Predictive Value of Serum β2-Microglobulin for Outcomes in Patients with Acute Respiratory Distress Syndrome Caused by Bacterial Infection

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Research Article

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Abstract

Background

Acute respiratory distress syndrome (ARDS) is a heterogeneous disease with extremely high mortality. We hypothesized that the serum β2-microglobulin (β2MG) level would be elevated and be an independent risk factor for 28-day mortality in patients with ARDS.

Methods

We retrospectively enrolled 257 patients with ARDS caused by bacterial infection who were admitted consecutively into the Department of Pulmonary and Critical Care Medicine, Beijing Chao-Yang Hospital from January 1, 2015 to February 28, 2021. Patients were followed for up to 28 days from diagnosis and were divided into a survival group and non-survival group according to their clinical outcomes. The serum β2MG levels and other clinical data were collected. The relationship between serum β2MG levels and 28-day mortality was explored by performing a Cox regression analysis adjusted for age, updated Charlson comorbidity index, disorders of consciousness, septic shock, albumin level, cardiac troponin I level, procalcitonin level, lactic acid level, prothrombin time, and partial pressure of arterial oxygen/fraction of inspired oxygen ratio.

Results

In this cohort, 161 patients survived, and 96 patients died within 28 days of diagnosis, yielding a 28-day mortality of 37.4%. The median level of β2MG for all enrolled patients was 4.6 (interquartile range [IQR]: 2.9–8.5) mg/L. Higher β2MG levels were significantly associated with 28-day mortality when the β2MG level was analysed as a continuous variable (hazard ratio [HR]: 1.050; 95% confidence interval [CI]: 1.012–1.091; $P = 0.010$) and when it was categorized into tertiles (HR: 1.482; 95% CI: 1.069–2.045; $P = 0.018$). The serum β2MG level exhibited a diagnostic accuracy for predicting mortality that was not inferior to those of the Acute Physiology and Chronic Health Evaluation score ($P = 0.153$) and Sequential Organ Failure Assessment score ($P = 0.114$).

Conclusions

The level of serum β2MG is elevated and is an independent risk factor of 28-day mortality in patients with ARDS, suggesting that it has predictive value for the outcomes of these patients.

Background

Acute respiratory distress syndrome (ARDS) is a heterogeneous disease process that may be triggered by a variety of direct or indirect pulmonary injuries, such as pneumonia, aspiration, chest trauma, sepsis, and

acute pancreatitis. Despite the use of low tidal volume ventilation, conservative liquid strategies, and extracorporeal membrane oxygenation, the rate of mortality due to ARDS remains extremely high [1, 2]. Early detection of prognostic risk factors is very important for reducing ARDS mortality. Numerous studies have attempted to define contributors to ARDS mortality, with conflicting results [1, 3–6], which may be related to changes in clinical management strategy.

β2-microglobulin (β2MG) is an 11.8-kDa, non-glycosylated polypeptide that is present in all nucleated cells [7]. As a low-molecular-weight protein, β2MG is released into the circulation at a constant rate, freely filtered by the glomeruli, and completely reabsorbed and catabolized in the renal tubules. These properties may make it an ideal endogenous biomarker for estimating the glomerular filtration rate and acute kidney injury (AKI) [8–12]. Numerous studies have shown that the serum β2MG level is not only used in assessing renal function by estimating the glomerular filtration rate and monitoring the effects of treatment [13, 14] but also associated with a number of clinical states, including chronic inflammatory diseases, malignancies, and adverse outcomes in exacerbated chronic obstructive pulmonary disease and critical illnesses [12, 15–18]. ARDS is accompanied by an overwhelming inflammatory response and severe organ dysfunction, especially AKI. We hypothesized that for patients with ARDS, the serum β2MG levels would be elevated at the time of ARDS occurrence and would be related to poor prognosis.

Methods

Ethical Approval

This study was conducted in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards and was approved by the Ethics Committee of the Beijing Chao-Yang Hospital, Capital Medical University (No. 2020-ke-429).

Study Design and Population

We retrospectively enrolled adult patients (aged ≥ 18 years old) with ARDS (in accordance with the Berlin definition) [1] caused by bacterial infection who were admitted consecutively into the Department of Pulmonary and Critical Care Medicine, Beijing Chao-Yang Hospital from January 1, 2015 to February 28, 2021. Patients who lacked β2MG data and patients with ARDS induced by causes other than bacterial infection were excluded. Other exclusion criteria included diseases that have a great impact on death, such as active malignant tumour, cerebral stroke, acute myocardial infarction, serious trauma, and a major operation (defined as lasting longer than 45 minutes) within the past month. Enrolled patients were followed for up to 28 days from diagnosis by the hospital electronic information system or by telephone and were divided into the survival group and non-survival group according to their clinical outcomes. A flow chart of patient enrolment and outcomes is shown in Fig. 1.

Clinical Data Collection

Data, which included demographic information, clinical history (medical history, exposure history, underlying comorbidities), symptoms, vital signs and laboratory findings within 24 h after ARDS diagnosis, treatments, complications, and patient survival at 28 days post-diagnosis, were collected from the medical records of the enrolled patients and analysed.

The concentrations of serum β2MG, serum creatinine (Scr), blood urea nitrogen (BUN), albumin, total bilirubin (TBIL), alanine aminotransferase (ALT), and fasting plasma glucose (FPG) were measured using Latex immune turbidity and Oxidase method by Beckman Coulter UniCel DXC800 (Beckman Coulter, Inc., USA). The levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and cardiac troponin I (cTnI) were measured by using a fluorescence immunoassay (TZ-310 Dry fluorescence immunoassay; ReLIA Biotechnologies Ltd., China). White blood cell (WBC) counts were performed by using an XT-1800i automatic haematology analyser (SYSMEX Co., Ltd, Japan). The C-reactive protein (CRP) levels were measured by using a solid-phase sandwich format immunometric assay by NycoCardTM READER II (Alere Technologies AS, Norway). The procalcitonin (PCT) levels were measured by performing an immunochromatographic assay by B·R·A·H·M·S GmbH (Thermo Fisher Scientific Inc., Germany). The prothrombin time (PT) was measured using a coagulation method by Instrumentation Laboratory (Wofen medical device Trading Co., Ltd, USA). The lactic acid level and partial pressure of arterial oxygen (PaO_2) were measured via spectrophotometry performed with an ABL90 blood gas analyser (Radiometer Medical ApS, Denmark). Body mass index (BMI) was calculated with the formula: BMI = weight (kg)/height $(m)^2$. We estimated the creatinine clearance rate (Ccr) (mL/min) with the Cockroft-Gault equation: Ccr = ([140 – age in years] × body weight in kg)/(72 × Scr in mg/dL). For women, the calculated values were multiplied by 0.85.

Definitions

ARDS was defined as described in the Berlin definition [1]. Patients were divided into three groups according to their oxygenation levels [1]: (1) Mild: 200 mmHg (1 mmHg = 0.133 kPa) < PaO_2/FiO_2 (fraction of inspired oxygen) ≤ 300 mmHg with positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥ 5 cmH_2O (1 cmH_2O = 0.098 kPa); (2) Moderate: 100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg with PEEP ≥ 5 cmH_2O; and (3) Severe: PaO_2/FiO_2 ≤ 100 mmHg with PEEP ≥ 5 cmH_2O. The severity of comorbid diseases, such as coronary heart disease, congestive heart failure, cerebrovascular disease, diabetes mellitus, dementia, connective tissue disease, liver disease, and kidney disease, was recorded and scored in accordance with the Charlson comorbidity index updated by Quan et al. (updated CCI) [19]. Disorders of consciousness were identified in accordance with the Glasgow Coma Scale [20]. Septic shock was defined in accordance with the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [21]. AKI was defined in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines (i.e., Scr levels increased by ≥ 0.3 mg/dL (≥26.5 μmol/L) within 48 h or by 1.5 times the baseline level within seven days) [22]. We applied the Acute Physiology and Chronic Health Evaluation (APACHE) II score and Sequential Organ Failure Assessment (SOFA) score to assess the disease severity [23, 24].

Statistical Analyses

Categorical variables are described as numbers and percentages (%), and continuous variables are described as the mean and standard deviation (SD) or the median and interquartile range (IQR). The Shapiro-Wilk test was used to verify normality. Differences between the survival and non-survival groups were assessed by the two-sample *t*-test for normally distributed continuous variables, the Mann-Whitney *U* test for non-normally distributed continuous variables, or the χ^2 test for categorical variables. A Spearman rank correlation analysis was used to analyse the correlation between β2MG levels and other basic variables. Both univariate and multivariate Cox regression analyses were applied to evaluate the relationship between risk factors and 28-day mortality. Results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Serum β2MG levels were adjusted for age, updated CCI, disturbance of consciousness, septic shock, serum albumin level, cTnI level, PCT level, PT, lactic acid level, and PaO_2/FiO_2 ratio in the multivariate Cox regression analysis. Survival rates grouped by β2MG tertile are presented as cumulative survival curves adjusted for the above-mentioned variables. Receiver operating characteristic (ROC) analyses were performed to calculate the sensitivity and specificity of risk factors for predicting 28-day mortality. The areas under receiver operating curves (ROC-AUCs) for different risk factors were compared using the method of DeLong et al. (1988) by MedCalc. All other statistical analyses were performed using SPSS version 21.0 (Statistical Package for the Social Sciences, Chicago, IL USA). All tests were two-tailed; differences with a value of $P < 0.05$ were considered statistically significant.

Results

Patient Enrolment

A total of 257 patients with ARDS were included in this study. A flow chart of patient enrolment and outcomes is shown in Fig. 1.

Characteristics of Survivors vs Non-survivors among Patients with ARDS

Table 1 shows the demographic and clinical characteristics of the enrolled patients. In this cohort, 161 patients survived and 96 patients died within 28 days after the diagnosis of ARDS, yielding a 28-day mortality rate of 37.4%. The median level of β2MG for all patients with ARDS, regardless of their 28-day survival, was 4.6 (IQR: 2.9 - 8.5) mg/L. Compared with the non-survivors, the survivors were younger ($P = 0.002$) and had lower updated CCIs ($P < 0.001$), lower serum β2MG levels ($P < 0.001$), lower Scr levels ($P < 0.001$), lower BUN levels ($P < 0.001$), lower cTnI levels ($P = 0.001$), lower NT-proBNP levels ($P < 0.001$), lower PCT levels ($P = 0.008$), lower lactic acid levels ($P < 0.001$), shorter PTs ($P = 0.001$), higher albumin levels ($P < 0.001$), and higher PaO_2/FiO_2 ratios ($P < 0.001$). Survivors also had lower APACHE II scores ($P < 0.001$) and lower SOFA scores ($P < 0.001$) than did non-survivors. More non-survivors than survivors had AKI ($P < 0.001$) or acute myocardial injury ($P = 0.003$). There was no difference in the duration of mechanical ventilation (MV) between survivors and non-survivors ($P = 0.959$).

Univariate and Multivariate Survival Analyses

A univariate Cox regression analysis revealed that the level of serum β2MG is a predictor of 28-day mortality in patients with ARDS (HR: 1.096; 95% CI: 1.064 - 1.128; $P < 0.001$) (Table 2). Other predictors of 28-day mortality in these patients included age, updated CCI, septic shock, Scr level, BUN level, Ccr, albumin level, PCT level, lactic acid level, PT, PaO_2/FiO_2 ratio, APACHE II score, and SOFA score ($P < 0.05$ for each).

To reduce data duplication, we did not include the APACHE II score or the SOFA score in our multivariate Cox proportional hazards analysis. Additionally, because we found that the serum β2MG level was positively correlated with the Scr level (Spearman correlation coefficient: 0.815), the BUN level (Spearman correlation coefficient: 0.723), AKI (Spearman correlation coefficient: 0.683), and the NT-proBNP level (Spearman correlation coefficient: 0.564) and was negatively correlated with the Ccr (Spearman correlation coefficient: - 0.811) in our cohort ($P < 0.001$ for each) (Table 3), we did not include these variables in the multivariate survival analysis either. The metabolism of NT-proBNP is influenced by renal function, and therefore we further analysed the correlation between the serum β2MG level and NT-proBNP level in patients with a Ccr of > 60 mL/min and found a positive correlation between them (Spearman correlation coefficient: 0.338; $P < 0.001$). Of the 257 patients in this study, 173 (67.3%) had a CRP level equal to 120 mg/mL (the upper limit value for CRP testing in our laboratory at that time), and therefore we further analysed the 84 patients with a CRP level of <120 mg/mL and found a significant positive correlation between the serum β2MG level and CRP level (Spearman correlation coefficient: 0.562; $P < 0.001$).

A higher β2MG level was significantly associated with 28-day mortality after adjusting for age, updated CCI, disorders of consciousness, septic shock, albumin level, cTnI level, PCT level, lactic acid level, PT, and PaO_2/FiO_2 ratio (HR: 1.050; 95% CI: 1.012 - 1.091; $P = 0.010$) (Table 2).

When stratified by serum β2MG level tertiles, the 28-day mortality from the lowest to highest tertile was 12.5% (12/85), 38.5% (37/88), and 49.0% (47/84), respectively. The mortality risk was significantly higher in the highest category group (HR: 1.482; 95% CI: 1.069–2.045; $P = 0.018$) after adjusting for age, updated CCI, disorders of consciousness, septic shock, albumin level, cTnI level, PCT level, lactic acid level, PT, and PaO_2/FiO_2 ratio (Fig. 2).

The Prognostic Value of β2MG Levels on 28-Day Mortality

The serum β2MG level showed a diagnostic accuracy for mortality prediction (AUC = 0.711; 95% CI: 0.652 - 0.766; sensitivity: 76.0%, specificity: 55.3%; $P < 0.001$) superior to that of AKI (AUC = 0.620; 95% CI: 0.558 - 0.680; sensitivity: 75.0%, specificity: 49.1%; $P < 0.001$; $P = 0.001$ for these two curves) and Ccr (AUC = 0.665; 95% CI: 0.604 - 0.723; sensitivity: 66.7%, specificity: 60.9%; $P < 0.001$; $P = 0.032$ for these two curves) and not inferior to that of the APACHE II score (AUC = 0.661; 95% CI: 0.599–0.718; sensitivity: 71.9%, specificity: 54.0%; $P < 0.001$; $P = 0.153$ for these two curves) or SOFA score (AUC =

0.659; 95% CI: 0.598 - 0.717; sensitivity: 59.4%, specificity: 65.8%; $P < 0.001$; $P = 0.114$ for these two curves) (Fig. 3), when the cut-off value for the β2MG level was 4.0 mg/L.

Discussion

Our study observed that the levels of β2MG in patients with ARDS were elevated and were significantly higher in non-survivors than in survivors. A multivariate Cox proportional hazards analysis revealed that the β2MG level is an independent predictor for 28-day mortality in patients with ARDS, after adjusting for age, updated CCI, disorders of consciousness, septic shock, albumin level, cTnI level, PCT level, PT, lactic acid level, and PaO_2/FiO_2 ratio. To our knowledge, this is the first report suggesting that the serum β2MG level might have a predictive value for the outcomes of patients with ARDS.

As a low molecular-weight protein, β2MG is an ideal endogenous biomarker for estimating the glomerular filtration rate and AKI [8, 12] and is also associated with a number of clinical states. Several previous studies have shown that levels of serum β2MG are higher in patients with inflammatory bowel disease or systemic lupus erythematosus than in healthy controls, suggesting that it might also be a useful biomarker for the assessment of these autoimmune diseases [25, 26]. In addition, elevated levels of serum β2MG have been also observed in patients with haemato-oncological pathology and solid tumours despite their preserved renal function [15, 27]. Some research has suggested that β2MG is probably a general biomarker that reflects acute or chronic changes during inflammation and infection [28, 29]. Levels of serum β2MG are independently associated with major cardiovascular events in the general population as well as in patients with asymptomatic carotid atherosclerosis, patients with isolated systolic hypertension, and patients with acute heart failure who do not have severe renal insufficiency [10, 30-32]. Mao et al. reported that β2MG levels are associated with poor outcomes in patients with exacerbated chronic obstructive pulmonary disease [18].

ARDS is a clinical syndrome with extremely high mortality, characterized by severe hypoxemia and an overwhelming inflammatory response, accompanied by multiple organ dysfunctions. Kohanpour et al. stated that an increase in serum β2MG levels can occur with physical exercise under hypoxic conditions [33]. Hadzimuratovic et al. observed increased serum β2MG levels in neonatal asphyxia [34]. These findings suggest that elevated serum β2MG levels are associated with hypoxemia. Some studies have found that an increase in serum β2MG levels is also present during infectious diseases as well as in inflammatory responses [28, 29]. In our study, the serum β2MG levels were found to be elevated in patients with bacterial infection-induced ARDS. A rank correlation analysis revealed that the serum β2MG levels were negatively correlated with the PaO_2/FiO_2 ratio and positively correlated with the PCT and CRP levels. These correlations suggest that elevated serum β2MG levels during ARDS may be associated with hypoxemia and infection as well as with inflammation. In addition, ARDS is often accompanied by multiple organ dysfunctions, such as AKI and myocardial injury, which are significantly associated with a poor prognosis in patients with ARDS [35, 36]. Previous studies have shown that serum β2MG levels are correlated with renal injury [8, 12] as well as with cardiac function [32, 37, 38]. Both AKI and myocardial injury were present in approximately half of the patients in our cohort, and our

correlation analysis revealed that the serum β2MG levels are positively correlated with AKI, NT-proBNP levels, and cTnI levels and are negatively correlated with the Ccr and left ventricular ejection fraction. An analysis conducted after stratification of the patients according to their Ccrs [39] showed that serum β2MG levels are also positively correlated with NT-proBNP levels in patients with a Ccr of > 60 mL/min. These conditions suggest that, in the case of ARDS caused by bacterial infection, severe hypoxemia, infection, and inflammatory responses, as well as the impairment of organ function, result in increased β2MG production and decreased renal filtration, ultimately leading to elevated serum β2MG levels, which are positively correlated with disease severity and sensitively predict an elevated risk of death.

The ROC curves generated from our data show that the predictive value of serum β2MG levels for patient outcome is superior to that of AKI and Ccr, which may additionally illustrate that the correlation between serum β2MG levels and mortality is not solely a consequence of renal impairment. Further comparison of these ROC curves showed that serum β2MG levels are not inferior to currently applied critical illness scores, such as the APACHE II score and SOFA score, for predicting 28-day mortality in patients with ARDS caused by bacterial infection. Therefore, the serum β2MG level may be an ideal screening tool that can be reliably and cost effectively measured.

We applied the updated CCI [19] to assess patient comorbidities, including coronary heart disease, congestive heart failure, cerebrovascular disease, diabetes mellitus, dementia, connective tissue disease, liver disease, and kidney disease, and found it was significantly associated with 28-day mortality in patients with bacterial infection-induced ARDS. This result is consistent with previous research [40]. We also found that the lactic acid level was an independent risk factor for 28-day mortality in patients with bacterial infection-induced ARDS. Lactic acid is directly produced by anaerobic glucose metabolism and is the product of pyruvate transformation through glycolysis. An acceleration of lactate synthesis may be observed under conditions of increased glucose uptake from circulation, of increased glycogenolysis and glycolysis owing to enhanced epinephrine secretion, of inhibition of pyruvate dehydrogenase or of glycogen synthesis during sepsis and, finally, during tissue hypoxia. Therefore, the lactic acid level is considered to be a sensitive biomarker, which can reflect the oxygen supply in cells and the perfusion of surrounding tissues in the early stage of disease, and can be used to assess disease severity and to predict the occurrence of and death risk from septic shock and multiple organ dysfunction syndrome [21, 41]. Demirel reported that the lactate level is a good predictor of in-hospital mortality in pneumonia cases [42]. During ARDS, owing to severe hypoxemia and varying degrees of tissue perfusion insufficiency, glucose anaerobic metabolism increases, resulting in increased lactic acid production, which indicates a poor prognosis [5, 6].

Severe hypoxemia is a characteristic manifestation of ARDS. The PaO_2/FiO_2 ratio is an integral part of the assessment of patients with ARDS and is an important criterion for severity grading in the Berlin standard [1]. Although some studies have found that the PaO_2/FiO_2 ratio is not a good prognostic factor for ARDS [4], as an important indicator of the severity of lung injury, however, most studies have shown that the decreased PaO_2/FiO_2 ratio is associated with increased mortality or failure of non-invasive MV in

patients with ARDS [21, 43, 44]. Similarly, our study showed that the PaO_2/FiO_2 ratio was a protective factor for the prognosis of patients with ARDS.

There are some limitations to our study. First of all, this research was conducted in a single centre, which could have biased its results. Second, owing to the small sample size in this study, to avoid overfitting, only a limited number of clinical variables were entered into the Cox regression analysis, and it is possible that potentially relevant variables were not evaluated. Third, owing to the retrospective nature of this study, we could not simultaneously assay the levels of β2MG in the urine, and thus it was not possible to determine how much of the increase in serum β2MG levels can be attributed to renal injury and how much of the increased production is a consequence of the disease state. Fourth, although the ROC curve in our study showed predictive value for the outcome of patients with ARDS, we could not verify the applicability of this clinical indicator because of the small sample size. Future prospective studies will be necessary to identify and verify the prognostic value of serum β2MG levels in patients with ARDS caused by bacterial infection.

Conclusions

This prospective study showed that the level of serum β2MG, measured within 24 hours after the diagnosis of ARDS, was elevated and may be a promising early biomarker of adverse outcomes in patients with ARDS caused by bacterial infection. Further prospective research will be necessary to verify this finding, which may help clinicians undertake timely and effective programmes to improve the outcomes of these patients.

Abbreviations

ARDS, acute respiratory distress syndrome; β2MG, β2-microglobulin; AKI, acute kidney injury; Scr, serum creatinine; BUN, blood urea nitrogen; TBIL, total bilirubin; ALT, alanine aminotransferase; FPG, fasting plasma glucose; NT-proBNP, N-terminal pro-brain natriuretic peptide; cTnI, cardiac troponin I; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; PT, prothrombin time; BMI, body mass index; Ccr, creatinine clearance rate; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; CPAP, continuous positive airway pressure; CCI, Charlson comorbidity index; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; MV, mechanical ventilation; SD, standard deviation; IQR, interquartile range; HR, hazard ratio; CI, confidence interval; ROC, receiver operating characteristic.

Declarations

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Not applicable.

Authors' contributions

NC, JW and LMZ contributed to the conception and design of the study. LMZ and JW took part in managing the research. XKF and CGJ contributed to the acquisition of data. All authors were involved in data analysis and interpretation and development of the manuscript. All authors read and approved the final manuscript. LMZ and JW contributed equally to this article and shared corresponding authorship.

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Availability of data and materials

All data analysed during the study are presented in the main manuscript. The anonymous dataset is available from the corresponding author upon reasonable request.

Ethics and approval and consent to participate

This retrospective study involving human participants was approved by the ethics committee of the Beijing Chao-Yang Hospital, Capital Medical University (2020-ke-429) and was in accordance with 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1
Demographic and Clinical Characteristics of Patients with ARDS

Clinical characteristics	Total ARDS (N = 257)	Survivors (n = 161)	Non-Survivors (n = 96)	*P* value
Age (years)	70 (57, 80)	68 (55, 77)	74 (62, 81)	0.002
Male, n (%)	167 (65.0)	102 (63.4)	65 (67.7)	0.479
Current smoker, n (%)	107 (41.6)	69 (42.9)	38 (39.6)	0.607
CCI updated	2 (0, 3)	1 (0, 3)	2 (1, 3)	< 0.001
BMI	24.3 ± 4.6	24.4 ± 4.4	24.3 ± 5.0	0.860
Disorders of consciousness, n (%)	60 (23.3)	33 (20.5)	27 (28.1)	0.162
Septic shock, n (%)	127 (49.4)	67 (41.6)	60 (62.5)	0.001
β2MG (mg/L)	4.6 (2.9, 8.5)	3.8 (2.5, 6.5)	6.2 (4.1, 12.3)	< 0.001
Scr (μmol/L)	113.0 (67.4, 207.8)	90.5 (63.0, 190.8)	139.4 (92.3, 286.7)	< 0.001
Ccr (mL/min)	43.0 (25.2, 81.5)	55.9 (29.8, 104.6)	33.2 (18.6, 57.9)	< 0.001
BUN (mmol/L)	11.3 (6.1, 17.8)	9.1 (4.9, 15.6)	15.4 (10.2, 25.0)	< 0.001
AKI, n (%)	154 (59.9)	82 (50.9)	72 (75.0)	< 0.001
Albumin (g/L)	26.3 (23.4, 30.1)	27.0 (24.1, 31.0)	24.8 (21.4, 29.3)	< 0.001
TBIL (μmol/L)	20.8 (13.1, 31.6)	20.8 (12.7, 31.0)	20.8 (13.2, 35.2)	0.674

Data are the mean ± SD, median (IQR), or n (%). *P* values comparing the Survivor and non-Survivor groups are from a 2-sample *t*-test, Mann-Whitney *U* test, or χ^2 test. Differences with values of $P < 0.05$ were considered statistically significant.

* χ^2 test comparing the Survivor and non-Survivor groups. † χ^2 test comparing all subcategories.

Abbreviations: ARDS, acute respiratory disease syndrome; CCI, Charlson comorbidity index; BMI, body mass index; β2MG, β2-microglobulin; Scr, serum creatinine; Ccr, creatinine clearance rate; BUN, blood urea nitrogen; AKI, acute kidney injury; TBIL, total bilirubin; ALT, alanine aminotransferase; NT-proBNP, N-terminal pro-brain natriuretic peptide; cTnI, cardiac troponin I; FPG, fasting plasma glucose; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; PT, prothrombin time; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; Mild, 200 mmHg < PaO_2/FiO_2 ratio ≤ 300 mmHg; Moderate, 100 mmHg < PaO_2/FiO_2 ratio ≤ 200 mmHg; Severe, PaO_2/FiO_2 ratio ≤ 100 mmHg; MV, mechanical ventilation; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; SD, standard deviation; IQR, interquartile range.

Clinical characteristics	Total ARDS (N = 257)	Survivors (n = 161)	Non-Survivors (n = 96)	*P* value
ALT (U/L)	31.0 (18.5, 66.4)	29.7 (17.8, 59.6)	32.9 (18.8, 84.5)	0.337
NT-proBNP (pg/mL)	1830.6 (522.3, 5176.3)	1084.0 (318.3, 4112.5)	2863.0 (1446.0, 7080.1)	< 0.001
cTnI (ng/mL)	0.10 (0.04, 0.41)	0.06 (0.02, 0.29)	0.17 (0.06, 0.56)	0.001
Acute myocardial injury, n (%)	127 (49.4)	59 (61.5)	68 (42.2)	0.003
FPG (mmol/L)	8.6 (6.6, 11.4)	8.1 (6.5, 10.6)	8.9 (7.1, 12.4)	0.124
WBC ($\times 10^9$/L)	16.5 (11.7, 21.3)	16.3 (11.7, 21.0)	16.9 (13.1, 23.1)	0.489
CPR (mg/L)	120 (98, 120)	120 (102, 120)	120 (86, 120)	0.595
PCT (ng/mL)	5.6 (0.7, 18.8)	3.5 (0.4, 15.9)	6.3 (1.9, 24.6)	0.008
PT (s)	13.9 (12.6, 16.2)	13.5 (12.2, 15.6)	15.0 (13.3, 17.4)	0.001
Lactic acid (mmol/L)	1.8 (1.3, 2.7)	1.6 (1.1, 2.3)	2.3 (1.5, 4.0)	< 0.001
PaO_2/FiO_2 ratio	157 (105, 199)	172 (117, 208)	134 (81, 178)	< 0.001*
Mild, n (%)	63 (24.5)	48 (29.8)	15 (15.6)	< 0.001†
Moderate, n (%)	131(51.0)	86 (53.4)	45 (46.9)	
Severe, n (%)	63 (24.5)	27 (16.8)	36 (37.5)	

Data are the mean ± SD, median (IQR), or n (%). *P* values comparing the Survivor and non-Survivor groups are from a 2-sample *t*-test, Mann-Whitney *U* test, or χ^2 test. Differences with values of $P < 0.05$ were considered statistically significant.

* χ^2 test comparing the Survivor and non-Survivor groups. † χ^2 test comparing all subcategories.

Abbreviations: ARDS, acute respiratory disease syndrome; CCI, Charlson comorbidity index; BMI, body mass index; β2MG, β2-microglobulin; Scr, serum creatinine; Ccr, creatinine clearance rate; BUN, blood urea nitrogen; AKI, acute kidney injury; TBIL, total bilirubin; ALT, alanine aminotransferase; NT-proBNP, N-terminal pro-brain natriuretic peptide; cTnI, cardiac troponin I; FPG, fasting plasma glucose; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; PT, prothrombin time; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; Mild, 200 mmHg < PaO_2/FiO_2 ratio ≤ 300 mmHg; Moderate, 100 mmHg < PaO_2/FiO_2 ratio ≤ 200 mmHg; Severe, PaO_2/FiO_2 ratio ≤ 100 mmHg; MV, mechanical ventilation; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; SD, standard deviation; IQR, interquartile range.

Clinical characteristics	Total ARDS (N = 257)	Survivors (n = 161)	Non-Survivors (n = 96)	*P* value
Duration of MV (days)	8 (5, 16)	8 (5, 17)	8 (5, 14)	0.959
APACHE II score	24 (19, 30)	22 (17, 28)	27 (21, 32)	< 0.001
SOFA score	8 (5, 11)	7 (4, 10)	9 (7, 12)	< 0.001

Data are the mean ± SD, median (IQR), or n (%). *P* values comparing the Survivor and non-Survivor groups are from a 2-sample *t*-test, Mann-Whitney *U* test, or χ^2 test. Differences with values of $P < 0.05$ were considered statistically significant.

* χ^2 test comparing the Survivor and non-Survivor groups. † χ^2 test comparing all subcategories.

Abbreviations: ARDS, acute respiratory disease syndrome; CCI, Charlson comorbidity index; BMI, body mass index; β2MG, β2-microglobulin; Scr, serum creatinine; Ccr, creatinine clearance rate; BUN, blood urea nitrogen; AKI, acute kidney injury; TBIL, total bilirubin; ALT, alanine aminotransferase; NT-proBNP, N-terminal pro-brain natriuretic peptide; cTnI, cardiac troponin I; FPG, fasting plasma glucose; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; PT, prothrombin time; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; Mild, 200 mmHg < PaO_2/FiO_2 ratio ≤ 300 mmHg; Moderate, 100 mmHg < PaO_2/FiO_2 ratio ≤ 200 mmHg; Severe, PaO_2/FiO_2 ratio ≤ 100 mmHg; MV, mechanical ventilation; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; SD, standard deviation; IQR, interquartile range.

Table 2
Univariate and Multivariate Survival Analysis of the 28-Day Mortality Risk in Patients with ARDS

Clinical characteristics	Univariate HR (95% CI)	*P* value	Multivariate HR (95% CI)	*P* value
β2MG (mg/L)	1.096 (1.064, 1.128)	< 0.001	1.050 (1.012, 1.091)	0.010
Age (years)	1.019 (1.005, 1.033)	0.008	1.004 (0.987, 1.021)	0.652
CCI updated	1.251 (1.127, 1.388)	< 0.001	1.150 (1.017, 1.300)	0.025
Disorders of consciousness, n (%)	1.557 (0.998, 2.431)	0.051	1. 099 (0.669, 1.804)	0.709
Septic shock, n (%)	2.043 (1.351, 3.090)	0.001	1.145 (0.717, 1.829)	0.570
Albumin (g/L)	0.928 (0.893, 0.964)	< 0.001	0.964 (0.924, 1.006)	0.093
cTnI (ng/mL)	1.032 (0.937, 1.137)	0.522	1.204 (0.894, 1.173)	0.733
PCT (ng/mL)	1.020 (1.002, 1.038)	0.026	1.005 (0.986, 1.025)	0.602
PT (s)	1.018 (1.003, 1.033)	0.020	1.006 (0.989, 1.023)	0.524
Lactic acid (mmol/L)	1.104 (1.062, 1.146)	< 0.001	1.045 (1.001, 1.092)	0.047
PaO_2/FiO_2 ratio	0.994 (0.991, 0.998)	0.001	0.996 (0.992, 1.000)	0.028
Male, n (%)	1.143 (0.745, 1.753)	0.542		

A Cox proportional hazards analysis was performed. Data are the HR (95% CI). Adjusted for age, updated CCI, disorders of consciousness, septic shock, albumin, cTnI, procalcitonin, prothrombin time, lactic acid, and PaO_2/FiO_2 ratio. Differences with values of $P < 0.05$ were considered statistically significant.

Abbreviations: ARDS, acute respiratory disease syndrome; β2MG, β2-microglobulin; CCI, Charlson comorbidity index; cTnI cardiac troponin I; PCT, procalcitonin; PT, prothrombin time; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; BMI, body mass index; Scr, serum creatinine; Ccr, creatinine clearance rate; BUN, blood urea nitrogen; AKI, acute kidney injury; TBIL, total bilirubin; ALT, alanine aminotransferase; NT-proBNP, N-terminal pro-brain natriuretic peptide; FPG, fasting plasma glucose; WBC, white blood cell; CRP, C-reactive protein; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; HR, hazard ratio; CI, confidence interval.

Clinical characteristics	Univariate HR (95% CI)	*P* value	Multivariate HR (95% CI)	*P* value
BMI	0.988 (0.943, 1.034)	0.604		
Current smoker, n (%)	0.906 (0.602, 1.364)	0.637		
Scr (μmol/L)	1.002 (1.001, 1.003)	0.001		
Ccr (mL/min)	0.986 (0.979, 0.992)	< 0.001		
BUN (mmol/L)	1.035 (1.022, 1.048)	< 0.001		
AKI, n (%)	2.503 (1.576, 3.796)	< 0.001		
TBIL (μmol/L)	1.002 (1.000, 1.003)	0.115		
ALT (U/L)	1.000 (1.000, 1.001)	0.242		
NT-proBNP (pg/mL)	1.000 (1.000, 1.000)	0.207		
FPG (mmol/L)	1.021 (0.980, 1.064)	0.312		
WBC ($\times 10^9$/L)	1.007 (0.984, 1.030)	0.549		
CRP (mg/L)	0.998 (0.994, 1.003)	0.486		
APACHE II score	1.056 (1.032, 1.081)	< 0.001		

A Cox proportional hazards analysis was performed. Data are the HR (95% CI). Adjusted for age, updated CCI, disorders of consciousness, septic shock, albumin, cTnI, procalcitonin, prothrombin time, lactic acid, and PaO_2/FiO_2 ratio. Differences with values of $P < 0.05$ were considered statistically significant.

Abbreviations: ARDS, acute respiratory disease syndrome; β2MG, β2-microglobulin; CCI, Charlson comorbidity index; cTnI cardiac troponin I; PCT, procalcitonin; PT, prothrombin time; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; BMI, body mass index; Scr, serum creatinine; Ccr, creatinine clearance rate; BUN, blood urea nitrogen; AKI, acute kidney injury; TBIL, total bilirubin; ALT, alanine aminotransferase; NT-proBNP, N-terminal pro-brain natriuretic peptide; FPG, fasting plasma glucose; WBC, white blood cell; CRP, C-reactive protein; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; HR, hazard ratio; CI, confidence interval.

Clinical characteristics	Univariate HR (95% CI)	*P* value	Multivariate HR (95% CI)	*P* value
SOFA score	1.096 (1.050, 1.143)	< 0.001		

A Cox proportional hazards analysis was performed. Data are the HR (95% CI). Adjusted for age, updated CCI, disorders of consciousness, septic shock, albumin, cTnI, procalcitonin, prothrombin time, lactic acid, and PaO_2/FiO_2 ratio. Differences with values of $P < 0.05$ were considered statistically significant.

Abbreviations: ARDS, acute respiratory disease syndrome; β2MG, β2-microglobulin; CCI, Charlson comorbidity index; cTnI cardiac troponin I; PCT, procalcitonin; PT, prothrombin time; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; BMI, body mass index; Scr, serum creatinine; Ccr, creatinine clearance rate; BUN, blood urea nitrogen; AKI, acute kidney injury; TBIL, total bilirubin; ALT, alanine aminotransferase; NT-proBNP, N-terminal pro-brain natriuretic peptide; FPG, fasting plasma glucose; WBC, white blood cell; CRP, C-reactive protein; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; HR, hazard ratio; CI, confidence interval.

Table 3
Spearman Rank Correlation Between β2MG and Basic Variables in Patients with ARDS

Variables	Correlation coefficient	*P* value
Age (years)	0.243	< 0.001
Male, n (%)	-0.029	0.649
BMI	0.001	0.989
Disturbance of consciousness, n (%)	0.160	0.010
Septic shock, n (%)	0.277	< 0.001
CCI updated	0.234	< 0.001
Current smoker, n (%)	-0.037	0.559
Scr (μmol/L)	0.814	< 0.001
Ccr (mL/min)	-0.810	< 0.001
BUN (mmol/L)	0.723	< 0.001
AKI, n (%)	0.681	< 0.001
Albumin (g/L)	-0.235	< 0.001
TBIL (μmol/L)	0.082	0.190
ALT (U/L)	-0.063	0.312
cTnI (ng/mL)	0.364	< 0.001
NT-proBNP (pg/mL)	0.563	< 0.001
NT-proBNP* (pg/mL)	0.338	< 0.001
LVEF (%)	-0.294	< 0.001
FPG (mmol/L)	-0.009	0.886
WBC ($\times 10^9$/L)	0.136	0.029
CRP (mg/L)	0.114	0.068

Abbreviations: β2MG, β2-microglobulin; ARDS, acute respiratory disease syndrome; BMI, body mass index; CCI, Charlson comorbidity index; Scr, serum creatinine; Ccr, creatinine clearance rate; BUN, blood urea nitrogen; AKI, acute kidney injury; TBIL, total bilirubin; ALT, alanine aminotransferase; cTnI, cardiac troponin I; NT-proBNP, N-terminal pro-brain natriuretic peptide; NT-proBNP*, in the group with Ccr of > 60 mL/min; LVEF, left ventricular ejection fraction; FPG, fasting plasma glucose; WBC, white blood cell; CRP, C-reactive protein; CRP*, CRP level of < 120 mg/L; PCT, procalcitonin; PT, prothrombin time; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

Variables	Correlation coefficient	*P* value
CRP* (mg/L)	0.562	< 0.001
PCT (ng/mL)	0.421	< 0.001
PT (s)	0.201	0.002
Lactic acid (mmol/L)	0.187	0.003
PaO_2/FiO_2 ratio	-0.165	0.008
APACHE II score	0.517	< 0.001
SOFA score	0.566	< 0.001

Abbreviations: β2MG, β2-microglobulin; ARDS, acute respiratory disease syndrome; BMI, body mass index; CCI, Charlson comorbidity index; Scr, serum creatinine; Ccr, creatinine clearance rate; BUN, blood urea nitrogen; AKI, acute kidney injury; TBIL, total bilirubin; ALT, alanine aminotransferase; cTnI, cardiac troponin I; NT-proBNP, N-terminal pro-brain natriuretic peptide; NT-proBNP*, in the group with Ccr of > 60 mL/min; LVEF, left ventricular ejection fraction; FPG, fasting plasma glucose; WBC, white blood cell; CRP, C-reactive protein; CRP*, CRP level of < 120 mg/L; PCT, procalcitonin; PT, prothrombin time; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

Figures

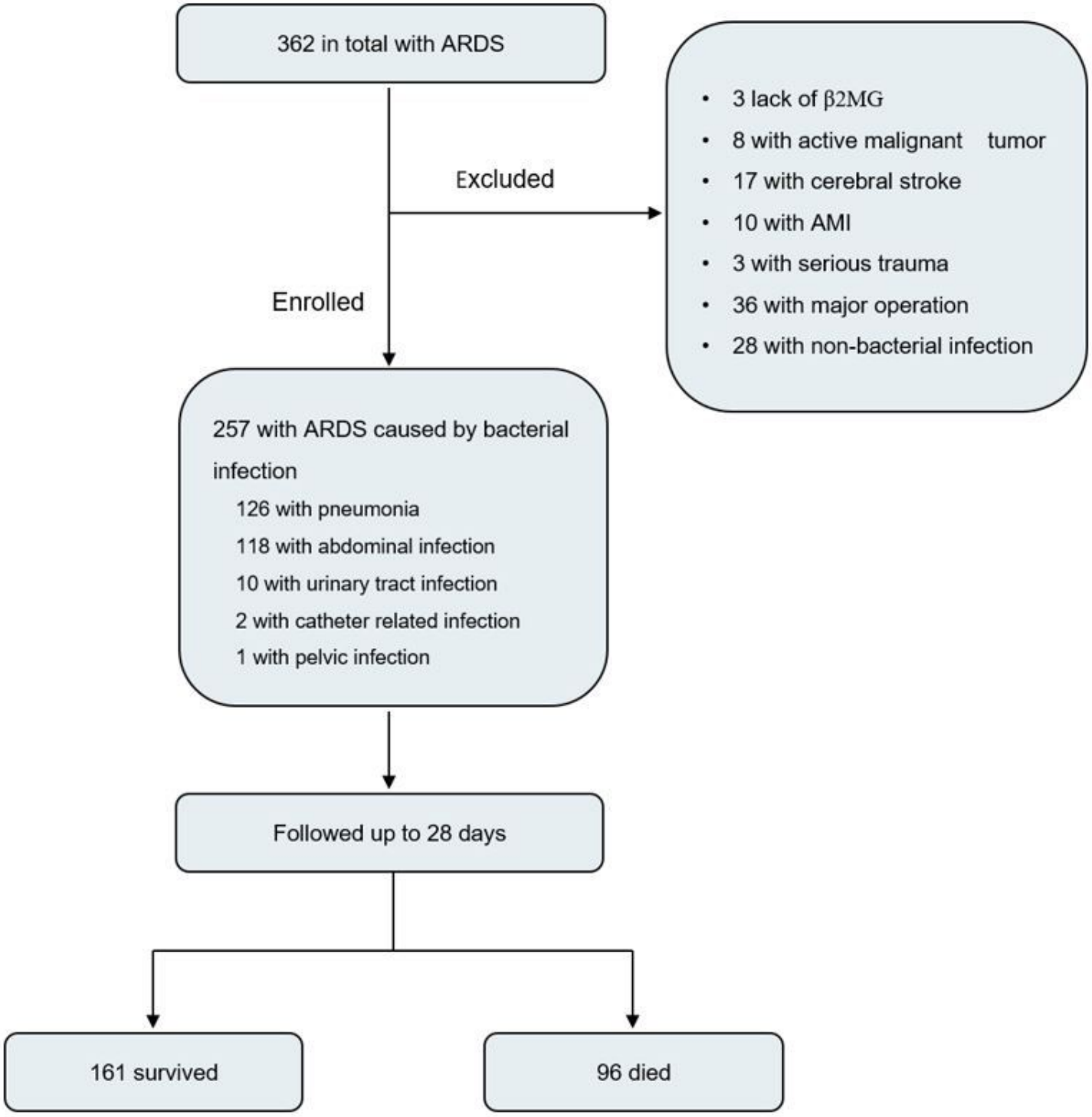


Figure 1

Flow chart of the patient enrollment and outcomes in this study. Abbreviations: ARDS, acute respiratory disease syndrome; AMI, acute myocardial infarction; β2MG, β2-microglobulin.

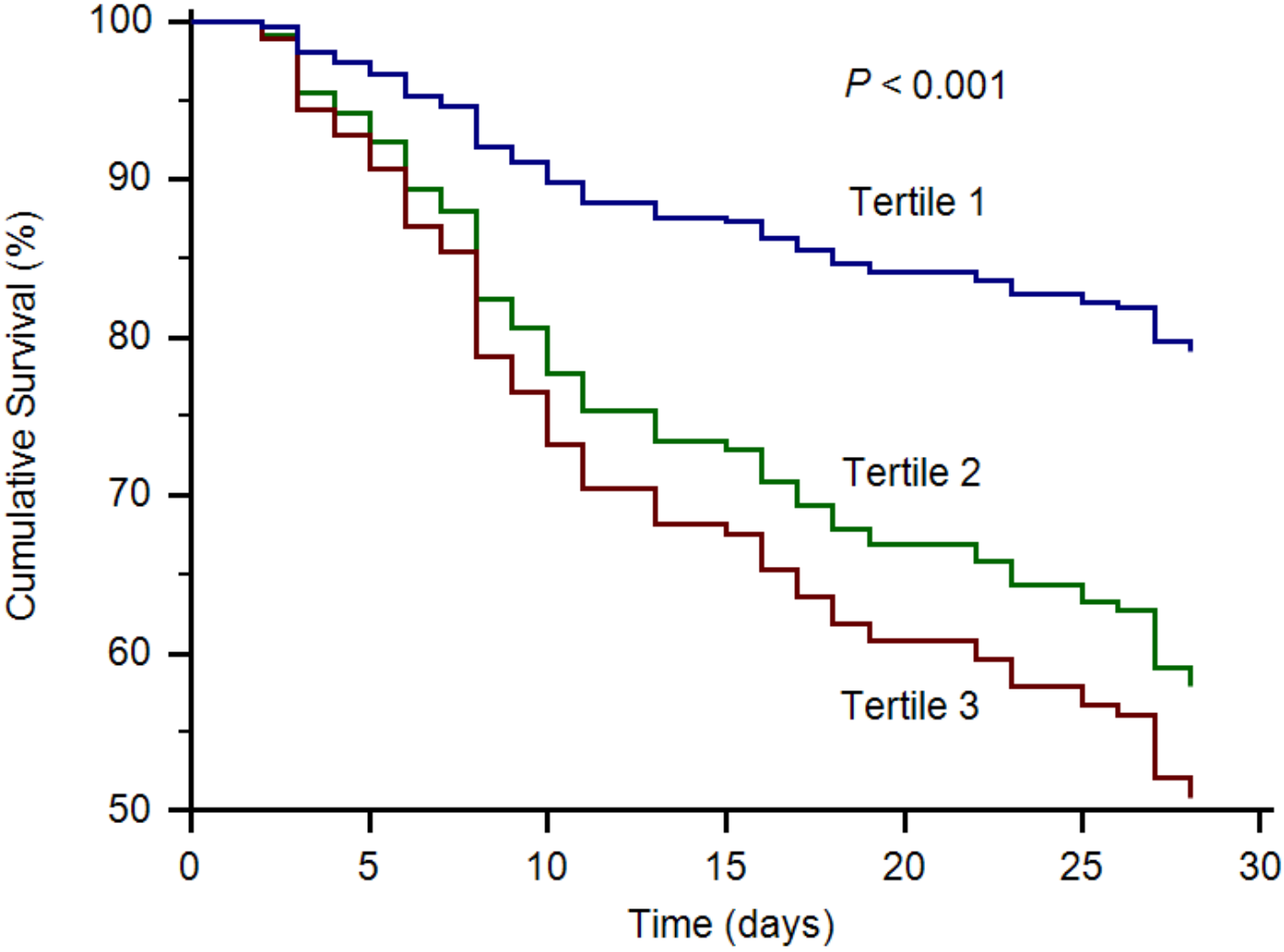
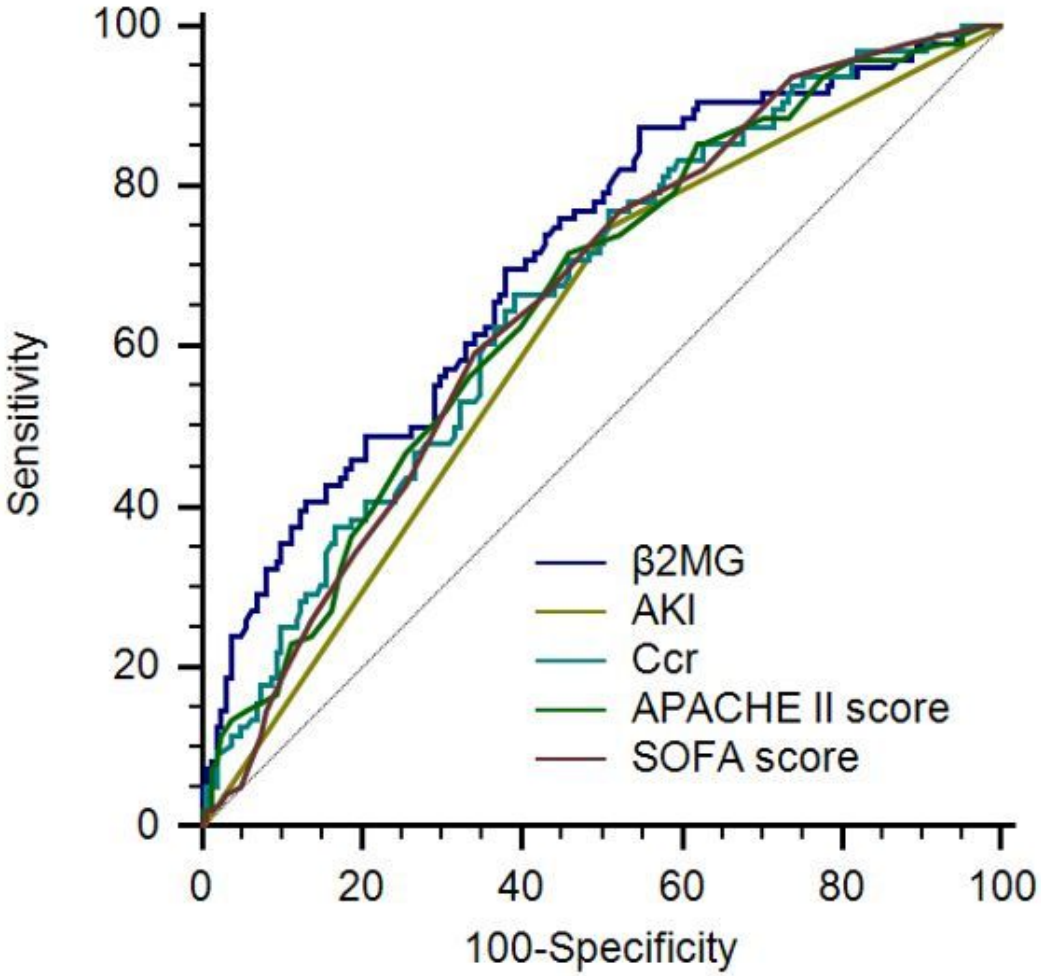


Figure 2

Survival curves of patients with ARDS stratified by β2MG tertile. Data were adjusted for age, updated CCI, disorders of consciousness, septic shock, albumin level, cTnI level, PCT level, PT, lactic acid level, and PaO2/FiO2 ratio. Tertile 1, β2MG < 3.5 mg/L; Tertile 2, β2MG = 3.5 - 6.5 mg/L; Tertile 3, β2MG > 6.5 mg/L; HR: 1.482; 95% CI: 1.069 -2.054; P = 0.018 Abbreviations: ARDS: acute respiratory disease syndrome; β2MG, β2-microglobulin; CCI, Charlson comorbidity index; cTnI, cardiac troponin I; PCT, procalcitonin; PT, prothrombin time; PaO2, partial pressure of arterial oxygen; FiO2, fraction of inspired oxygen.



Variables	Best cutoff	Sensitivity	Specificity	AUC (95%CI)	*P* Value	*P* Value*
β2MG (mg/L)	> 4.0	76.0	55.3	0.711 (0.652 - 0.766)	<0.001	
AKI	+	75.0	49.1	0.620 (0.558 - 0.680)	<0.001	0.001
Ccr	≤ 42.1	66.7	60.9	0.665 (0.604 -0.723)	<0.001	0.032
APACHE II Score	> 22	71.9	54.0	0.661 (0.599 - 0.718)	<0.001	0.153
SOFA Score	> 8	59.4	65.8	0.659 (0.598 - 0.717)	<0.001	0.114

Figure 3

Prediction of 28-day mortality in patients with ARDS. β2MG showed a diagnostic accuracy for mortality screening that is superior to AKI (P = 0.001) and Ccr (P = 0.032) and not inferior to the APACHE II Score (P = 0.153) and SOFA Score (P = 0.114). * Comparing between β2MG and other variables. Abbreviations: ARDS, acute respiratory disease syndrome; ROC, receiver operating characteristic; AUC, area under curve; β2MG, β2-microglobulin; AKI, acute kidney injury; Ccr, creatinine clearance rate; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.