive Care Over Nations (ICON) did an international audit of ICU patients worldwide and showed that the morbidity and mortality of sepsis were 29.5% and 25.8%, respectively [3, 4]. The latest cross-section study conducted in mainland China revealed that sepsis affected 20.6% patients admitted to ICUs with a 90-day mortality of 35.5% [5]. Although great progress has been made in the early recognition and treatment of sepsis and septic shock, it still remains the leading cause of death among patients admitted to ICU owing to a lack of efficient yet specific therapies [6, 7]. Meanwhile, the high mortality of septic patients is also largely attributed to the shortage of sensitive yet specific biomarkers or scoring systems, which are capable of predicting poor outcomes in early phase [8]. However, the current used indicators or scoring systems of sepsis long-term prognosis has the disadvantage of imprecision and inaccessibility. Thus, it is imperative

to introduce novel biomarkers as well as refine the scoring systems to accurately yet efficiently assess the mid- or long-term outcomes of septic patients.

As the largest organ, liver plays an indispensable role in maintaining homeostasis of metabolism and immunomodulatory [9]. Evidences have shown that the liver is one of the most vulnerable organs under septic exposure, and once septic patients develop liver dysfunction or failure, the mortality risk will significantly increase [10]. Therefore, it is reasonable to believe that some indicators of liver injury may be correlated with the prognosis of septic patients. As we all known that the alanine transaminase (ALT) and aspartate aminotransferase (AST) have long been regarded as the most commonly used biological indicators for evaluating progression of multiple liver diseases [11]. DRR represented the ratio of the serum activities of AST to ALT, which was originally used to clarify disparate causes of liver damage [12]. Recently, ALT, AST and DRR were reportedly to be important prognostic indicators for various malignant tumors, including multiple myeloma, colonic carcinoma, pancreatic carcinoma and so on [13–19].

The distribution of AST is noted in different tissues and organs, which presents with extensive elevation under expose to not only liver damage but other conditions with great need in high metabolic activity, especially for tumor progression [20, 21]. In addition to malignant tumors, previous studies also indicated that these biomarkers were also associated with the development and progression of acute ischemic stroke, renal dysfunction, respiratory dysfunction, peripheral arterial occlusive disease [22–25]. As these diseases are accompanied by abnormalities in cell metabolism, an increase in anaerobic glycolysis tends to cause a disproportionate increase in AST and ALT [26].

Of note, sepsis shares several pathophysiological similarities with malignancy and other diseases, including immune compromised state, nutrient deficiency, abnormality of cell metabolism [27]. In addition, liver injury is commonly complicated in septic condition, which makes DRR a potentially ideal biomarker to predict the poor prognosis of septic patients. To the best of our knowledge, no studies have specifically evaluated the predictive value of DRR in the prognosis of septic patients. Thus, the aim of the current study was to investigate the relationship between DRR and long-term clinical outcomes of sepsis patients.

2 Materials And Methods

2.1 Subjects and study design

This single-center retrospective study involved septic patients who were admitted to surgical ICU of a tertiary hospital, the First Medical Center of Chinese People's Liberation Army (PLA) General Hospital from January 2014 and December 2018. All adult patients (aged >18 years) meeting the Surviving Sepsis Guidelines for the diagnosis of sepsis (Sepsis 3.0) were potentially eligible for this study. We excluded patients who (1) died within 24 hours after admission; (2) were transferred to our hospital over 72 hours since injury; (3) had any acute or chronic liver disease, including acute alcoholic liver injury, chronic

hepatitis, cirrhosis, primary liver cancer; (4) were prescribed with liver-eliminated drugs previously; (5) had incomplete medical data record. All enrolled patients signed informed consent forms and expressed support for our study. This study was complied with the Declaration of Helsinki and was approved by the Committee on the Ethics of Medicine, First Medical Center of Chinese PLA General Hospital in June 30, 2019.

2.2 Data extraction process

The electronic patient record system was applied for collecting medical data of all enrolled patients, including patients' demographic characteristics, body mass index (BMI), source of infection, comorbidities, hospital length of stay (LOS). Moreover, clinical interventions, number of operations, blood transfusion volume and results of laboratory tests were also collected. Of note, disparate prognostic score of each patient was assigned within 24 hours after admission, including sequential organ failure assessment (SOFA) score and acute physiology and chronic health evaluation II (APACHE II) score. We selected all-cause 180-day mortality as the primary endpoint.

The DRR during admission is calculated by AST/ALT. Of note, the levels of AST and ALT were measured by colorimetric methods within 24 hours since admitting to the surgical ICU of our center.

2.3 Statistical analysis

All statistical analyses were conducted by the IBM SPSS Statistics 24 software. As stratifying by 180-day survival status, baseline characteristics of enrolled patients were compared accordingly. Continuous data were presented as mean (standardized differences) or median (interquartile range), while categorical/ranked data were documented as count (percentage). Student t-test, Mann–Whitney U test or Chi-squared test were applied as appropriate for the comparison of listed variables.

Univariate and multivariate analyses were performed with Cox regression models to assess the effect of DRR and other variables on primary outcome. Variables that had a significance of $P < 0.1$ in each univariable analysis were subsequently incorporated into multivariate Cox regression analysis by using "Enter" method. Factors with an adjusted $P < 0.05$ in multivariate analysis were considered as independent predictors associated with 180-day mortality.

The potential prognostic value of the DRR was assessed by using ROC curve analysis. An optimal cut-off value was determined in accordance with the maximum of Youden index at this point. Meanwhile, we further conducted subgroup analysis by dividing patients into high and low DRR group based on optimal cut-off value. In addition to the comparison of baseline characteristic between those two groups, the effect of DRR level on septic patients' 180-day survival was analyzed with Kaplan–Meier method as well, in which P value of Log-rank test lower than 0.05 was deemed as statistical significance.

3 Results

3.1 Patients enrollment

There were 261 adult patients admitted to the surgical ICU during our study period, who met the Sepsis 3.0 criteria and were potentially eligible for screening. Septic patients who transferred to our center over 72 hours after initial injury (n = 45), had acute or chronic liver disease (n = 20), stayed less than 24 hours in ICU (n = 8), and had incomplete data (n = 5) were excluded. Consequently, 183 patients were enrolled in the current study. The detailed process of enrollment was shown in *Figure 1.*

As summarized in *Table 1,* the baseline characteristics of incorporated patients were comparedbetween survivors and non-survivors group. Among 183 septic patients, 139 patients (76%) were alive after 180-day follow-up. Compared with the survival group, patients in the non-survivors group were relatively older (75.50 ± 16.98 vs 61.05 ± 15.76; $P < 0.001$) and had lower BMI (22.40 ± 3.88 vs 24.08 ± 3.94; $P = 0.014$). As for the bioindicators, the serum levels of IL−6 (205.50 [91.26, 938.05] vs 55.00 [27.41, 117.40] pg/ml, $P < 0.001$), DRR (2.16 ± 0.88 vs 1.64 ± 1.23, $P = 0.010$), creatinine (185.63 ± 174.69 vs 127.27 ± 106.32 umol/L, $P = 0.041$) and urea nitrogen (15.12 ± 10.14 vs 10.95 ± 7.58 mmol/L, $P = 0.015$) in the non-survivors group were significantly higher compared to those of the survivors group. Clearly, patients had more deteriorative prognostic score in non-survival group, including SOFA score (8.05 ± 3.62 vs 6.38 ± 2.98, $P = 0.003$) and APACHE score (17.39 ± 5.36 vs 12.08 ± 4.78, $P < 0.001$). Besides, prolonged hospital LOS (15 [5, 28.75] vs 10 [6, 19] days, $P = 0.034$) as well as increased requirement of red blood cell (RBC) transfusion [6.86 [2.40, 20.81] vs 0 [0, 4.1] units, $P < 0.001$] were also observed in non-survivor arm. Additionally, the most common source of infection in the survival and non-survival groups was the abdomen and lungs, respectively. In terms of clinical interventions, in addition to tracheotomy, the frequency of mechanical ventilation, renal replacement therapy (RRT) and deep vein catheterization in the non-survival group were significantly higher than those in the survival group. Of note, gender and prevalence of other relevant comorbidities were comparable between two groups.

3.2 Predictors of 180-day mortality

To identified the risk factors of increased 180-day mortality, we conducted Cox regression analysis accordingly (*Table 2).*. In univariate analyses, age, woman, procalcitonin, DRR, creatinine, urea nitrogen, SOFA score, APACHE II score, as well as transfusion volume were potential risk factors of increased mortality within 180 days. As shown in multivariate analyses, DRR remained its statistical significance after adjusting for other confounders (HR = 1.421, 95% CI 1.073–1.883, $P = 0.014$), indicating DRR was independently associated with 180-day mortality among patients diagnosed with sepsis or septic shock. In addition, we have also demonstrated that age (HR = 1.043, 95% CI 1.013–1.074, $P = 0.004$), procalcitonin (HR = 0.984, 95% CI 0.973–0.996, $P = 0.011$), APACHE II (HR = 1.112, 95% CI 1.023–1.210, $P = 0.013$) were significantly associated with increased 180-day mortality.

3.4 Receiver operator characteristics analyses

The SOFA score showed a moderate predictive value for mortality after 180 days (area under the curve 0.636;95% CI 0.543–0.730; *P* = 0.006). A best cut-off value of 6.5 for the SOFA score revealed a sensitivity and specificity of 68.0% and 58.0%, respectively. The diagnostic accuracy for the DRR was more reliable with an area under the curve 0.708 (95% CI 0.629–0.786, *P* < 0.001). DRR of 1.29 was determined as the best cut-off value with a sensitivity of 89% and a specificity of 62.0%. Additionally, ALT, AST, creatinine and urea nitrogen showed low predictive values for 180-day mortality. The characteristic of ROC curves for those indicators were shown in *Figure 2* and *Table 3.*

3.5 Subgroup analyses stratified by De Ritis ratio value

Based on optimal cut-off value calculated by ROC analysis, patients were divided into high DRR and low DRR groups. As presented in *Table 4,* age (68.20 ± 17.26 vs 59.47 ± 15.80 years, *P* = 0.001), IL–6 (89.96 [32.61, 275.35] vs 57.43 [32.39, 122.35] pg/ml, *P* = 0.016), creatinine (165.46 ± 156.24 vs 108.04 ± 60.24 umol/L, *P* = 0.001), urea nitrogen (13.55 ± 9.11 vs 9.76 ± 6.86 mmol/L, *P* = 0.002), APACHE II score (14.39 ± 5.14 vs 11.94 ± 5.49, *P* = 0.002), transfusion volume (2.95 [0, 14.80] vs 0 [0, 3] units, *P* < 0.001) were significantly higher among septic patients with relatively high DRR compared to those with low DRR, while ALT (17.20 [10.35, 41.05] vs 37.10 [24.75, 89.70] U/L, *P* < 0.001) was lower in this group.

After performing Kaplan–Meier analysis and Log-rank test, we demonstrated that 180-day mortality was significantly lower in patients with DRR value < 1.29 compared to those with DRR values ≥ 1.29 (6.49% vs 36.79%, *P* < 0.001] (*Figure 3)*.. Similarly, the trend of low or high SOFA score towards 180-day survival was plotted and analyzed as well. Evidently, DRR cut-off value had a better performance in discriminating 180-day prognosis for septic patients compared to optimal cut-off value of SOFA score, and a superior 180-day survival could be identified in patients with low DRR.

4 Discussion

4.1 Major findings

DRR has been reported closely related to the adverse clinical outcomes of several malignancies or other diseases. However, to our knowledge, no literature was available with regard to the predictive significance of DRR in prognosis of septic patients, and the current work may be the first to directly evaluate correlation between the DRR and long-term mortality among patients diagnosed with sepsis or septic shock.

In this study, we demonstrated that DRR at admission was a potential predictor of increased 180-day mortality among septic patients. The DRR of non-survivors were relatively higher than those from the survivors group. Besides, after performing univariate and multivariate Cox regression analyses, we revealed that DRR was independently associated with 180-day mortality among patients with sepsis or

septic shock. The predicting accuracy of DRR was analyzed by using ROC curve, which indicated a better performance of DRR than other indicators, including SOFA score, ALT, AST, creatinine and urea nitrogen, in predicting 180-day mortality. As we stratified all enrolled patients by applying optimal DRR cut-off value of 1.29, a superior 180-day survival could be identified in septic patients with relatively low DRR compared to those with DRR higher than 1.29. Meanwhile, compared to optimal cut-off value of SOFA score, DRR cut-off value had a better performance in discriminating long-term prognostic condition of septic patients.

4.2 Relation to previous works

In 1957, professor De Ritis initially proposed that the ratio of AST to ALT could distinguish the causes of acute hepatitis, which was further named as DRR and applied for identifying the severity of viral hepatitis and alcoholic hepatitis. Recent studies have revealed a close relationship between DRR and the prognosis of some other disease such as malignant tumors. In 2013, Tan et al. retrospectively analyzed 84 patients with distal cholangiocarcinoma after pancreatoduodenectomy and found that in addition to lymph node invasion and nerve invasion, DRR>2.0 was also an effective predictor for long-term survival of patients with distal cholangiocarcinoma [28]. In 2015 Bezan et al. retrospectively analyzed the clinical data of 698 European patients with non-metastatic renal cell carcinoma and found that preoperative DRR was closely related to prognostic factors such as tumor pathological T staging and tissue necrosis, and increased DRR (> 1.26) was an independent risk factor for adverse outcomes[29]. In 2016, Nishikawa et al. found that DRR was one of the independent predictors of relapse-free survival after single-factor and multi-factor analysis of 109 patients with epithelial carcinoma of the upper urethra after nephrectomy[30]. In 2019, Yun-Sok Ha et al. retrospectively analyzed the clinical data of 118 patients with gallbladder cancer and found that increased DRR was significantly correlated with poor prognosis, which may improve the accuracy of predicting adverse outcomes in gallbladder cancer patients[13]. In addition, DRR is also closely related to the prognosis of multiple myeloma, pancreatic cancer, small-cell lung cancer, and other malignant tumors. Some studies had shown that not only tissue damage, but also pathological cell proliferation would cause a disproportionate increase in AST and ALT, which could be explained from Warburg effect and glycolysis[20, 21, 26].

Not only in malignant tumors, the predictive value of DRR in other diseases is also noteworthy. For example, DRR was the independent risk factors of acute ischemic stroke (AIS) and peripheral arterial occlusive disease, as reported by Gao, F. and Rief, P. respectively[22, 23]. Rahmani J et al. found that high levels of gamma-glutamyl transpeptidase, A Lkaline Phosphatase, AST/ALT were all associated with an increased mortality rate of patients with cardiovascular disease through systematic review and meta-analysis including more than 1 million participants[31]. The potential explanation is issued by a better distributive capacity of AST than ALT, which is prone to be disturbed or affected by various factors[32].

4.3 Interpretations

As the most commonly used indicator of liver injury, why is the ratio of AST to ALT (DRR) closely related to the poor prognosis of patients with sepsis? The reasons may be as follows: Firstly, both ALT and AST were mainly distributed in the cytoplasm and mitochondria of hepatocytes, which were released into intercellular space as a result of increasing damage of liver cells. Therefore, the elevation of ALT and AST was positively correlated with the degree of liver damage[33]. As we know, the major characteristic of sepsis deterioration is intractable tissue or organ damage, especially the liver as a sign of poor prognosis in septic patients[34]. The dysfunction or failure of liver is responsible for disease progression and even causes unexpected death[35]. Clinical data indicated that septic patients were more likely to develop liver dysfunction, which did brings about significantly increased risk of dying during hospitalization [10, 36]. Secondly, studies have shown that the elevation of ALT and AST is related to the anaerobic fermentation of glucose[12, 21]. Septic patients are often in a high metabolic state that requires a large amount of nutrients and oxygen, which causes temporary hypoxia in multiple tissues and cells. At the same time, collapse of liver microcirculation is responsible for aggravated tissue ischemia and hypoxia under sepsis exposure[30]. Lack of nutrients and oxygen can lead to the occurrence of hypoproteinemia and hyperlactic acidemia in septic patients. Several studies have demonstrated that both hypoproteinemia and hyperlactic acidemia are closely associated with the poor prognosis of septic patients[37–39]. Other researchers have pointed out that AST was critically involved in glycolysis due to its important role in malate-aspartic acid shuttle, which might also account for increased DRR in septic patients[40]. To sum up, the DRR value might partially reflects the impairment of liver function and the lack of nutritional support, which could be a potential indicator for long-term clinical outcomes of septic patients.

4.4 Clinical implications

In the past ten years, even though early diagnosis and treatment have presented great progress, sepsis is still one of the leading causes of death among patients in ICUs[6]. Considering the large population in China, sepsis will be a great threat to people's life and a heavy burden on the health care system. Therefore, early identification and timely prevention will undoubtedly improve the prognosis of patients with sepsis[41]Researches showed that multiple factors, including patient admission scores, patients comorbid disease and demographic indicators like age, gender, race, were capable of affecting the prognosis of patients with sepsis, accompanied by numerous laboratory indexes such as neutrophil to lymphocyte ratio, platelet, albumin, procalcitonin, C-reactive protein, creatinine, urea nitrogen and lactate [38, 39, 42–47]. Continuous monitoring of these indicators is conducive to early identification and timely treatment of septic patients.

At present, there is still no ideal clinical index that can accurately and sensitively predict the poor prognosis of septic patients, especially for middle and late mortality prediction. The commonly used SOFA and APACHE scoring systems show disadvantages of low sensitivity and complex calculation. How to find a simple and fast clinical prediction index is difficult yet urgent. The results of this study suggest that DRR is one of the risk factors for poor prognosis of sepsis patients, which is helpful for clinicians to

stratify treatments based on prognostic risks of these patients. As an easily and accessibly determined indicator, DRR is expected to be an ideal prognostic factor in septic patients and promotes exploring accurate treatments of sepsis.

The increase of DRR in septic patients is closely related to the liver injury and nutritional disorder. Therefore, on the one hand, the clinicians can monitor the changes of liver function and further take corresponding measures to reduce the occurrence of septic liver injury. On the other hand, the nutritional status of septic patients can be improved by strengthening their nutritional support. Undoubtedly, that improvements of liver function and nutritional status are conducive to the rapid recovery of septic patients, which are important factors influencing the prognosis of sepsis.

4.5 Limitations

The current study was subject to several limitations. Firstly, in view of the single-center retrospective design of the present study, dynamic alterations in DRR were not observed during hospitalization, though we provided that an elevated DRR at admission was significantly associated with higher 180-day mortality in septic patients. This relationship needs more prospective cohort studies or multi-center RCTs to testify in the future. Secondly, the sample size included in this study was relatively small, which potentially introduce patient's selection biases. Thirdly, the specificity of DRR in predicting 180-day mortality of septic patients is relatively low (only 62%). Other undetected diseases, especially liver-related diseases, may affect the serum levels of DRR, which could undoubtedly influence the prediction efficiency of DRR on the prognosis of septic patients. Perhaps adding DRR to the existing prognosis scoring systems might improve its predicted effects. Fourthly, we excluded patients with acute or chronic liver diseases and those who prescribed with liver-eliminated drugs, which to some extent narrowed the application scope of DRR. As with sepsis patients complicated with liver disease, DRR is not appropriate for accurate prediction. Finally, other confounders like the use of various medications were not incorporated as variates, which might have effect on the prognosis of septic patients. Although this effect was trivial and will not reverse our results, it might be more convincing to take these factors into consideration.

5 Conclusions

In conclusion, wet found that an elevated DRR was significantly associated with higher 180-day mortality among septic patients, and DRR might further be an optimal biomarker for predicting the mid-stage and late-stage prognosis in sepsis. Clinicians should closely monitor the changes in DRR at admission and after hospitalization. Also, the liver function and nutritional status of septic patients should be improved to increase their survival rate. More prospective cohort studies or multi-center randomized controlled trials are needed to conform the predictive power of DRR in predicting mid-stage and late-stage mortality of septic patients.

Declarations

Ethics approval and consent to participate

All enrolled patients signed informed consent forms and expressed support for our study. This study was complied with the Declaration of Helsinki and was approved by the Committee on the Ethics of Medicine, First Medical Center of Chinese PLA General Hospital in June 30, 2019.

Consent for publication

Not applicable.

Availability of data and materials

The datas used to support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors have declared that no competing interests exist.

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Author contributions

DXH and YMY co-conceived the study. ZPY, RQY, RC, LSY, LYX and ZSY participated in material collection. ZPY, YRQ, RC wrote and edited the manuscript. ZPY undertook the statistical analyses. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline Characteristics for all patients stratified by survivors and non-survivors after 180 days.

Characteristic	180 days.		p value
	Survivors (n=139)	Non-survivors (n=44)	
Age (yrs), mean (SD)	61.05 (15.76)	75.50 (16.98)	**0.001**
Male, n (%)	76 (54.7)	31 (70.5)	0.064
BMI, mean (SD)	24.08 (3.94)	22.40 (3.88)	**0.014**
Bioindicator			
Hemoglobin(g/L), mean (SD)	103.65 (20.46)	100.09 (22.00)	0.325
CRP(mg/L), mean (SD)	11.35 (7.52)	11.53 (7.49)	0.889
Procalcitonin(ng/ml), median (IQR)	11.92 (2.98,76.37)	9.16 (3.17,22.82)	0.329
IL-6(pg/ml), median (IQR)	55.00 (27.41,117.40)	205.50 (91.26,938.05)	**<0.001**
ALT(U/L), median (IQR)	32.90 (15.30,78.70)	20.15 (9.25,41.50)	0.066
AST(U/L), median (IQR)	34.30 (19.90,67.60)	41.45 (21.45,89.43)	0.474
DRR, mean (SD)	1.64 (1.23)	2.16 (0.88)	**0.010**
Serum albumin(g/L), mean (SD)	29.04 (5.24)	28.66 (8.02)	0.717
Total bilirubin(umol/L), median (IQR)	18.90 (11.90,38.30)	14.20 (8.53,30.40)	0.558
Creatinine(umol/L), mean (SD)	127.27 (106.32)	185.63 (174.69)	**0.041**
Urea nitrogen(mmol/L), mean (SD)	10.95 (7.58)	15.12 (10.14)	**0.015**
Prognostic scoring systems, mean (SD)			
SOFA	6.38 (2.98)	8.05 (3.62)	**0.003**
APACHCE Ⅱ	12.08 (4.78)	17.39 (5.36)	**<0.001**
Source of Infection (n, %)			
Lung	36 (25.9)	25 (56.8)	**0.029**
Abdominal	59 (42.4)	12 (27.3)	0.072
Urinary tract	27 (19.5)	4 (9.1)	0.111
Skin and soft tissue	6 (4.3)	1 (2.3)	0.869
Others	11 (7.9)	2 (4.5)	0.674
Comorbidity (n, %)			
Hypertension	55 (39.6)	21 (47.7)	0.338
Diabetes	38 (27.3)	10 (22.7)	0.545
CHD	13 (9.4)	13 (29.5)	**0.001**
Cerebral Infarction	19 (13.7)	9 (20.5)	0.276
COPD	7 (5.0)	3 (6.8)	0.650
CRI	15 (10.8)	6 (13.6)	0.606

CHF	4 (2.9)	3 (6.8)	0.461
Malignant neoplasm	9 (6.5)	3 (6.8)	0.936
Clinical intervention (n, %)			
Mechanical ventilation	34 (24.5)	18 (40.9)	**0.035**
Tracheotomy	6 (4.3)	4 (9.1)	0.404
RRT	61 (43.9)	38 (86.4)	**<0.001**
Deep vein catheterization	107 (77.0)	41 (93.2)	**0.017**
No. of operations, mean (SD)	0.71 (0.70)	0.98 (0.95)	0.085
Transfusion volume (units), median (IQR)	0 (0,4.1)	6.86 (2.40,20.81)	**<0.001**
LOS (d), median (IQR)	10 (6,19)	15 (5,28.75)	**0.034**

Abbreviations: BMI, body mass index; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DRR, De Rites ratio; SOFA, sequential organ failure score; APACHE, acute physiology and chronic health evaluation scoring system; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CRI, chronic renal insufficiency; CHF, chronic heart failure.; RRT, renal replacement therapy. LOS, length of stay.

Table 2. COX regression analysis of risk factors for 180-day mortality.

Variables	Univariate analyses			Multivariate analyses		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age	1.055	1.032,1.079	**<0.001**	1.043	1.013-1.074	**0.004**
Gender	0.557	0.291,1.064	**0.076**	0.784	0.397-1.618	0.510
Hemoglobin	0.993	0.978,1.007	0.328			
CRP	1.004	0.966,1.044	0.839			
Procalcitonin	0.989	0.980,0.999	**0.031**	0.984	0.973-0.996	**0.011**
Lactic acid	1.006	0.976,1.037	0.688			
DRR	1.265	1.052,1.520	**0.013**	1.421	1.073-1.883	**0.014**
Creatinine	1.002	1.001,1.004	**0.004**	1.003	1.000-1.006	0.093
Urea nitrogen	1.044	1.015,1.074	**0.003**	0.958	0.913-1.005	0.080
Fibrinogen	0.894	0.759,1.052	0.178			
D-Dimer	1.008	0.953,1.066	0.774			
SOFA	1.157	1.060,1.263	**0.001**	1.030	0.887-1.197	0.696
APACHE	1.172	1.112,1.234	**<0.001**	1.112	1.023-1.210	**0.013**
Transfusion Volume	1.040	1.020,1.061	**<0.001**	1.017	0.986-1.049	0.284

Abbreviations: BMI, body mass index; CRP, C-reactive protein; IL-6, Interleukin-6; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DRR, De Rites ratio; SOFA, sequential organ failure score; APACHE, acute physiology and chronic health evaluation scoring system; LOS, length of stay.

Bold numbers were statistically significant ($P < 0.05$).

Table 3. Characteristic of ROC curves

	Cut off value	Sensitivity	Specificity	AUC	95%CI	P-value
DRR	1.29	89	62	0.708	0.629-0.786	**<0.001**
SOFA	6.5	68	58	0.636	0.543-0.730	**0.006**
ALT	17.85	69	48	0.592	0.491-0.694	0.066
AST	54.20	46	68	0.536	0.436-0.636	0.474
Creatinine	144.5	48	78	0.622	0.521-0.722	**0.015**
Urea nitrogen	10.28	64	60	0.628	0.533-0.724	**0.010**

Abbreviations: DRR, De Rites ratio; SOFA, sequential organ failure score; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 4. Baseline Characteristics for all patients stratified by Low DRR and High DRR

Characteristic	DRR		p value
	Low DRR (DRR<1.29, n=77)	High DRR (DRR≥1.29， n=106)	
Age (yrs), mean (SD)	59.47 (15.80)	68.20 (17.26)	**0.001**
Male, n (%)	49 (63.6)	58 (54.7)	0.227
BMI, mean (SD)	24.21 (3.73)	23.28 (4.12)	0.120
Bioindicator			
Hemoglobin (g/L), mean (SD)	105.22 (19.96)	101.03 (21.37)	0.180
CRP (mg/L), mean (SD)	11.98 (7.57)	10.97 (7.44)	0.370
Procalcitonin (ng/ml), median (IQR)	11.92 (3.44，63.65)	10.82 (2.41，42.47)	0.462
IL-6 (pg/ml), median (IQR)	57.43 (32.39，122.35)	89.96 (32.61，275.35)	**0.016**
ALT (U/L), median (IQR)	37.10 (24.75，89.70)	17.20 (10.35，41.05)	**<0.001**
AST (U/L), median (IQR)	32.00 (19.90，50.75)	39.80 (21.10，95.65)	0.104
Serum albumin (g/L), mean (SD)	29.19 (5.23)	28.78 (6.53)	0.651
Total bilirubin (umol/L), median (IQR)	18.90 (12.80，46.20)	15.25 (10.18，31.60)	0.022
Creatinine (umol/L), mean (SD)	108.04 (60.24)	165.46 (156.24)	**0.001**
Urea nitrogen (mmol/L), mean (SD)	9.76 (6.86)	13.55 (9.11)	**0.002**
Prognostic scoring systems, mean (SD)			
SOFA	6.39 (3.12)	7.07 (3.27)	0.161
APACHCE Ⅱ	11.94 (5.49)	14.39 (5.14)	**0.002**
Source of Infection (n, %)			
Lung	15 (19.4)	46 (43.4)	**0.001**
Abdominal	34 (44.2)	37 (34.9)	0.205
Urinary tract	16 (20.8)	15 (14.2)	0.238
Skin and soft tissue	4 (5.2)	3 (2.8)	0.765
Others	8 (10.4)	5 (4.7)	0.140
Comorbidity (n, %)			
Hypertension	34 (44.2)	42 (39.6)	0.539
Diabetes	20 (26.0)	28 (26.4)	0.947
CHD	7 (9.1)	19 (17.9)	0.091
Cerebral Infarction	12 (15.6)	16 (15.1)	0.928
COPD	4 (5.2)	6 (5.7)	1.000

CRI	8 (10.4)	13 (12.3)	0.694
CHF	1 (1.3)	6 (5.7)	0.259
Malignant neoplasm	4 (5.2)	8 (7.5)	0.526
Clinical intervention (n, %)			
Mechanical ventilation	15 (19.5)	37 (34.9)	**0.022**
Tracheotomy	5 (6.5)	5 (4.7)	0.847
RRT	32 (41.6)	67 (63.2)	**0.004**
Deep vein catheterization	61 (79.2)	87 (82.1)	0.628
No. of operations, mean (SD)	0.66 (0.70)	0.85 (0.81)	0.106
Transfusion volume (units), median (IQR)	0 (0,3)	2.95 (0, 14.80)	**<0.001**
LOS (d), median (IQR)	9 (6,20)	12 (6,23)	0.435
Mortality (n, %)	5 (6.49)	39 (36.79)	**<0.001**

Abbreviations: BMI, body mass index; CRP, C-reactive protein; IL-6, Interleukin-6; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SOFA, sequential organ failure score; APACHE, acute physiology and chronic health evaluation scoring system; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CRI, chronic renal insufficiency; CHF, chronic heart failure.; RRT, renal replacement therapy. LOS, length of stay.

Figures

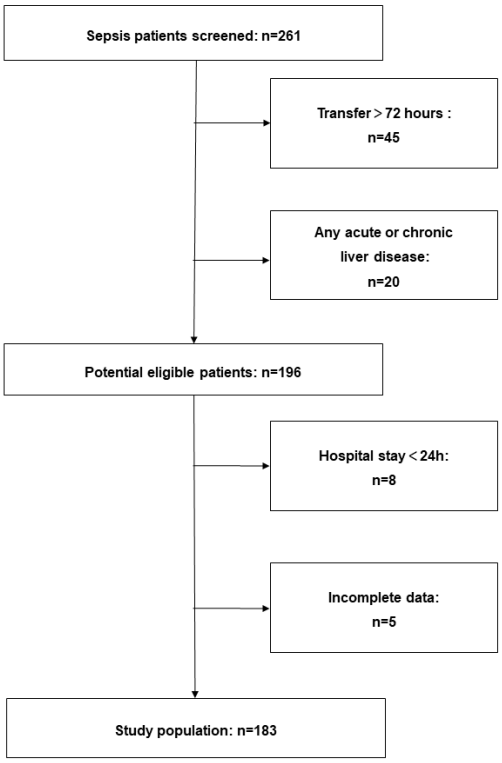

Figure 1

Flow diagram of screening and enrollment.

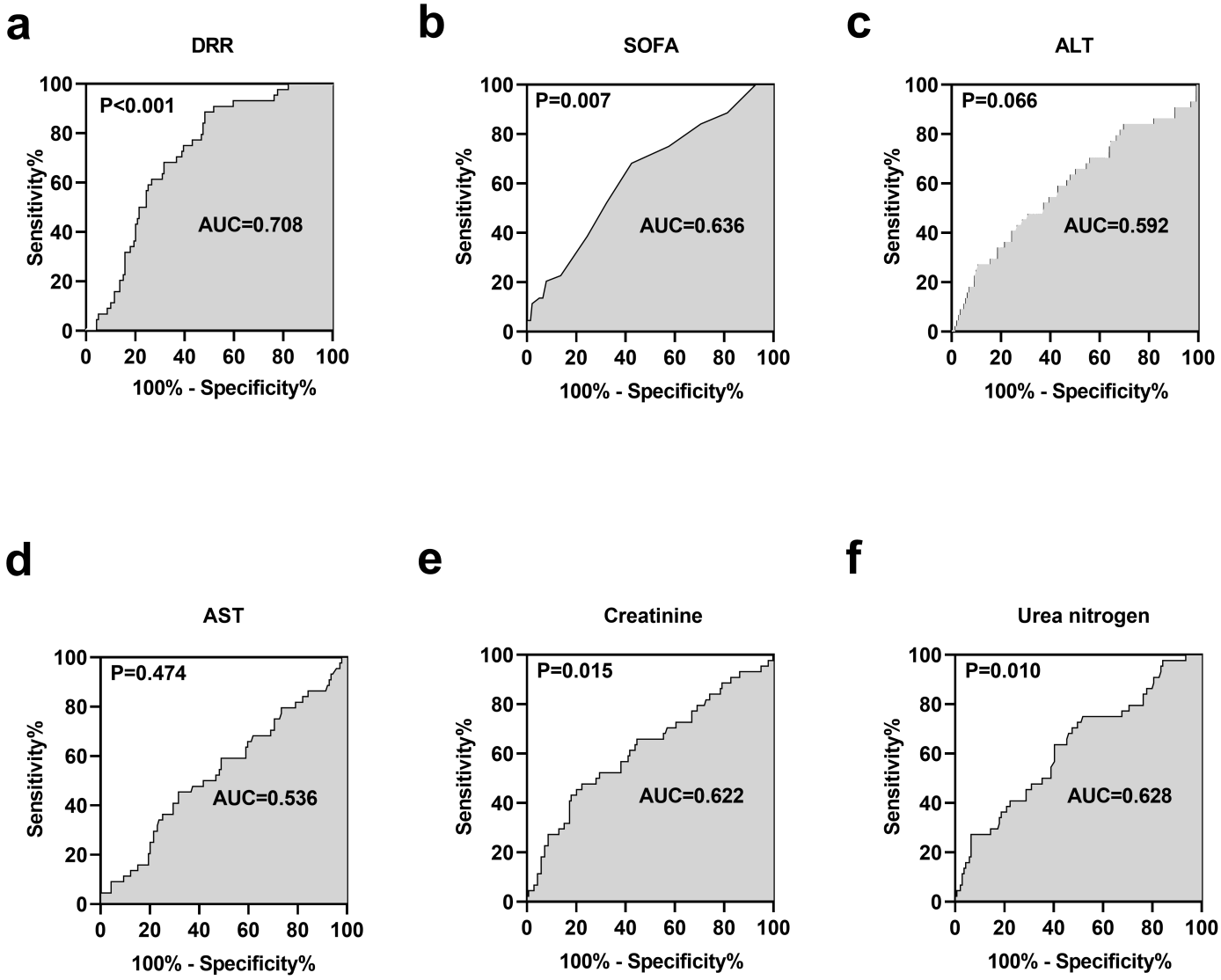

Figure 2

Receiver operator characteristic curve of variables for the prediction of 180-day mortality. (a) DRR. (b) SOFA. (c) ALT. (d) AST. (e) Creatinine. (f) Urea nitrogen. DRR: De Rites ratio; SOFA: sequential organ failure score; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

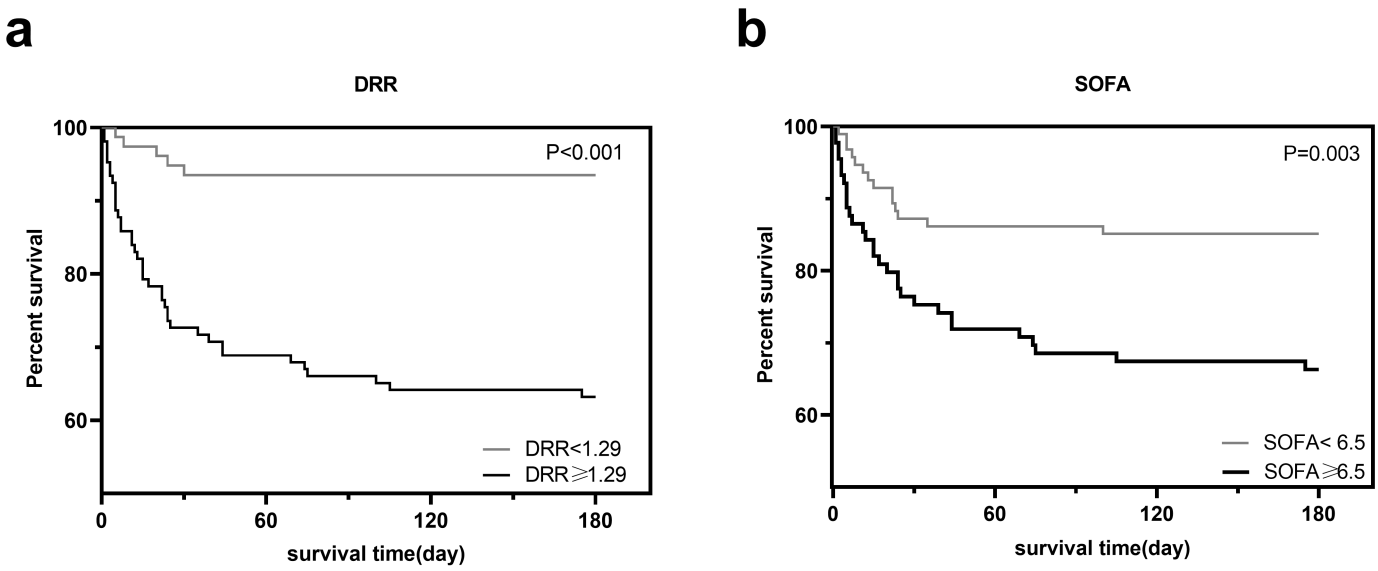

Figure 3

Kaplan-Meier survival curve for septic patients stratifying by DRR value and SOFA. (a) Comparing patients with a DRR<1.27 to those with a DRR≥1.27. (b) Comparing patients with a SOFA<6.5 to those with a SOFA≥6.5. DRR: De Rites ratio; SOFA: sequential organ failure score.