Serum β2-microglobulin: An independent risk factor for mortality in patients with acute respiratory distress syndrome caused by bacterial infection

Liming Zhang (zhangliming@bjcyh.com)
Beijing Institute of Respiratory Medicine and Beijing Chao-Yang Hospital, Capital Medical University
Na Cui
Beijing Institute of Respiratory Medicine and Beijing Chao-Yang Hospital, Capital Medical University
Xiaokai Feng
Beijing Institute of Respiratory Medicine and Beijing Chao-Yang Hospital, Capital Medical University
Chunguo Jiang
Beijing Institute of Respiratory Medicine and Beijing Chao-Yang Hospital, Capital Medical University
Jing Wang
Beijing Institute of Respiratory Medicine and Beijing Chao-Yang Hospital, Capital Medical University

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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 caused by bacterial infection.

Methods: We retrospectively enrolled 257 patients with ARDS caused by bacterial infection from January 1, 2015 to February 28, 2021. Patients were followed for up to 28 days 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 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, partial pressure of arterial oxygen/fraction of inspired oxygen ratio, creatinine clearance rate, acute kidney injury and Sequential Organ Failure Assessment.

Results: In this cohort, 96 patients died in 28 days, yielding a 28-day mortality of 37.4%. The median level of serum β2MG for all enrolled patients was 4.7 (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]: 1.054; 95% confidence interval [CI]:1.005 - 1.105; $P = 0.031$) and when it was categorized into tertiles (HR: 3.239; 95% CI: 1.177 - 8.913; $P = 0.023$). The β2MG level exhibited a high diagnostic accuracy for predicting 28-day mortality (area under the curve [AUC] = 0.732; 95% CI:0.673-0.785; sensitivity:74.0%; specificity:64.0%; $P<0.001$).

Conclusions: The level of serum β2MG is elevated and is an independent risk factor of 28-day mortality in patients with ARDS caused by bacterial infection.

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, 3–5], 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 [6]. 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) [6–9]. 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 [10] but also associated with a number of clinical states, including chronic inflammatory diseases, malignancies, and adverse outcomes in chronic obstructive pulmonary disease (COPD), acute pulmonary embolism, and cardiovascular diseases even though patients with preserved renal function [11–16]. 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 independently.

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). Oral informed consent was obtained from all subjects and/or their legal guardian(s).

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 into the Department of Pulmonary and Critical Care Medicine, Beijing Chao-Yang Hospital from January 1, 2015 to February 28, 2021. All patients were included consecutively. 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 Figure 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 hours 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 levels of serum β2MG, serum creatinine (Scr), 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), and the normal range of β2MG was (1.0 - 3.0) mg/L. The levels of N-terminal pro-brain natriuretic peptide (NT-proBNP)

and cardiac troponin I (cTnI) were measured using a fluorescence immunoassay (TZ-310 Dry fluorescence immunoassay; ReLIA Biotechnologies Ltd., China). White blood cell (WBC) counts were performed using an XT-1800i automatic haematology analyser (SYSMEX Co., Ltd, Japan). The C-reactive protein (CRP) levels were measured 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 levels and partial pressure of arterial oxygen (PaO_2) were measured via spectrophotometry performed by 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) [17]. Disorders of consciousness were identified in accordance with the Glasgow Coma Scale [18]. Septic shock was defined in accordance with the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [19]. 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 hours or by 1.5 times of the baseline level within seven days) [20]. We applied the Sequential Organ Failure Assessment (SOFA) score to assess the disease severity [21].

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

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 levels, cTnI levels, PCT levels, PT, lactic acid levels, PaO_2/FiO_2 ratio, Ccr, AKI and SOFA score in the multivariate Cox regression analysis. Survival rates grouped by β2MG tertiles 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 characteristics curves (ROC-AUCs) for different risk factors were compared using the method of DeLong et al. (1988) by MedCalc [22]. 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 of257patients with ARDS were enrolled in this study.A flow chart of patient enrolment and outcomes is shown in Figure1.

Demographic and clinicalcharacteristics ofsurvivorsvs non-survivors

For all the 257 patients, 189 (73.5%) had a level of serum β2MG > 3.0 mg/L. Table 1 shows the demographic andclinicalcharacteristics ofthe 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 4.7 (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 cTnI levels ($P= 0.001$), lowerNT-proBNP levels ($P< 0.001$), lower PCT levels ($P= 0.008$), lowerlactic acid levels($P< 0.001$), shorter PTs($P = 0.001$), higher Ccr ($P< 0.001$), higheralbumin levels ($P= 0.002$),and higher PaO_2/FiO_2 ratios ($P< 0.001$).Survivors also hadlower SOFA scores($P< 0.001$) than non-survivors. More non-survivors had septic shock ($P = 0.001$) and AKI ($P< 0.001$)than survivors. There was no difference in the duration of mechanical ventilation (MV) between survivors and non-survivors ($P= 0.514$).

Analyses ofβ2MG and other variables by rank correlation

The serumβ2MG levelswere positively correlated with age,updated CCI,disorders of consciousness,septic shock,cTnI levels,PCTlevels,lactic acidlevels, PT,AKI and SOFA scores, and negativelycorrelated withalbuminlevel, PaO_2/FiO_2 ratio and Ccr ($P < 0.05$ for all). 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 levels and CRP levels (Spearman correlation coefficient: 0.547; $P < 0.001$) (Table 2).

Univariate and multivariate survival analyses

A univariate Cox regression analysis revealed thatthe level ofserum β2MGis apredictor of 28-day mortality in patients with ARDS (HR: 1.099; 95% CI: 1.068 - 1.131; $P < 0.001$)(Table 3). Other predictors of 28-day mortality in these patients included age, updated CCI,disorders of consciousness,septic shock, albuminlevel,PCTlevel,lactic acidlevel, PT,PaO_2/FiO_2 ratio,Scrlevel,Ccr, AKI and SOFA score ($P < 0.05$ for all).

Since there was similar clinical significance and a significant negative correlation between Scr and Ccr (Spearman correlation coefficient: - 0.887; $P < 0.001$), to reduce data duplication, we did not include Scr into the multivariate Cox proportional hazards analysis. 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, PaO_2/FiO_2 ratio, Ccr, AKI and SOFA score (HR: 1.054; 95% CI: 1.005 - 1.105; $P = 0.031$) (Table 3).

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: 3.239; 95% CI: 1.177 - 8.913; $P = 0.023$) after adjusting for age, updated CCI, disorders of consciousness, septic shock, albumin level, cTnI level, PCT level, lactic acid level, PT, PaO_2/FiO_2 ratio, Ccr, AKI and SOFA score (Figure 2).

Multivariate survival analysesstratified by Ccr

Further stratified analyses according to Ccr showed that serum β2MG level was independently associated with 28-day mortality not only in patients with Ccr ≤ 60 mL/min (HR: 1.054; 95% CI: 1.008 - 1.102; $P = 0.022$) but also in patients with Ccr > 60 mL/min (HR: 1.439; 95% CI: 1.047 - 1.979; $P = 0.025$) (Table 4).

Theprognosticvalue of serum β2MG levels on28-daymortality

Theserum β2MG levelshowedadiagnostic accuracy for prediction for mortality (AUC = 0.732; 95% CI:0.673- 0.785;sensitivity:74.0%, specificity: 64.0%; *P*< 0.001)superior to that ofPaO_2/FiO_2 ratio(AUC= 0.633; 95% CI: 0.570- 0.692; sensitivity:71.9%, specificity: 50.3%; *P*< 0.001;*P* =0.032 for these two curves), and not inferior to SOFA score (AUC= 0.701; 95% CI: 0.641- 0.756; sensitivity: 60.4%, specificity:68.3%; *P*< 0.001;*P* = 0.313 for these two curves) (Figure 3), when the cut-off value of the serum β2MG level was 4.6 mg/L.

Discussion

This study observed that the levels of serum β2MG in patients with ARDS caused by bacterial infection were elevated and were significantly higher in non-survivors than in survivors. A multivariate Cox proportional hazards analysis revealed that the serum 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, PaO_2/FiO_2 ratio, Ccr, AKI and SOFA score. To our knowledge, this is an earlier report suggesting that the serum β2MG level might have a predictive value for the outcomes of patients with ARDS caused by bacterial infection.

The level of serum β2MG depends on the factors of production (non-kidney factors) and elimination (kidney factors). Due to these properties, β2MG is not only an ideal endogenous biomarker for estimating the glomerular filtration rate and AKI [6-9] and the adverse outcomes of chronic kidney disease [23], but also associated with a number of clinical states beyond kidney disease [11-16]. 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 [16, 24]. Some research has suggested that β2MG is probably a general biomarker that reflects acute or chronic changes during inflammation and infection [25-27]. 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 [11, 28]. Levels of serum β2MG are independently associated with major cardiovascular events and mortality in the general population as well as in elderly patients and in patients with acute heart failure who do not have severe renal insufficiency [13, 15, 29]. Studies have shown that serum β2MG levels are also associated with poor outcomes in patients with COPD and in patients with acute pulmonary embolism [12, 14].

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 [30]. Hadzimuratovic et al. observed increased serum β2MG levels in neonatal asphyxia [31]. 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 during inflammatory responses [25, 27]. In this study, 189 (73.5%) patients had a level of serum β2MG > 3.0 mg/L, and the median 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 levels and CRP levels. These correlations suggest that elevated serum β2MG levels during ARDS may partially be associated with hypoxemia as well as with inflammation and infection. In addition, ARDS is often accompanied by organ dysfunctions, especially AKI. In this research, more than half of the patients developed AKI, accompanied by a decline in glomerular filtration rate (median Ccr 43.0 mL/min), which may lead to decreased clearance of serum β2MG. Altogether, in case of ARDS caused by bacterial infection, severe hypoxemia, infection, inflammatory responses, as well as the impairment of kidney function, result in increased β2MG production and decreased renal eliminate, ultimately leading to elevated serum β2MG levels, which are positively correlated with disease severity.

After adjusting for age, updated CCI, disorders of consciousness, septic shock, albumin level, cTnI level, PCT level, PT, lactic acid level, PaO_2/FiO_2 ratio, Ccr, AKI and SOFA score, the β2MG level was independently associated with 28-day mortality in patients with ARDS. Further stratified analyses revealed that serum β2MG level was independently associated with 28-day mortality regardless of Ccr ≤ 60 mL/min or Ccr > 60 mL/min [32]. It is generally believed that serum β2MG level is associated with renal function injury and its adverse prognosis [9, 23]. At present, the non-renal factors related to serum β2MG and mortality are not clear. Several studies have shown that β2MG can act as an inflammatory cytokine and fibrosis related factor [33] and participate in the development of kidney and liver fibrosis [34, 35]. Under pressure overload, β2MG promotes cardiac fibrosis and activation of cardiac fibroblasts [36]. Research by Wu et al showed that increased serum β2MG expression led to epithelial mesenchymal transition, alveolar wall/septal thicken, and pulmonary fibrosis in a rat model of COPD, and lead to decreased diffusion capacity in the lungs of patients with COPD [37]. These results suggest a possible direct pathogenic role for circulating β2MG. It is unknown currently whether a similar pathogenic role exists for β2MG in patients with ARDS. Kono et al reported that direct hemoperfusion with a β2MG-selective adsorbent column can eliminates inflammatory cytokines and improves pulmonary oxygenation in patients with ARDS/acute lung injury [38]. This supports a possible pathogenic role for circulating β2MG in ARDS.

We applied the updated CCI [17] to assess comorbidities of enrolled patients, including coronary heart disease, congestive heart failure, cerebrovascular disease, diabetes mellitus, dementia, connective tissue disease, liver disease, and kidney disease, and found that it was significantly associated with 28-day mortality in patients with bacterial infection-induced ARDS. This result is consistent with previous research [39].

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 [19, 40, 41]. Similarly, our study showed that the PaO_2/FiO_2 ratio was a protective factor for the prognosis of patients with ARDS.

In this study, SOFA score was also independently associated with 28-day mortality in patients with ARDS. Both the serum β2MG level and the SOFA score exhibited high diagnostic accuracy for predicting 28-day mortality with no significantly difference. And the diagnostic accuracy of serum β2MG level was not inferior to the combination of serum β2MG level and SOFA score. The serum β2MG level showed satisfactory forecasting ability for mortality significantly higher than that of the PaO_2/FiO_2 ratio. Since the PaO_2/FiO_2 ratio only reflects the severity of lung injury, while serum β2MG level is associated with hypoxemia, infection, systemic inflammatory response, renal injury and more comprehensively reacts the overall condition of ARDS. The diagnostic value of serum β2MG for mortality in patients with ARDS is better than that of PaO_2/FiO_2 ratio and is not inferior to SOFA score, which is commonly used as critical care score. Therefore, the serum β2MG may be an ideal screening tool for mortality in patients with ARDS as it can be easily and economically measured.

It is also worth mentioning that there are several limitations in the present study. First, 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 some potentially relevant variables were not evaluated. Third, 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 the causes of elevated β2MG and the specific mechanism associated with prognosis, to verify the prognostic value of serum β2MG levels in patients with ARDS caused by bacterial infection.

Conclusions

The level of serum β2MG, measured within 24 hours after the diagnosis of ARDS, is elevated and may be a promising early biomarker of prognosis 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

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. Oral informed consent was obtained from all subjects and/or their legal guardian(s).

Consent for publication

Not applicable.

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.

Competing interests

The authors declare that they have no competing interests.

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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. NC and XKF contributed equally to this article and shared first authorship. LMZ and JW contributed equally to this article and shared corresponding authorship.

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Author details

[1] Department of Respiratory and Critical Care Medicine, Beijing Institute of Respiratory Medicine and Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China; [2] Department of Respiratory and Critical Care Medicine, Qinghai Provincial People's Hospital, Qinghai University, Xining, China

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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
BMI (kg/m^2)	24.3 ± 4.6	24.4 ± 4.4	24.3 ± 5.0	0.860
Current smoker, n (%)	107 (41.6)	69 (42.9)	38 (39.6)	0.607
CCI updated	2 (1, 3)	1 (0, 3)	2 (1, 3)	< 0.001
Disorders of consciousness, n (%)	61 (23.7)	33 (20.5)	28 (29.2)	0.114
Septic shock, n (%)	127 (49.4)	67 (41.6)	60 (62.5)	0.001
β2MG (mg/L)	4.7 (2.9, 8.5)	3.7 (2.5, 6.4)	6.3 (4.3, 12.3)	< 0.001
β2MG level increased, n (%)	189 (73.5)	102 (63.4)	96 (90.6)	< 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, 103.6)	33.2 (18.6, 57.9)	< 0.001
AKI, n (%)	154 (59.9)	82 (50.9)	72 (75.0)	< 0.001
Albumin (g/L)	26.5 (23.6, 30.0)	27.1 (24.1, 30.8)	25.1 (22.0, 29.3)	0.002
TBIL (μmol/L)	20.8 (13.1, 31.6)	20.8 (12.7, 31.0)	20.8 (13.2, 35.2)	0.674
ALT (U/L)	31.0 (18.5, 66.4)	29.7 (17.8, 59.6)	32.9 (18.8, 84.5)	0.337
cTnI (ng/mL)	0.10 (0.04, 0.35)	0.10 (0.03, 0.24)	0.14 (0.06, 0.53)	0.001
NT-proBNP (pg/mL)	1830.6 (557.8, 4887.3)	1212.7 (325.8, 4050.0)	2812.0 (1447.0, 7078.3)	< 0.001
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 (86, 120)	120 (102, 120)	0.595
PCT (ng/mL)	5.6 (0.8, 18.4)	3.7 (0.4, 15.4)	6.3 (1.9, 24.6)	0.008

PT (s)	13.9 (12.7, 15.8)	13.8 (12.5, 15.0)	14.9 (13.3, 17.3)	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)	
Duration of MV (days)	8 (5, 17)	8 (5, 18)	8 (4, 16)	0.514
SOFA score	8 (5, 10)	7 (4, 9)	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: AKI, acute kidney injury; ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; BMI, body mass index; β2MG, β2-microglobulin; CCI, Charlson comorbidity index; Ccr, creatinine clearance rate; CRP, C-reactive protein; cTnI, cardiac troponin I; FiO_2, fraction of inspired oxygen; FPG, fasting plasma glucose; IQR, interquartile range; Mild, 200 mmHg < PaO_2/FiO_2 ratio ≤ 300 mmHg; Moderate, 100 mmHg < PaO_2/FiO_2 ratio ≤ 200 mmHg; MV, mechanical ventilation; NT-proBNP, N-terminal pro-brain natriuretic peptide; PaO_2, partial pressure of arterial oxygen; PCT, procalcitonin; PT, prothrombin time; Scr, serum creatinine; SD, standard deviation; Severe, PaO_2/FiO_2 ratio ≤ 100 mmHg; SOFA, Sequential Organ Failure Assessment; TBIL, total bilirubin; WBC, white blood cell.

Table 2

Rank correlation between β2MG and basic variables in patients with ARDS

Variables	Correlation coefficient	*P* value
Age (years)	0.246	< 0.001
Male	-0.031	0.618
BMI (kg/m^2)	0.007	0.916
Current smoker	-0.041	0.508
CCI updated	0.204	0.001
Disturbance of consciousness	0.166	0.008
Septic shock	0.278	< 0.001
Scr (μmol/L)	0.821	< 0.001
Ccr (mL/min)	-0.817	< 0.001
AKI	0.696	< 0.001
Albumin (g/L)	-0.231	< 0.001
TBIL (μmol/L)	0.082	0.189
ALT (U/L)	-0.057	0.362
cTnI (ng/mL)	0.362	< 0.001
NT-proBNP (pg/mL)	0.557	< 0.001
FPG (mmol/L)	0.003	0.963
WBC (×10^9/L)	0.153	0.014
CRP (mg/L)	0.113	0.071
CRP* (mg/L)	0.547	< 0.001
PCT (ng/mL)	0.421	< 0.001
PT (s)	0.202	0.001
Lactic acid (mmol/L)	0.214	0.001
PaO_2/FiO_2 ratio	-0.171	0.006
SOFA score	0.611	< 0.001

P < 0.05 were considered statistically significant.

* CRP level of <120 mg/L.

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

Table 3

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)	1.099 (1.068, 1.131)	< 0.001	1.054 (1.005, 1.105)	0.031
Age (years)	1.019 (1.005, 1.033)	0.008	1.016 (0.998, 1.034)	0.074
CCI updated	1.231 (1.097, 1.381)	< 0.001	1.176 (1.033, 1.340)	0.014
Disorders of consciousness	1.610 (1.036, 2.501)	0.034	0.871 (0.515, 1.473)	0.606
Septic shock	2.043 (1.351, 3.090)	0.001	0.996 (0.602, 1.648)	0.988
Albumin (g/L)	0.938 (0.902, 0.976)	0.001	0.966 (0.929, 1.005)	0.089
cTnI (ng/mL)	1.044 (0.950, 1.147)	0.374	1.003 (0.879, 1.144)	0.966
PCT (ng/mL)	1.021 (1.003, 1.039)	0.022	1.002 (0.982, 1.023)	0.828
PT (s)	1.019 (1.004, 1.034)	0.011	1.004 (0.987, 1.022)	0.611
Lactic acid (mmol/L)	1.104 (1.062, 1.146)	< 0.001	1.022 (0.976, 1.071)	0.350
PaO_2/FiO_2 ratio	0.994 (0.991, 0.998)	0.001	0.996 (0.992, 1.000)	0.030
Ccr (mL/min)	0.986 (0.979, 0.992)	< 0.001	1.002 (0.989, 1.016)	0.715
AKI	2.503 (1.576, 3.976)	< 0.001	1.169 (0.513, 2.665)	0.711
SOFA score	1.146 (1.096, 1.199)	< 0.001	1.087 (1.000, 1.182)	0.049
Male	1.143 (0.745, 1.753)	0.542		
BMI (kg/m^2)	0.988 (0.943, 1.034)	0.604		
Current smoker	0.906 (0.602, 1.364)	0.637		
Scr (μmol/L)	1.002 (1.001, 1.003)	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)	0.173		
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)	1.006 (0.998, 1.015)	0.151		

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, PaO_2/FiO_2 ratio, Ccr, AKI and SOFA score. $P < 0.05$ were considered statistically significant.

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

Table 4

Multivariate survival analysis of the 28-day mortality risk stratified by Ccr in patients with ARDS

Clinical characteristics	Ccr ≤ 60 mL/min group (n=155)		Ccr > 60 mL/min group (n=102)	
	Multivariate HR (95% CI)	*P* value	Multivariate HR (95% CI)	*P* value
β2MG (mg/L)	1.054 (1.008, 1.102)	0.022	1.439 (1.047, 1.979)	0.025
Age (years)	1.026 (1.004, 1.048)	0.018	0.965 (0.932, 0.999)	0.043
CCI updated	1.132 (0.980, 1.308)	0.093	1.599 (1.139, 2.245)	0.007
Disorders of consciousness, n (%)	0.888 (0.499, 1.578)	0.685	1.012 (0.196, 5.231)	0.989
Septic shock, n (%)	1.104 (0.616, 1.980)	0.740	0.670 (0.237, 1.897)	0.451
Albumin (g/L)	0.966 (0.923, 1.012)	0.144	0.956 (0.859, 1.064)	0.407
cTnI (ng/mL)	0.989 (0.860, 1.138)	0.880	1.302 (0.640, 2.651)	0.455
PCT (ng/mL)	0.999 (0.977, 1.021)	0.914	0.964 (0.915, 1.016)	0.176
PT (s)	1.003 (0.984, 1.021)	0.784	1.327 (1.055, 1.669)	0.016
Lactic acid (mmol/L)	1.025 (0.975, 1.077)	0.328	1.252 (0.869, 1.803)	0.225
PaO_2/FiO_2 ratio	0.996 (0.992, 1.001)	0.086	0.997 (0.989, 1.005)	0.486
SOFA score	1.059 (0.969, 1.157)	0.205	1.272 (1.003, 1.614)	0.047

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, PaO_2/FiO_2 ratio and SOFA score. $P < 0.05$ were considered statistically significant.

Abbreviations: ARDS, acute respiratory distress syndrome; β2MG, β2-microglobulin; CCI, Charlson comorbidity index; Ccr, creatinine clearance rate; CI, confidence interval; cTnI, cardiac troponin I; FiO_2, fraction of inspired oxygen; HR, hazard ratio; PaO_2, partial pressure of arterial oxygen; PCT, procalcitonin; PT, prothrombin time; SOFA, Sequential Organ Failure Assessment.

Figures

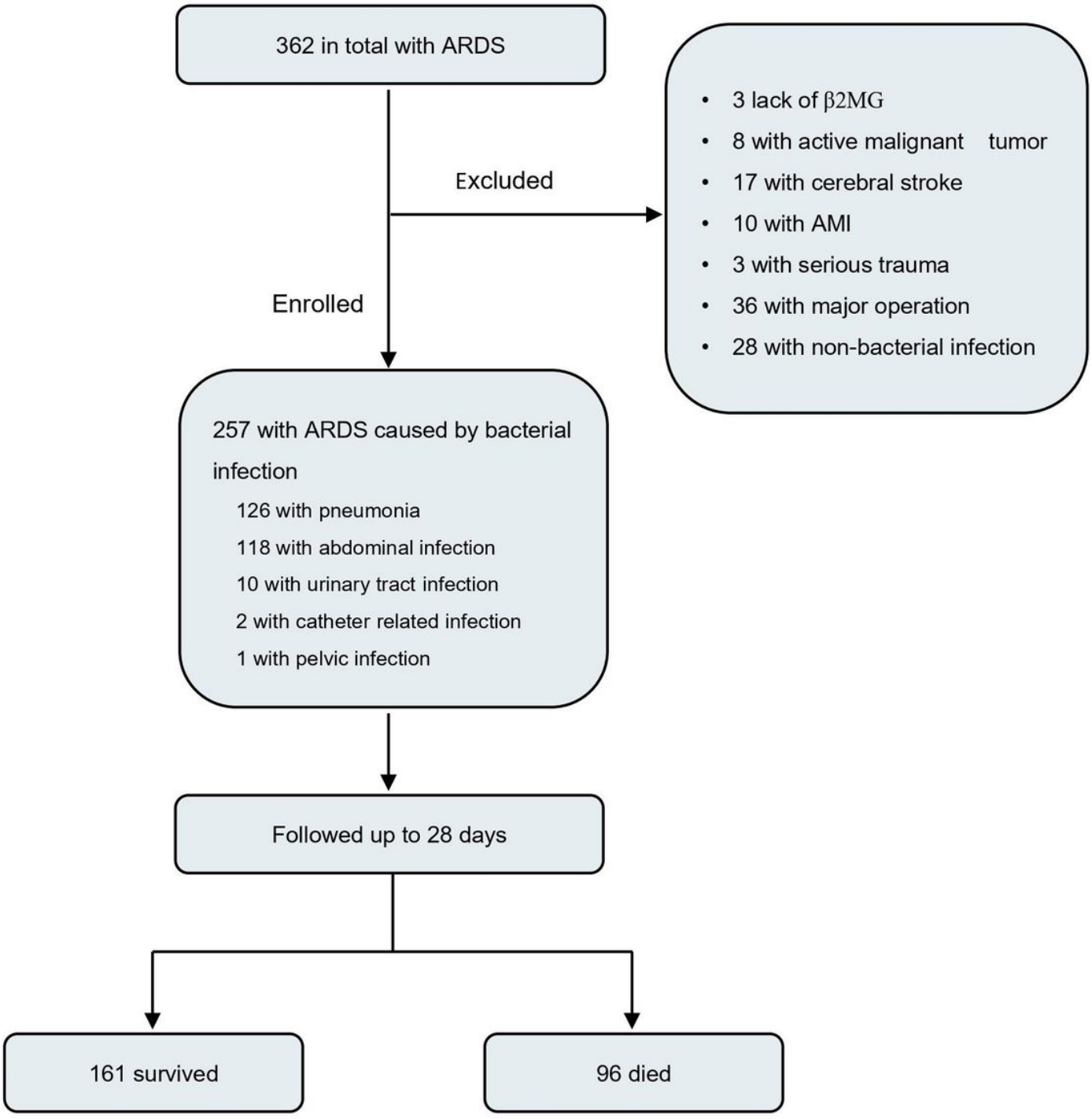

Figure 1

Flow chart of the patient enrollment and outcomes in this study.

Abbreviations: AMI, acute myocardial infarction; ARDS, acute respiratory distress syndrome; β2MG, β2-microglobulin.

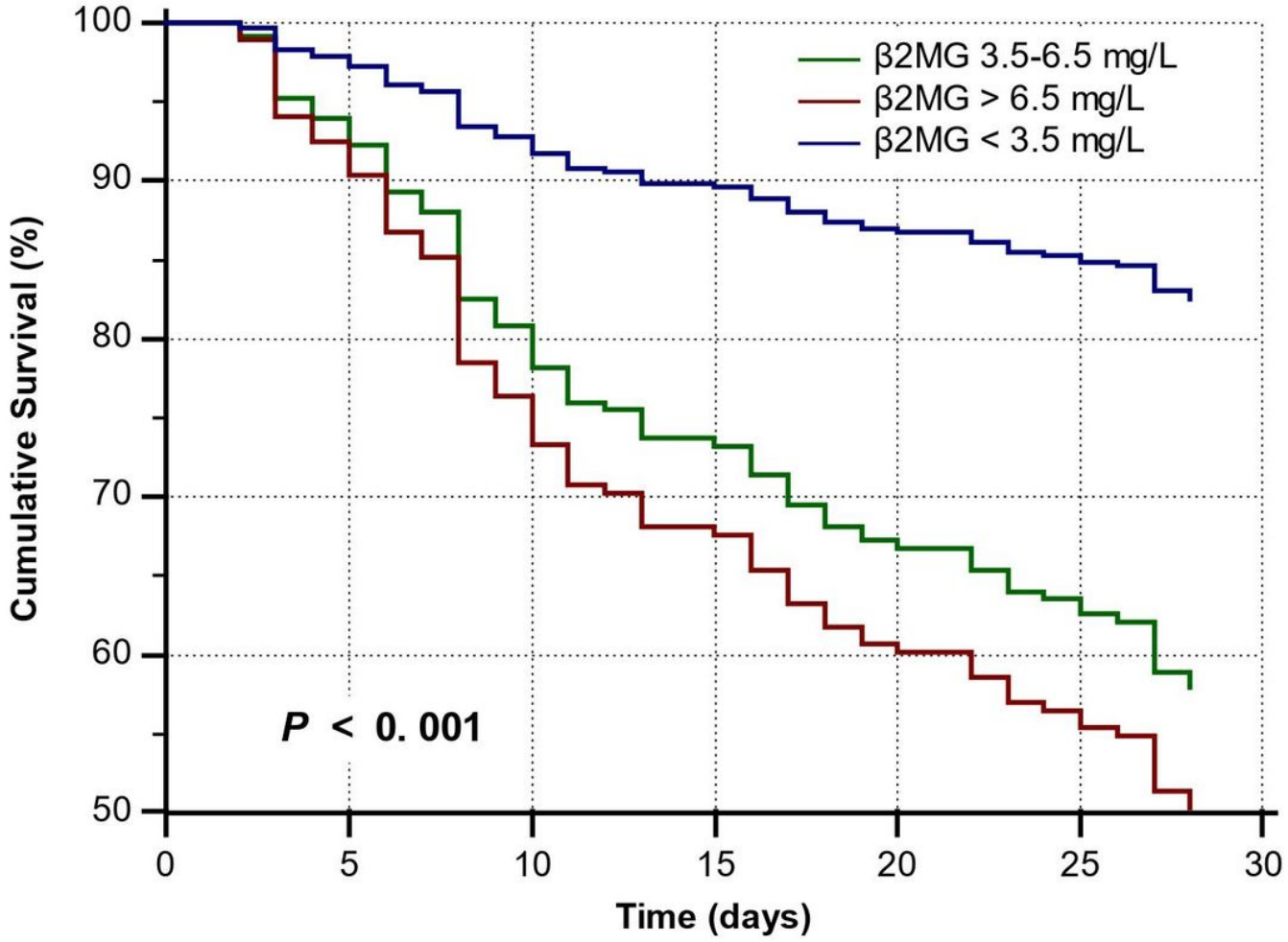

Figure 2

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 PaO_2/FiO_2 ratio, Ccr, AKI and SOFA score.

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; β2MG, β2-microglobulin; CCI, Charlson comorbidity index; Ccr, creatinine clearance rate; cTnI, cardiac troponin I; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PCT, procalcitonin; PT, prothrombin time; SOFA, Sequential Organ Failure Assessment.

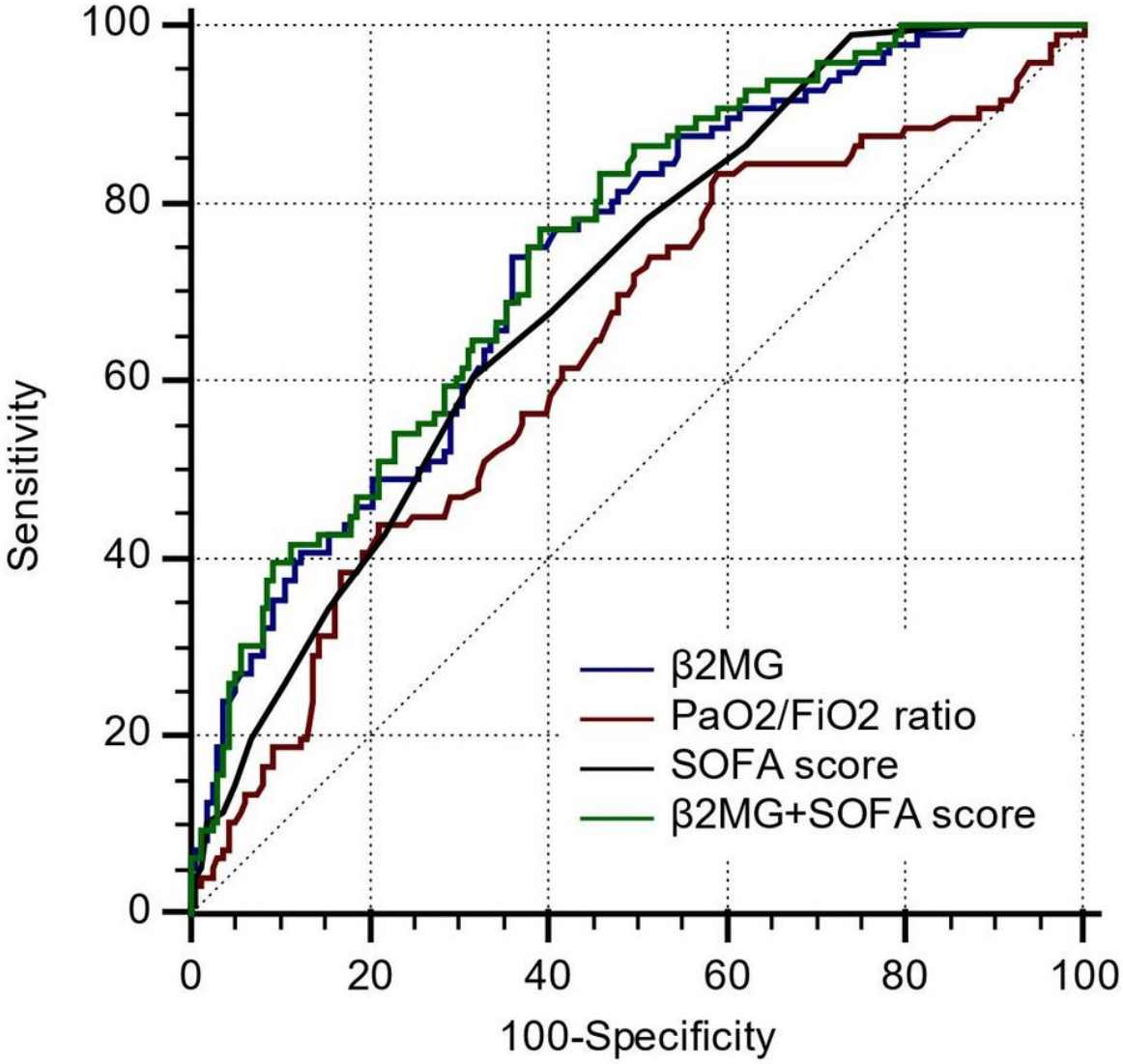

Figure 3

Prediction of 28-day mortality in patients with ARDS.

Supplementary Files

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