Diagnostic Accuracy of Plasma Ghrelin Concentrations in Pediatric Sepsis -associated ARDS: A Single-center Cohort Study

xiu yuan
Chongqing Medical University Affiliated Children's Hospital
Shaojun Li
Chongqing Medical University Affiliated Children's Hospital
Liang Zhou
Chongqing Medical University Affiliated Children's Hospital
yanru LI
Chongqing Medical University Affiliated Children's Hospital
tian tang
Chongqing Medical University Affiliated Children's Hospital
Yuwei Cheng
Chongqing Medical University Affiliated Children's Hospital
Xiaoxiao Ao
Chongqing Medical University Affiliated Children's Hospital
Liping Tan (tanlp0825@hotmail.com)
Chongqing Medical University Affiliated Children's Hospital

Research article

Keywords: sepsis, sepsis-associated PARDS, ghrelin, inflammatory factors, Child, respiratory distress syndrome

Posted Date: August 13th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-49171/v1

Abstract

Background: Ghrelin is the endogenous ligand of growth hormone secretagogue receptor 1a (GHSR1a), which can regulate immunity and inflammation. To assess the diagnostic value of plasma ghrelin levels in sepsis-associated pediatric acute respiratory distress syndrome (PARDS).

Methods: We recruited patients from the PICU of a third-class teaching hospital who met the diagnostic criteria for sepsis from January 2019 to January 2020. Clinical data, laboratory indicators, plasma ghrelin concentrations, and inflammatory factors of cohort were evaluated in detail, and patients were followed up for 28 days. The area under the receiver-operating characteristic curves (AUROC) was calculated using logistic regression to calculate and positivity cut-offs was tested. Ghrelin's ability to diagnose and differentiate sepsis-associated PARDS were determined. The log-rank test was used to compare the survival curves of different ghrelin level groups.

Main results: Sixty-six PICU patients (30 with ARDS, 36 without ARDS) who met the diagnostic criteria of sepsis were recruited. The ghrelin level was significantly higher in the sepsis patients of the ARDS group than in those of the non-ARDS group. The AUROC of ghrelin was 0.708 (95% confidence interval: 0.584–0.833) and the positivity cutoff value was 445 pg/mL. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), and negative likelihood ratio (−LR) of plasma ghrelin for diagnosis of sepsis with PARDS were 86.7%, 50.0%, 59.1%, 81.8%,1.734, and 0.266, respectively. The survival rate of sepsis patients was significantly improved when the ghrelin level was >445 pg/mL.

Conclusions: Ghrelin plasma was higher in sepsis-associated PARDS, and accompanied by the increase of inflammatory factors. The increased plasma ghrelin may be due to the anti-inflammatory response, which may be a protective factor in children with sepsis. Yet, there is no evidence to prove that elevated ghrelin appears to be a promising diagnostic indicator of sepsis-associated PARDS. In addition, the ghrelin levels may be a positive predictor of sepsis.

Trial registration: Clinicaltrials, ChiCTR1900023254. Registered 1 December 2018 - Retrospectively registered, http://www.clinicaltrials. gov/ChiCTR1900023254.

Background

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection, and it is characterized by high incidence, high mortality, and high treatment costs[1]. Among all the organs that become vulnerable in sepsis, the lung is considered to be the most vulnerable target organ. Sepsis is often complicated with acute lung injury and even ARDS, and the latter is one of the main causes of death in sepsis[2]. Therefore, a correct and timely diagnosis and evaluation of sepsis are very important to reduce mortality associated with this condition. Currently, studies have shown the roles of various biomarkers such as cell surface markers, cytokines, procalcitonin (PCT), and C-reactive protein (CRP) in the diagnosis, severity, and prognosis of sepsis[3]. Initiation of a systemic inflammatory response

forms the basis of the pathogenesis of sepsis-associated PARDS. Some indicators such as tumor necrosis factor-α (TNF- α), interleukin-6 (IL-6), interleukin-10 (IL-10) are used in the clinical setting as early biomarkers to guide the early diagnosis and treatment of sepsis-associated ARDS[4–6]. However, the incidence of ARDS and the mortality factors of sepsis-related ARDS are unclear in pediatric patients. Although some progress has been made in research on the pathogenesis and treatment of sepsis-associated ARDS, many recent clinical studies and meta-analyses have demonstrated that the total mortality rate of sepsis-associated PARDS remains as high as 27–45%[7–9].

Ghrelin is an endogenous brain-gut peptide that was first discovered in 1999. It attracted considerable attention at that time, mainly because of its endocrine and appetite regulation[10]. Ghrelin is an endogenous ligand of the G protein-coupled growth hormone secretagogue receptor (GHSR1a). It is an appetite stimulant and has a regulatory effect on immunity[11]. Recent studies have focused on the anti-inflammatory effect of ghrelin. Ghrelin and its receptors are expressed in immune tissues and immune cells that possess anti-inflammatory effects and can inhibit the secretion of proinflammatory factors such as IL-6 and TNF-α in activated monocytes, T lymphocytes, and endothelial cells[12]. In addition to its anti-inflammatory effects, ghrelin can inhibit apoptosis and improve immunity. Recently, clinical studies have demonstrated increased plasma ghrelin concentration in systemic inflammatory models such as severe pancreatitis, acute colitis, inflammatory bowel disease, ankylosing spondylitis, and cystic fibrosis[13]. The serum ghrelin concentration has also been reported to increase in critically ill patients[14–16].

However, no studies have investigated the changes in the plasma ghrelin levels in sepsis-associated PARDS. In this single PICU cohort study, we explored the correlation between the ghrelin level and sepsis-related ARDS, determined the diagnostic value of ghrelin in sepsis-related PARDS, and analyzed the prognostic value of the plasma ghrelin level in children with sepsis.

Materials And Methods

Study design and participants

This study was approved by the local Ethics Committee (experimental study approval number 271/2019). Written informed consents were obtained from the patient, parent or designated legal guardian before inclusion in the study. Between January 2019 and January 2020, pediatric patients aged 1 month to 18 years at the PICU of the Children's Hospital affiliated to Chongqing Medical University who met the diagnostic criteria of sepsis[17] were recruited to the study. Patients with underlying diseases such as liver and kidney diseases, genetic and metabolic diseases, and autoimmune diseases and patients less than 1 month or older than 19 years of age were excluded from participation in this study (Fig. 1).

Data collection and ghrelin measurement

Data collection included demographic data (sex, age, and body weight), comorbidities (premature birth, history of lung diseases, chronic respiratory support, home mechanical ventilation, neuromuscular disease, tumor, immune deficiency, and immunosuppression), illness severity metric (pediatric sequential organ failure assessment score [PSOFA], pediatric logistic organ dysfunction [PELOD], pediatric risk of mortality score [PRISM], septic shock), supportive treatment of PICU, inflammatory factors (CRP, white blood cell count, and neutrophil ratio), metabolic indicators (blood glucose), primary infection and outcome metric (hospital days, ICU days, 28-day mortality). Patients were classified as having sepsis with ARDS if they met the Pediatric Acute Lung Injury Consensus Conference (PALICC) definition of ARDS; patients who did not meet this definition were classified as having sepsis without ARDS[18].

Peripheral venous blood samples of all patients were obtained at the 12 hours after admission and before therapeutic intervention. After the samples were collected, they were centrifuged within 2 h of collection at 3000 rpm for 20 minutes. The supernatant plasma was absorbed, packed and stored − 80℃ until the day of assay. The plasma ghrelin level was investigated using a human ghrelin enzyme-linked immunosorbent assay (ELISA) kit (Upstate Chemicon Linco, Millipore, USA) according to the manufacturer's protocol. Absorbance was read at 450 and 590 nm in a plate reader within 5 minutes. A reference curve was constructed by plotting the absorbance units of 450 nm subtract 590 nm on the Y-axis against the concentrations of the ghrelin standard on the X-axis. Then, the ghrelin concentration of sepsis patients was measured against this standard curve. Plasma levels of inflammatory molecules IL-6, IL-10, TNF-α, and IL-1β were measured by ELISA according to the manufacturer's instructions (Shen Zhen, NeoBioscience Technology, China). Absorbance was read at 450 nm in a plate reader within 5 min. A reference curve was constructed by plotting the absorbance at 450 nm on the Y-axis against the concentrations of the ghrelin standard on the X-axis. Then, we calculated the IL-6, IL-10, TNF-α, and IL-1β concentrations of patients with sepsis.

Data And Statistical Analysis

First, we compared the general characteristics of sepsis with or without ARDS. Then, we compared the plasma concentrations of ghrelin and inflammatory factors between sepsis with or without ARDS. Next, we studied the correlation between ghrelin and plasma concentrations of these inflammatory factors. Then, we calculated area under the ROC between ghrelin concentration and ARDS, and the positivity cut-offs. The diagnostic test was carried out according to the positivity cut-offs of ghrelin and whether or not sepsis-associated ARDS was present, and the relevant indices such as the sensitivity, specificity, PPV, NPV, and Youden index were reported. +LR was calculated from sensitivity (1-specificity), and − LR was calculated as (1-sensitivity)/specificity[19]. In addition, according to the positivity cut-offs of ghrelin, the patients were divided into two groups, and the survival curve of the two groups were compared.

The sample size calculation for patients was done according to the pre-experimental results, where the ghrelin levels in pediatric patients with sepsis with and without ARDS were 403.8 ± 173.8 and 645.9 ±

251.2, respectively, indicating that a sample size of 16 patients per group is required to obtain a power of 80% for a significance level of 0.05 with a two-tailed test.

The measurement of non-normally distributed data was expressed as median and quartile spacing. Two samples were compared using the Wilcoxon rank-sum test, and multiple samples were compared using the Kruskal–Wallis test. Normally distributed data were reported as means ± standard deviation (X ± S). The *t* test was used to compare the variance between two groups of independent samples. One-way analysis of variance was used to compare the means between multiple samples, and Person's correlation coefficient was used to test the correlation. Correlation analysis was performed suing Spearman's correlation coefficient. Logistic regression analysis was used to calculate the area under the ROC between ghrelin concentrations and ARDS, and the positivity cut-offs were calculated. The survival differences between the two data groups were compared and analyzed by the log-rank test. SPSS version 21.0 (SPSS, IBM, USA) was used for the statistical analysis.

Results

Characteristics of pediatric sepsis patients with or without ARDS

A total of 101 pediatric patients in the PICU met the diagnostic criteria of sepsis. Of these, 24 were excluded from the study analysis based on the exclusion criteria defined for this study. Finally, 66 patients were enrolled, of which 30 were with ARDS and 36 were without ARDS (Fig. 1). The demographic and clinical characteristics of the enrolled patients are shown in Table 1. The quartile spacing of age in sepsis with and without ARDS were 0.42–1.5 and 0.61–12.17 years, respectively, and no significant differences were found in the age and sex between groups (p = 2 and p = 0.16, respectively). The presence of underlying diseases, disease severity, and supportive treatment in the PICU during hospitalization did not differ between the two groups. The difference in primary infection at enrollment was significant between the two groups (p = 0.001). Pulmonary infection was the main infection in the sepsis group with ARDS. In the 28-day follow-up, 9 of the 30 patients in the sepsis with ARDS group died and 10 of the 36 patients in the sepsis without ARDS group died, and the difference between the two groups was not statistically significant (p = 0.843). Other patient outcomes (PICU hospitalization time, ventilator-free days [invasive ventilation], ventilator-free days [invasive and non-invasive ventilation], invasive ventilation duration for 28-day follow-up, duration of non-invasive and invasive ventilation in the 28-day follow-up) significantly differed between the sepsis with ARDS and sepsis without ARDS groups (p < 0.001, p < 0.001, p = 0.001; p < 0.001, and p = 0.001, respectively).

Table 1
Baseline patient characteristics

Parameter	All patients (n = 66)	Sepsis without ARDS (n = 36)	Sepsis with ARDS (n = 30)	P value
Baseline demographic				
Sex (male/female)	37/29	23/13	14/16	0.16
Age median [quartile (years)]	0.82 (0.32–5.31)	2.33 (0.61–12.17)	0.72 (0.42–1.5)	0.2
Body weight median [quartile (kg)]	10 (8-28.12)	12.25 (9.55–35.75)	8 (6–21)	0.058
Underlying diseases [n (%)]				
All underlying diseases	15 (22.7%)	5 (13.9%)	10 (33.3%)	0.064
Premature birth	3 (4.5%)	0 (0.0%)	3 (10%)	0.117
Previous lung diseases	9 (13.6%)	5 (13.9%)	4 (13.3%)	0.948
Neuromuscular disease	2 (3.0%)	0 (0.0%)	2 (6.7%)	0.394
Immune deficiency	2 (3.0%)	0 (0.0%)	2 (6.7%)	0.203
Disease severity				
PRISM Ⅲ	7 (3–12)	11 (6-16.25)	6 (3–9)	0.333
PELOD-2	5 (2–8)	7.5 (3.25-9)	5 (2–7)	0.577
pSOFA Scoring	4.5 (3–7)	5 (4–8)	5 (3–7)	0.378
Septic shock	37 (56.1%)	24 (66.7%)	13 (43.3%)	0.057
Supportive treatment of PICU during hospitalization [n (%)]				
HFOV	1 (1.6%)	0 (0.0%)	1 (3.3%)	0.476
ECMO	2 (3.2%)	0 (0.0%)	2 (6.7%)	0.223
CRRT	5 (7.9%)	1 (3.0%)	4 (13.3)	0.296
Vasoactive drugs	35 (55.6%)	13 (39.4%)	22 (73.3%)	0.007
Observation index				
Glucose concentration [median (quartile)]	5.95 (4.9–7.3)	6.3 (4.45–8.2)	6.6 (5.4–7.5)	0.597

Abbreviations: PRISM Ⅲ: Pediatric risk of mortality Ⅲ; PELOD-2: Pediatric Logistic Organ Dysfunction 2; SOFA: sepsis-related organ failure assessment; HFOV: high-frequency oscillation ventilation; ECMO: extracorporeal membrane oxygenation; CRRT: continuous renal replacement therapy; IL-6: interleukin-6; TNF- α: tumor necrosis factor-α; IL-10: interleukin-10; IL-1β: interleukin-1β.

Parameter	All patients (n = 66)	Sepsis without ARDS (n = 36)	Sepsis with ARDS (n = 30)	P value
White blood cell count [median (quartile)]	9.54 (6.63–14.93)	9.82 (6.33–16.25)	8.81 (5.26–22.48)	0.634
Proportion of neutrophils [median (quartile)]	0.72 (0.59–0.84)	0.73 (0.65–0.84)	0.71 (0.49–0.84)	0.529
C-reactive protein [median (quartile)]	29.5 (9.75–65.25)	10 (5.25–54.75)	31 (9–91)	0.747
Detection index				
Plasma ghrelin median [quartile (pg/ml)]	598.37(408.86–1153.0)	506.75 (297.46-1341.45)	645.01 (500.06-1147.6)	0.004
Plasma IL-6 median [quartile (pg/ml)]	100.72 (60.88-177.92)	80.74 (50.57-151.88)	114.71 (69.93-284.75)	0.015
Plasma TNF-α median [quartile (pg/ml)]	14.87 (7.33–25.97)	12.44 (2.94–17.65)	14.87 (8.06–35.46)	0.012
Plasma IL-10 median [quartile (pg/ml)]	11.73 (4.31–26.55)	11.97 (3.77–24.92)	12.76 (5.92–26.93)	0.057
Plasma IL-1β median [quartile (pg/ml)]	8.96 (4.11–33.62)	4.78 (3.53–10.59)	19.82 (7.76–141.50)	0.005
Primary infection [n (%)]				0.001
Pulmonary infection	n = 30 (45.4%)	n = 11 (30.5%)	n = 19 (63.3%)	...
Intracranial infection	n = 7 (10.6%)	n = 7 (19.4%)	n = 0 (0%)	...
Gastrointestinal infection	n = 21 (1.8%)	n = 16 (44.4%)	n = 5 (16.6%)	...
Bloodstream infection	n = 2 (3%)	n = 0 (0%)	n = 2 (6.6%)	...
Other infection	n = 6 (9%)	n = 2 (5.4%)	n = 4 (12.12%)	...
Outcome index				
Hospital days [median (quartile)]	14.5 (8–23)	14.5 (3.25-20)	19 (15–31)	0.03
ICU days [median (quartile)]	6.5 (3–12)	6 (2-9.5)	10 (7–15)	0.000
28-day mortality [n (%)]	19 (28.8%)	10 (27.8%)	9 (30%)	0.843

Abbreviations: PRISM Ⅲ: Pediatric risk of mortality Ⅲ; PELOD-2: Pediatric Logistic Organ Dysfunction 2; SOFA: sepsis-related organ failure assessment; HFOV: high-frequency oscillation ventilation; ECMO: extracorporeal membrane oxygenation; CRRT: continuous renal replacement therapy; IL-6: interleukin-6; TNF- α: tumor necrosis factor-α; IL-10: interleukin-10; IL-1β: interleukin-1β.

Table 2
Diagnostic evaluation index of plasm ghrelin

Index	Ghrelin
AUC(95% Cl)	0.708(0.584–0.833)
Cutoff values	445 pg/ml
Sensitivity	0.867
Specificity	0.500
PPV	0.591
NPV	0.818
+LR	1.734
−LR	0.266
Yuden index	0.367
Abbreviations: OR: odds ratio; Cl: Confidence level; AUC: area under the curve; PPV: positive predictive value; NPV: negative predictive value; +LR: positive likelihood ratio; -LR: negative likelihood ratio.	

Analysis Of Ghrelin Plasma Levels

The plasma ghrelin level was significantly higher in the sepsis with ARDS group than in the sepsis without ARDS group ($p = 0.048$). The levels of inflammatory cytokines IL-6, TNF-α, and IL-1β in the sepsis with ARDS group were all significantly higher than that in the sepsis without ARDS group ($p = 0.049$, $p = 0.006$, $p = 0.048$, respectively), while the IL-10 level in sepsis patients with ARDS did not significantly differ from that in sepsis patients without ARDS ($p = 0.106$; Fig. 2).

The plasma ghrelin level was positively correlated with the IL-6, TNF-α, and IL-1β ($r = 0.401$, $p = 0.001$; $r = 0.296$, $p = 0.015$; and $r = 0.390$, $p = 0.001$; respectively), while it was not correlated with the CRP, leukocyte, and neutrophil counts ($r = 0.178$, $p = 0.155$; $r = -0.122$, $p = 0.397$; $r = -0.101$, $p = 0.485$; respectively; Fig. 3).

Pulmonary infection was the primary infection in the patients, and other primary infections included intracranial, gastrointestinal, and blood infections (Table 1). and there was no significant difference in the plasma ghrelin level in different primary infection causing of sepsis ($p = 0.550$; Fig. 4A).

Our study found that the ghrelin levels were lower in sepsis patients with mechanical ventilation than in those without mechanical ventilation ($P = 0.010$; Fig. 4B).

Diagnostic And Prognostic Efficacy Of Plasma Ghrelin

The AUROC for ghrelin was 0.708 (95% CI: 0.584–0.833, P < 0.001), and the optimal cutoff values were 445 pg/ml. When the ghrelin value was 445, the sensitivity and specificity of the plasma ghrelin level for predicting sepsis with ARDS were 0.867 and 0.500, respectively, and the PPV, NPV, +LR, −LR, and Yuden index of ghrelin testing for the diagnosis of sepsis with ARDS were 59.1%, 81.8%, 1.734, 0.266, and 0.367, respectively.

The results of the survival analysis showed that high ghrelin plasma concentration was a good predictor for a favorable prognosis in patients with sepsis. As shown in the curve, the 28-day survival rate of patients with sepsis was significantly improved when ghrelin was greater than 445 pg/mL than when it was less than 445 pg/mL (P = 0.040; Fig. 6).

Discussion

Ghrelin is an endogenous ligand for the growth hormone secretagogue receptor 1a, and its primary function is to regulate inflammation and immunity[20–23]. In an animal model of sepsis, ghrelin was shown to improve tissue hypoperfusion with severe sepsis[24]. Another clinical study reported that the plasma ghrelin concentrations was significantly increased in adult patients with sepsis, suggesting that high ghrelin levels are a predictor of survival in sepsis[25]. Previous animal studies in animal models of hemorrhagic shock have found that ghrelin might be a protective factor in lung injury[26]. In the model of LPS-induced rat alveolar macrophage (AM) sepsis, ghrelin protects AM against apoptosis *in vivo* and *in vitro* through GHSR-1a, which helps reduce sepsis-induced ARDS[27]. To the best of our knowledge, there is no scientific report on the protective effect of ghrelin in lung injury. Our results showed that the plasma ghrelin level was significantly higher in children with sepsis with ARDS than in those with sepsis without ARDS. Moreover, we found that the IL-6, TNF- α, and IL-1β concentrations remained consistent. Further analysis showed that the ghrelin level was positively correlated with the CRP, IL-6, TNF-α, and IL-1β concentrations, and the plasma ghrelin level in sepsis patients was significantly higher in those receiving mechanical ventilation compared to those without mechanical ventilation. Therefore, we believe that ghrelin may play a protective role in sepsis-mediated lung injury in children with sepsis, as a result of the anti-inflammatory effects due to anti-inflammatory cytokines.

Globally, sepsis is a serious problem in children, and is associated with high mortality and economic burden, and the case fatality rate further increases in patients with sepsis who have ARDS[28]. The SOFA, PELOD, and PRISM scores can be used to judge the severity and prognosis of the disease, including sepsis, but its value in predicting ARDS is limited; developing reliable biomarkers enhance the early identification of ARDS, which can provide a reference for early intervention and the development of new treatments[29–31]. We conducted a ghrelin diagnostic test for pediatric sepsis patients with ARDS. The ROC curve of ghrelin revealed that the AUC of sepsis with ARDS was 0.708, with moderate discrimination. According to the best cutoff value of ghrelin, authenticity evaluation showed good sensitivity and poor specificity, better NPV and general PPV, general negative likelihood ratio and positive likelihood ratio.

Therefore, there is no evidence to show that ghrelin may be used as a biomarker for the early prediction of ARDS in sepsis patients.

Studies from animal models have demonstrated that ghrelin injection into rats with sepsis led to an increase in the ghrelin level in their lungs, alleviation of lung injury, increase in the pulmonary blood flow, downregulation of proinflammatory cytokines, inhibition of NF-kB activation, and increased survival rate[32]. The results of an adult critical illness/sepsis cohort study showed that sepsis patients with higher ghrelin levels had better survival[15, 33]. There are no relevant studies among pediatric patients with sepsis; therefore, we analyzed the survival rates of pediatric sepsis patients with different plasma ghrelin concentrations. Our study found that the survival rate of patients was higher when their plasma ghrelin concentration was > 445 pg/mL than when their plasma ghrelin concentration was < 445 pg/ml. Therefore, ghrelin may be a positive predictor of sepsis in both children and adults.

This is the first study to explore the correlation between the ghrelin level and sepsis with ARDS in children with sepsis, verifying the diagnostic value of ghrelin in children with sepsis-associated ARDS. Furthermore, this study analyzed the prognostic value of the plasma ghrelin level in children with sepsis. There are some limitations in this study. First, this is a single-center PICU cohort of children with sepsis, and the extrapolation of the conclusion is limited. Second, this study did not explore other biomarkers with the potential to have a joint diagnostic value in combination with ghrelin.

Conclusion

Our study suggests that ghrelin may be a protective factor for lung injury in children with sepsis. But there is no evidence to show that the ghrelin level may be a promising diagnostic indicator of sepsis with PARDS. In addition, the ghrelin levels may be a positive predictor of sepsis.

Abbreviations

PARDS
Pediatric acute respiratory distress syndrome
GHSR1a
Growth hormone secretagogue receptor 1a
PPV
Positive predictive value
NPV
Negative predictive value
+LR
Positive likelihood ratio
−LR
Negative likelihood ratio
PCT

Procalcitonin

CRP

C-reactive protein

TNF-α

Tumor necrosis factor-α

IL-6

Interleukin-6

IL-10

Interleukin-10

PSOFA

Pediatric sequential organ failure assessment score

PELOD

Pediatric logistic organ dysfunction

PRISM

Pediatric risk of mortality score

PALICC

Pediatric Acute Lung Injury Consensus Conference

ELISA

Enzyme-linked immunosorbent assay

AM

Alveolar macrophage

Declarations

Ethics approval and consent to participate: All procedures performed in studies involving human participants were following the Ethics Committee of Children's Hospital of Chongqing Medical University(experimental study approval number 271/2019).

Consent for publication: Not applicable.

Availability of data and materials: The necessary clinical data of the patient are presented in the case report. There is no dataset to be shared in public repositories.

Competing interests: No conflict of interest.

Funding: This research was supported by the projects of basic and frontier research, Chongqing Science and Technology Commission (Fund number: cstc2014jcyjA10032).

Authors' contributions: All the authors were responsible for the content of this manuscript and approved to submit. LT designed the study. XY performed study selection, assessment of validity, data analysis, and writing of the paper, SL participated in the revision of the paper, while LZ, TT, YC, and XA performed data extraction and retrieval of bibliographies.

Acknowledgements: Not applicable.

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Figures

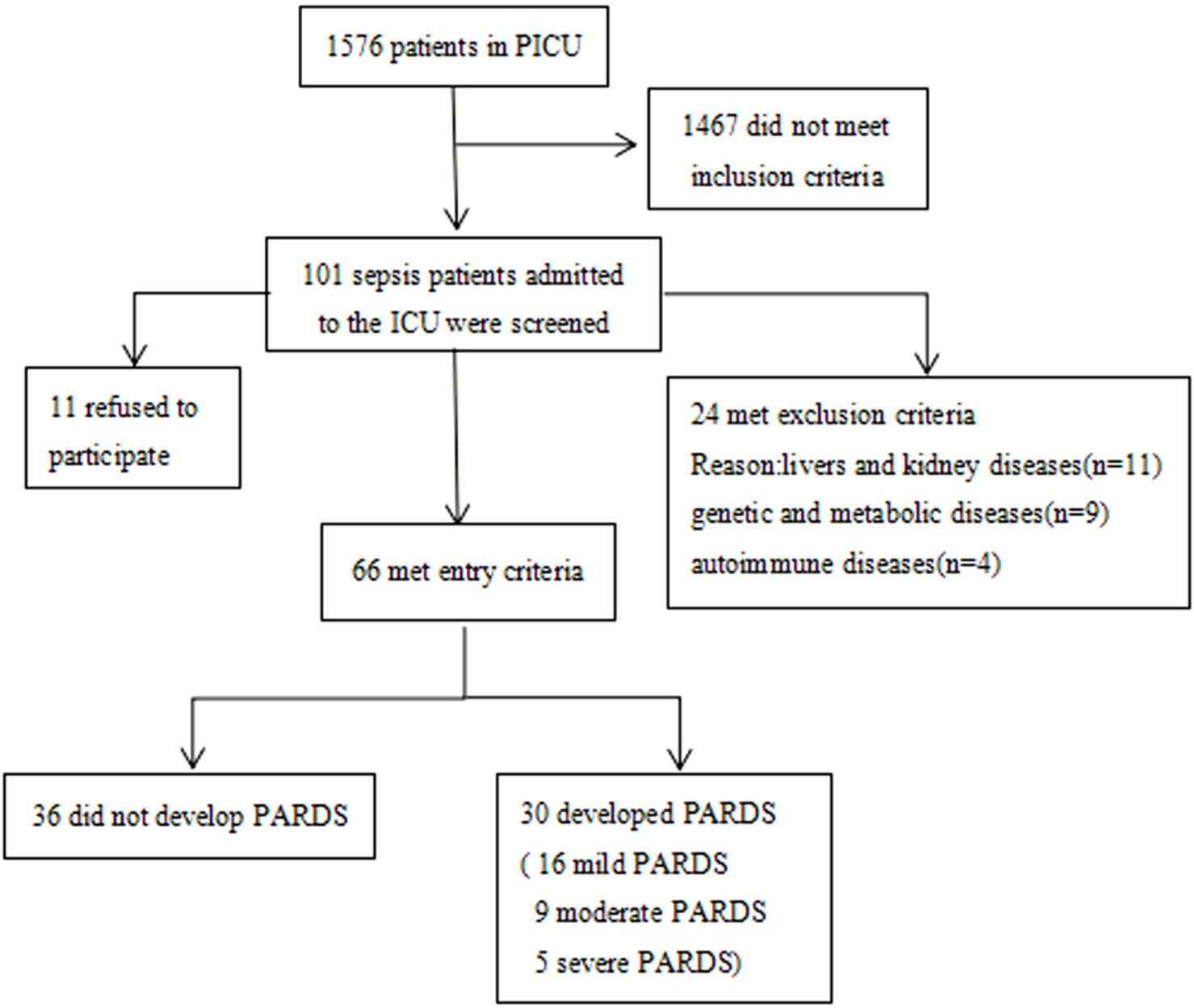

Figure 1

Flowchart of all the patients included in this study.

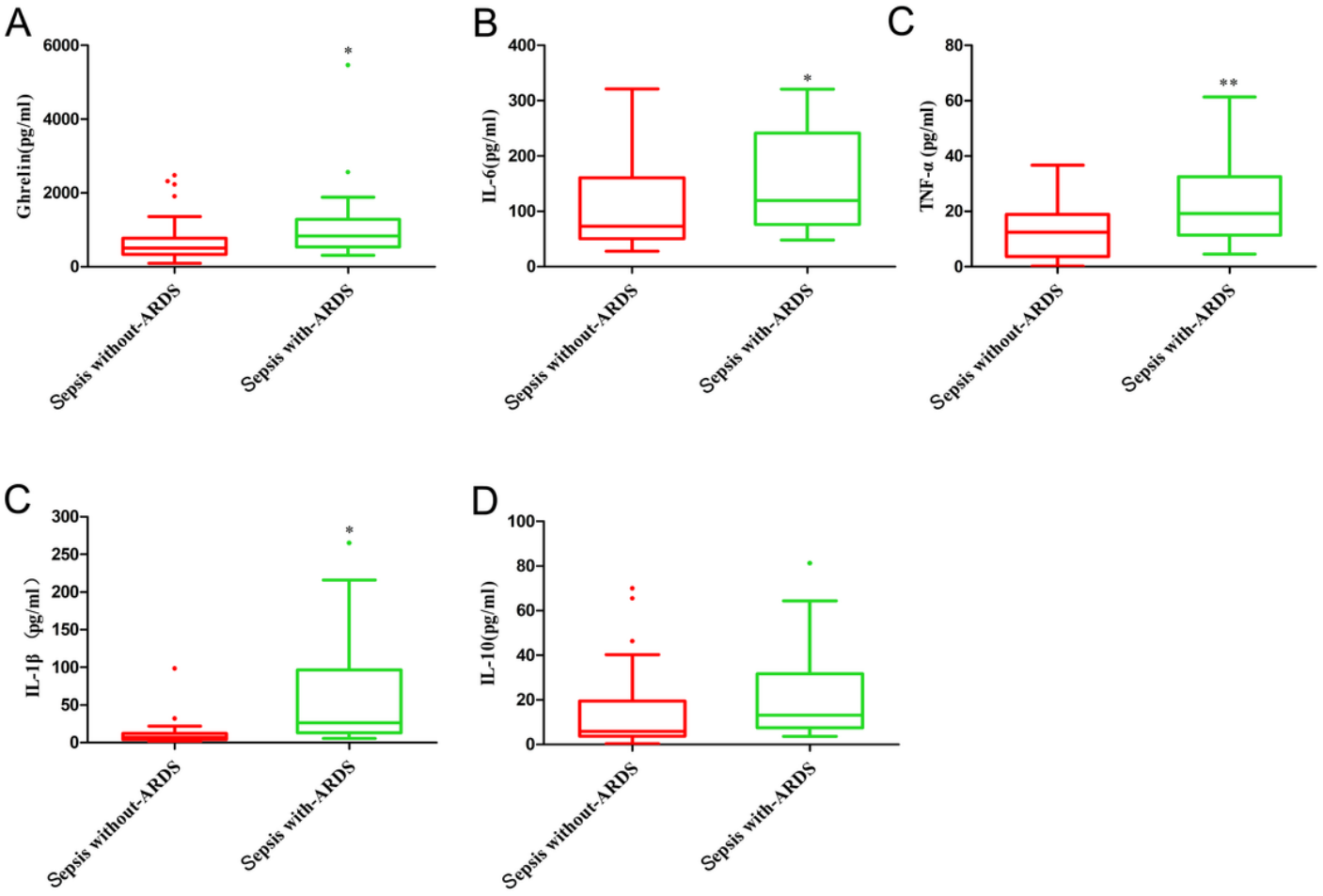

Figure 2

Plasma ghrelin level and concentration of inflammatory factors in sepsis with and without ARDS. (A) ghrelin, (B) IL-6, (C) TNF-α, (D) IL-1β, and (E) IL-10. Note: *, $p < 0.05$; **, $p < 0.001$.

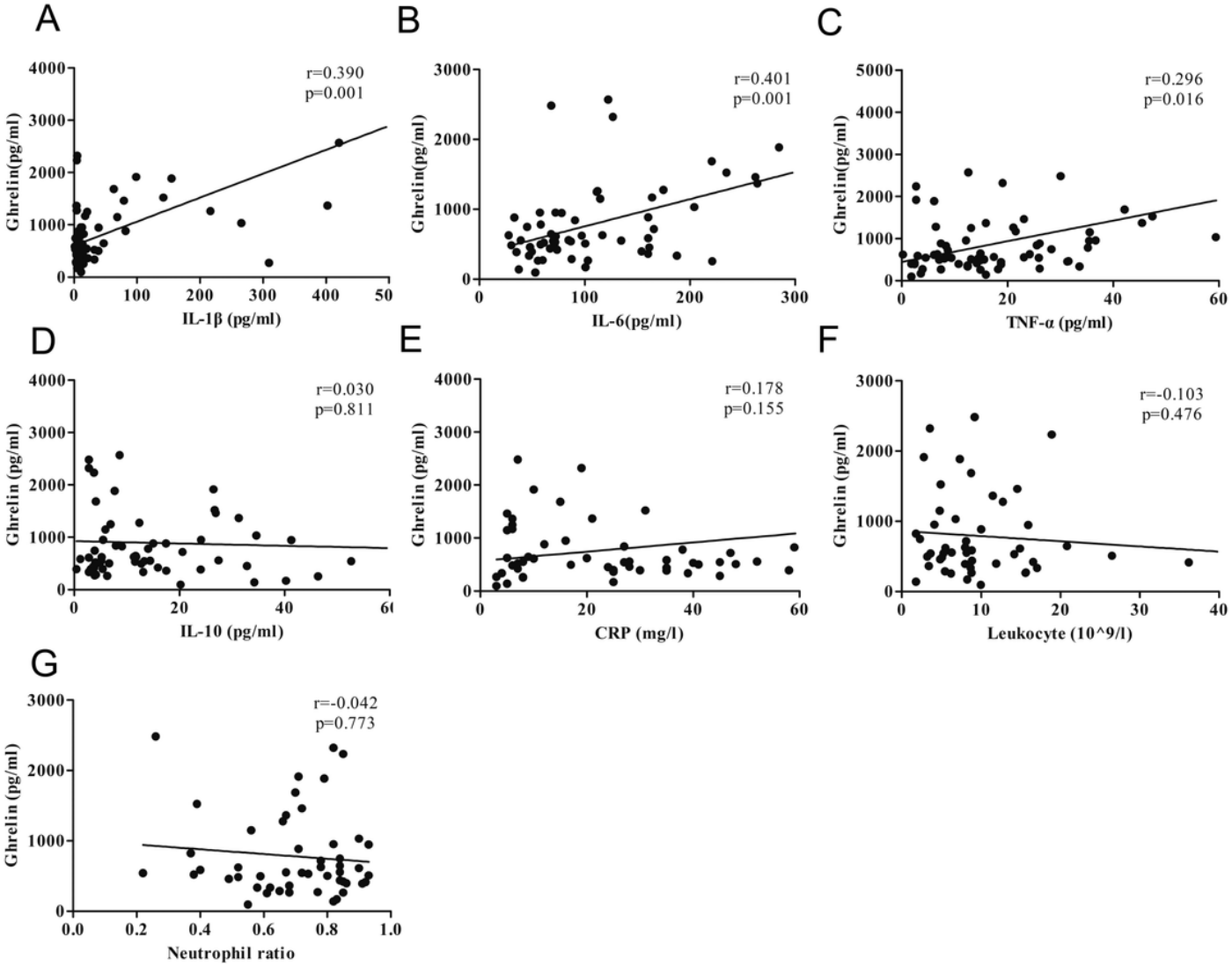

Figure 3

Correlation between the ghrelin level and plasma concentrations of inflammatory factors.

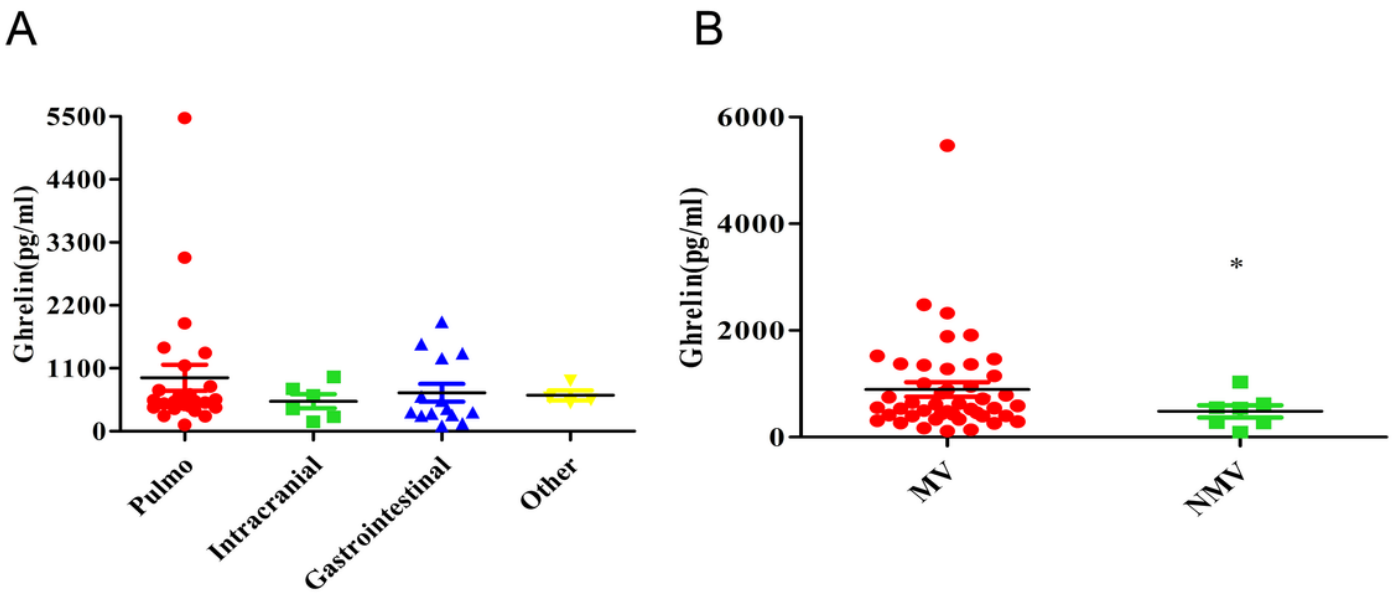

Figure 4

Relationship between the plasma ghrelin level and other clinical factors in patients with sepsis. (A) Primary infection. (B) mechanical ventilation. Note: *, $p < 0.01$. MV, mechanical ventilation; NMV, no mechanical ventilation.

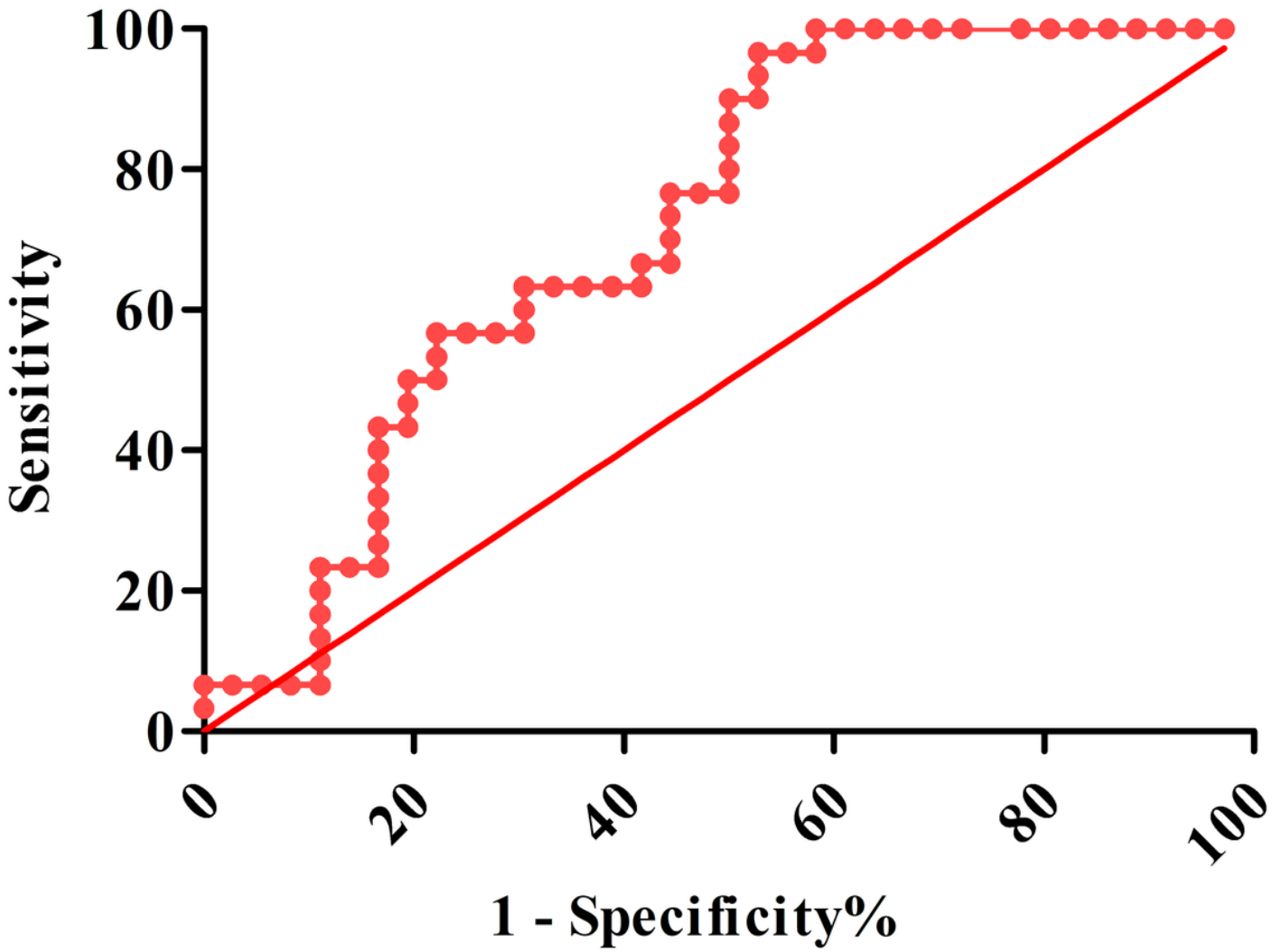

Figure 5

ROC of plasm ghrelin level for diagnosis ARDS in sepsis.

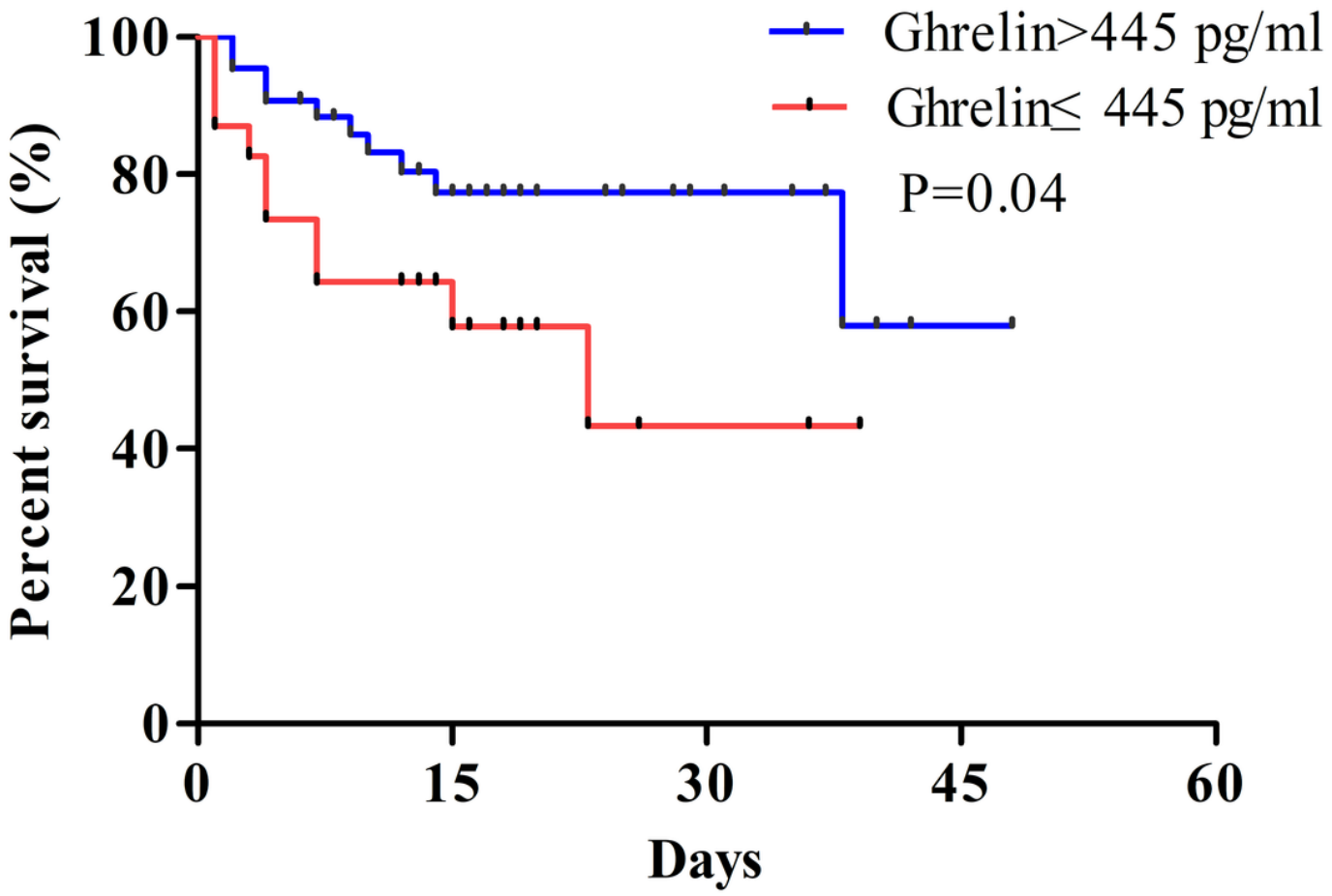

Figure 6

Survival analysis of plasma ghrelin level for sepsis. Note: The log-rank test was used to test the difference in survival rate between groups where the plasma ghrelin value was ≥445 pg/mL and <445 pg/ml.