Urea to Albumin Ratio Is an Independent Predictor of In-Hospital Mortality in Patients With Severe Pneumonia: A Retrospective Cohort Study

Yu Tian
Guangzhou Medical University
Yihao Li
Guangzhou Medical University
Jieru Chen (chenjieru77@163.com)
Guangzhou Medical University
Zixin Jiang
Guangzhou Medical University

Research

Keywords: Severe pneumonia, Urea to albumin ratio, Intensive care unit, In-hospital mortality

Posted Date: May 13th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-510525/v1

Urea to albumin ratio is an independent predictor of in-hospital mortality in patients with severe pneumonia: a retrospective cohort study

Yu Tian[1], Yihao Li[2], Jieru Chen[1]*, Zixin Jiang[1]*

[1]ty2020guangzhou@163.com; [2]dr_liyihao@163.com; *Correspondence: chenjieru77@163.com; 147533981@qq.com

Abstract

Background: Severe pneumonia (SP) is a major complication of respiratory system disease that is associated with high mortality and morbidity. Our objective was to identify risk factors predictive of SP patients and its mortality in intensive care unit (ICU).

Methods: We conducted a single-center retrospective observational study involving 212 patients with SP in ICU from June 1st, 2016 to June 1st, 2020. The receiver operating characteristic (ROC) curve was constructed to assess the predictive significance of urea to albumin ratio (U/A). Kaplan-Meier survival curves were plotted with log-rank tests to compare survival of patients with different value of U/A. Multivariate COX regression models were used to calculate the adjusted hazard ratios (HR). Additionally, interaction analysis showed the association between U/A and in-hospital mortality

was influenced by sex. Primary outcome was in-hospital mortality.

Results: A total of 212 patients were enrolled in the analysis. In the hospital, 101 (47.6%) patients had died. ROC analysis showed that the current cut-off of 0.2555 had a sensitivity of 84.2% for in-hospital mortality (AUC = 0.63, 95%CI: 0.55-0.70, P = 0.001). The multivariate COX analysis showed that the incidence of death was higher with the higher U/A group than the lower group (HR: 2.234, 95%CI: 1.146-4.356, P = 0.018). Besides, this pattern persisted in subgroup analyses considering sex. (HR: 9.380, 95%CI: 2.248-39.138, P = 0.002)

Conclusions: A high level of U/A is an independent risk factor for in-hospital mortality in patients with SP.

Keywords: Severe pneumonia, Urea to albumin ratio, Intensive care unit, In-hospital mortality

Background

Severe community-acquired pneumonia (SCAP) is a life-threatening multifactorial clinical condition leading to a rapid deterioration of organ function associated with high mortality during hospitalization (ranging from 25% to more than 50%) [1, 2]. SP in ICU must be treated promptly and effectively because

of high mortality [3]. Therefore, severity evaluation is an essential component of the initial assessment of these patients. However, there is no consensus on the optimal evaluation approach.

Risk factors for poor outcomes in patients with CAP include higher blood urea nitrogen and lower albumin [3-7]. B/A levels has also been reported to be associated with a high risk of 30-day mortality in ventilator-associated pneumonia (VAP) patients [8]. Mahmood Y et al. applied elevated urea and decreased albumin to COVID-19 pneumonia patients to predict the admission to ICU [9]. Moreover, evidence is accumulating that a high blood urea nitrogen/albumin ratio (B/A) is relevant with critical illness [10]. However, there is no study on SP patients.

We conducted the SP patients in ICU and U/A to evaluate the in-hospital mortality associated with different levels of U/A. We hypothesized that higher U/A group would be associated with a higher risk of death than the lower group.

Method

Study design and Participants

We performed a retrospective and cohort study between June 1st, 2016, and June 1st, 2020, in the ICU of the Second

Affiliated Hospital of Guangzhou Medical University after obtaining institutional approval. Written informed consent was approved by the retrospective nature.

Patients who were admitted to participating ICU were screened and, if eligible, were included. We screened the patients 18 years of age or older who were admitted to the ICU for SP. Patients were excluded for the reasons: (1) ICU duration<24h; (2) end-stage renal failure (on dialysis); (3) chronic liver disease.

Definitions

To confirm reported clinical SP, the events were defined in a standardized approach with the use of criteria from the guidelines of SP in China (2016 version). Pneumonia was diagnosed when met one of the first four criteria and criteria 5: (1) new cough or the ordinary respiratory disease worsened, with sputum and/or chest pain or not; (2) fever; (3) pulmonary moist rale and/or consolidation; (4) peripheral blood leucocyte count > 10×10^9/L or < 4×10^9/L with a nuclear shift to the left or not; (5) new chest radiographic infiltrate with pleural effusion or not and less possibility of alternative diagnoses. Pneumonia patients were diagnosed with SP when met one of the major

criteria or three of the minor criteria. The major criteria include: (1) invasive mechanical ventilation and (2) septic shock needing vasopressor. The minor ones are: (1) respiratory rate ≥ 30 breaths/min; (2) multilobar infiltrates; (3) PaO2/FiO2 ratio ≤ 250; (4) uremia (BUN level > 20mg/dL); (5) confusion/disorientation; (6) leukopenia (WBC count < 4×10^9/L); (7) thrombocytopenia (platelet count < 100×10^9 /L); (8) hypothermia (core temperature < 36°C); and (9) hypotension requiring massive fluid resuscitation.

Data collection and outcome

Data included demographic data, hospital-acquired pneumonia (HAP), underlying disease, radiological findings, treatment, clinical data, laboratory results, and clinical outcomes. Demographic data were age and gender. Underlying diseases included hypertension, diabetes mellitus, coronary heart disease (CHD), stroke, chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD). Clinical and laboratory results contained mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), acute physiology and chronic health evaluation II (APACHE II) score, alanine aminotransferase (ALT), aspartate aminotransferase (AST),

creatinine, urea, albumin, white blood cell (WBC), neutrophil count, lymphocyte count, monocyte count, platelet count, red blood cell (RBC), hemoglobin, and hematocrit (HCT). Samples of peripheral blood were stored by tubes with ethylenediamine teraacetic acid. Primary outcome was in-hospital mortality.

Statistics analysis

The patients were divided into 2 groups according to the ROC analysis cutoff values. The ROC curve was used to examine the predictive power, and the area under the ROC curve (AUC) was represented the predictive power. Differences between two groups were tested using *t* test, Mann-Whitney *U* test or *Chi-Square* test where appropriate. The incidence of death was estimated by using the Kaplan-Meier method and compared with the log-rank test. The associations between U/A and the primary outcome were examined with use of multivariate COX models. Hazard ratios (HR), with the U/A $\leq$ 0.2555 group used as the reference, were adjusted for sex and other significant univariate ($P < 0.05$ in univariate analysis). A formal test of interaction between U/A and sex was performed. The data missing under 5% were replaced by the mean or median.

Statistical analyses were performed with the use of SPSS, version 22.0, and $P < 0.05$ was considered significant.

Results

Baseline Characters

From 1st June 2016 to 30th June 2020, a total of 227 patients were screened in the ICU, and 212 patients were eventually enrolled in the study (Figure 1). Patients' characteristics are presented in Table 1. Of these 212 cases, the median age was 73.0 (61.0, 82.8), 0.8% of the patients were male, and 16.0% were hospital-acquired pneumonia (Table 1). Overall, the underlying disease of the patients were including hypertension, DM, CHD, stroke, COPD, CKD. The median Apache II score was 20.0 (16.0, 26.0) within the 24 hours after ICU admission. The radiological findings showed that 82.5% of the patients had bilateral pneumonia and 31.1% had pleural effusion. No significant difference in the radiological findings was observed ($P = 0.389$, $P = 0.494$, respectively). During the follow-up, 101 (47.6%) cases of death were recorded during hospitalization. Compare to the $U/A \leq 0.2555$ group, patients in the $U/A > 0.2555$ group required more continuous renal replacement treatment therapy (CRRT) and had higher in-hospital mortality

as well as APACHE II score ($P < 0.001$, $P < 0.001$, $P < 0.001$, respectively).

Risk Factors for Higher Mortality in SP Patients

Factors associated with higher in-hospital mortality are listed in Table 2. All significant factors identified as predictors of in-hospital mortality ($P < 0.05$ in the COX univariate regression analysis and clinical concern(sex)) were used for the multivariate analysis based on the COX proportional hazards regression. Multivariate COX analyses identified two prognostic factors for in-hospital mortality, including vasopressor use and CRRT ($P = 0.004$, $P = 0.041$, respectively).

U/A as a Predictor of Mortality in SP by ROC Curve Analysis

The results of ROC analysis for U/A in predicting in-hospital mortality are shown in figure 2. It suggested that U/A had a modest power for predicting in-hospital mortality (AUC = 0.63, 95%CI: 0.55-0.70, $P = 0.001$). The optimal cutoff value of the U/A for predicting in-hospital mortality was 0.2555 (sensitivity 84.2%, specific 37.8%).

U/A Associated with Mortality in SP

According to the cutoff value, the 211 SP patients were divided into two groups. The Kaplan-Meier survival curves showed that higher U/A group had a higher in-hospital mortality rate than lower U/A group (Log-rank test chi-square 13.71, $P < 0.001$).

To elucidate the specific relationship between U/A and in-hospital mortality, we used different models (Table 3, $U/A \leq 0.2555$ as the reference group). Using the multivariable COX proportional hazards model, which adjusted vital factors (univariate COX analysis, $P < 0.05$ and age), we discovered that in-hospital mortality was still significant higher in the group with $U/A > 0.2555$. In model 3 adjusted for age, sex, invasive mechanical ventilation, CRRT, vasopressor use, creatinine, alanine aminotransferase, and aspartate aminotransferase, the HR for in-hospital mortality was 2.234 (95%CI: 1.146-4.356, $P = 0.018$).

Relationship between Mortality and U/A in the Sex Subgroups

Results of interaction analysis between U/A and sex are given in Table 4. There was a significant interaction on in-hospitality mortality between them ($\beta = 4.290$, $P = 0.004$). Thus, a sex-stratified analysis was conducted. In the female subgroup, COX analyses showed significant mortality increases with high value

of U/A > 0.2555 (HR: 9.380, 95%CI: 2.248-39.138, P = 0.002). However, a pattern of increasing mortality risk with different level of U/A was not observed in the male subgroup (P = 0.112).

Discussion

Our analysis suggested that the first U/A after admitted to ICU is an independent risk factor for in-hospital mortality in SP patients. Interestingly, this study also demonstrated that U/A was an independent predictor of in-hospital mortality in female subgroups, but not in males.

Urea and albumin are very easy and quick to get. Studies has shown that the higher urea and lower albumin indicated worse clinical outcome in CAP patients [3-7]. Motoi et al. revealed that the blood urea nitrogen/serum albumin (B/A) ratio performed well for predicting mortality and the severity of CAP [10]. Ding-Yun Feng et al.'s study showed that the B/A ratio was associated with poorer survival outcomes in 30-day ventilation acquired pneumonia (VAP) [11]. However, very few studies in the literature have evaluated whether U/A are predictive of worse outcomes in SP patients. Thus, according to the previous researches, we speculate that the U/A may be an important indicator of mortality in SP patients. The results of

our study were consistent with this speculation. The present data indicated U/A had a significant predictive value.

An earlier study calculated the optimal cutoff point of B/A value for 30-day mortality using ROC curves in CAP patients. The point was at 0.165 [9]. Seung Ryu et al. found that, in aspiration pneumonia patients, the AUC for B/A ratio was at 0.70 for predicting mortality within 28 days [12]. Our study included both CAP and HAP participants in the ICU. In our ROC curve analysis, we determined a cutoff value of 0.2555 for in-hospital mortality and the AUC was 0.63. The risk of death was higher among the patients whose value of U/A was > 0.2555 than those whose U/A was ≤ 0.2555 (HR: 2.234, 95%CI: 1.146-4.356, P = 0.018). Although the AUC of U/A was not so good, it is easy and quick to use, giving more information to identify the high-risk group.

However, the underlying mechanism has remained unclear. Urea is a marker associated with systemic disease. Although urea is not a direct mark of infection, it can be a risk factor because high value leads to high susceptibility to infection. Some previous studies suggested that urea affects the prognosis of critical patients regardless of the creatine level [13, 14]. In these prediction model, urea is a significant risk factor for

pneumonia. Moreover, urea is an indirect marker of a metabolic systemic pathway [15]. In pneumonia patients, elevations of serum urea are indicators of protein catabolism. Water deficiency appears to be common in pneumonia patients. In the process of dehydration, the concentration of urea increased. Meanwhile, the effect of increased urea reabsorption in the kidney causes high urea concentration [12]. Additionally, urea level is regarded as a predictive marker reflecting the cumulative effects of hemodynamic damage, which is essential in critical illness.

Serum albumin plays a significant role in maintaining physiological homeostasis, including keeping a colloid osmotic pressure [16]. On the other hand, hypoalbuminemia can result in the pulmonary edema due to decreased colloid osmotic pressure which can result in mortality[17]. Xue et al. suggested that hypoalbuminemia in the early stage had a high incidence of infection and mortality [18]. At the same time, pneumonia is an inflammation with high catabolism condition. Systemic inflammatory response can decrease serum albumin levels [16]. Obviously, hypoalbuminemia is often observed in malnutrition patients, resulting in worse outcomes. It is interesting to note that earlier studies mostly focused on CAP showed that non-

survivors have significantly lower urea and higher albumin than those of survivors. The study reported before demonstrated that urea to albumin ratio is an independent marker of the severity of CAP and mortality [16]. Our findings are consistent with previous conclusions.

Another notable finding was the independent effect of increased U/A on the elevated risk associated with in-hospital mortality in female SP patients. To the authors' knowledge, this research may be the first time to revealed the association between U/A and in-hospital mortality in the female. Our study found an interaction between U/A and sex. In subgroup analyses by sex, U/A was still an independent risk factor for in-hospital mortality in female. Nevertheless, the same pattern was not observed in the male subgroups.

A previous study reported that males had a higher fractional synthesis rate of albumin than females regardless of age and protein intake. Male had higher albumin concentration than female [19]. Therefore, the increase of U/A in critical illness was not so obvious. Gary Weaving et al demonstrated that albumin value in females decreased more quickly [20]. This is owing to the different values of parameters between males and females. Our results are consistent with the previous studies.

Further studies are needed to examine why U/A is associated with mortality in female patients.

Our research has some limitations. First, the retrospective design of the study could lead to residual confounders bias. It might be insufficient to draw the same conclusion in other population. Second, the samples were small, so the predictive value of the U/A needs to be further validated in other observational studies. Third, the AUC of the ROC curve was 0.63. It showed that the U/A had moderate predictive function on the prognosis of SP. Fourth, in the present study, we investigated first time U/A value in patients with SP who were admitted to the ICU for first time. The relationship between the variation of U/A level and the primary outcome remains uncertain. Finally, our analysis relies on in-hospital mortality and just reflets the time within hospital.

In conclusion, our study demonstrated that the U/A is an independent risk factor for in-hospital mortality.

Abbreviations

SP: Severe pneumonia; ICU: Intensive care unit; ROC curve: Receiver operating characteristic curve; U/A: Urea to albumin ratio; HR: Hazard ratios; SCAP: Severe community-acquired pneumonia; VAP: Ventilator-associated pneumonia; HAP: Hospital acquired pneumonia; CHD:

Coronary heart disease; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; CRRT: Continuous renal replacement therapy; MAP: Mean arterial pressure; APACHE: Acute physiology and chronic health evaluation; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; WBC: White blood cell; RBC: Red blood cell; HCT: Hematocrit; LOS: Length of stay

Acknowledgements

None applicable.

Authors' contributions

Yu Tian and Yihao Li contributed equally to this work.

Funding

Not applicable.

Availability of data and materials

The data used to support the findings of this study are included within the article.

Declarations

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted and with the 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 conflict of interest.

Author details

[1]Department of Intensive Care Unit, The Second Affiliated Hospital, Guangzhou Medical University, Guangzhou 510000, PR China. [2]Department of Anesthesiology, The Second Affiliated Hospital, Guangzhou Medical University, Guangzhou 510000, PR China.

Reference

1. Cillóniz C, Dominedò C, Garcia-Vidal C, Torres A. **Community-acquired pneumonia as an emergency condition**. *Current opinion in critical care;* 2018;**24**(6):531-539. https://doi.org/10.1097/MCC.0000000000000550
2. Montull B, Menéndez R, Torres A, Méndez R. **Predictors of severe sepsis among patients hospitalized for community-acquired pneumonia**. *MLO: medical laboratory observer;* 2016;**48**(3):8, 10-12. https://core.ac.uk/reader/154764369?utm_source=linkout
3. Bodmann KF. **Current guidelines for the treatment of severe pneumonia and sepsis**. *Chemotherapy.* 2005;**51**(5):227-233. https://doi.org/10.1159/000087452
4. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, Lewis SA, Macfarlane JT. **Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study**. *Thorax.* 2003;**58**(5):377-382. https://doi.org/10.1136/thorax.58.5.377
5. Farr BM, Sloman AJ, Fisch MJ. **Predicting death in patients hospitalized for community-acquired pneumonia**. *Annals of internal medicine.* 1991;**115**(6):428-436. https://doi.org/10.7326/0003-4819-115-6-428
6. Raz R, Dyachenko P, Levy Y, Flatau E, Reichman N. **A predictive model for the management of community-acquired pneumonia**. *Infection.* 2003;**31**(1):3-8. https://link.springer.com/article/10.1007%2Fs15010-002-2083-4
7. Potgieter PD, Hammond JM. **The intensive care management, mortality and prognostic indicators in severe community-acquired pneumococcal pneumonia**. *Intensive care medicine.* 1996;**22**(12):1301-1306. https://doi.org/10.1007/bf01709542
8. Lee JH, Kim J, Kim K, Jo YH, Rhee J, Kim TY, Na SH, Hwang SS. **Albumin and C-reactive protein have prognostic significance in patients with community-acquired pneumonia**. *Journal of critical care.* 2011;**26**(3):287-294. **https://doi.org/10.1016/j.jcrc.2010.10.007**
9. Feng DY, Zhou YQ, Zou XL, Zhou M, Yang HL, Chen XX, Zhang TT. **Elevated Blood Urea Nitrogen-to-Serum Albumin Ratio as a Factor That Negatively Affects the**

Mortality of Patients with Hospital-Acquired Pneumonia. *The Canadian journal of infectious diseases & medical microbiology.* 2019;**2019**:1547405. https://doi.org/10.1155/2019/1547405

10. Hachim MY, Hachim IY, Naeem KB, Hannawi H, Salmi IA, Hannawi S. **D-dimer, Troponin, and Urea Level at Presentation With COVID-19 can Predict ICU Admission: A Single Centered Study**. *Frontiers in medicine.* 2020;**7**:585003. https://doi.org/10.3389/fmed.2020.585003

11. Ugajin M, Yamaki K, Hirasawa N, Yagi T. **Predictive values of semi-quantitative procalcitonin test and common biomarkers for the clinical outcomes of community-acquired pneumonia**. *Respiratory care.* 2014;**59**(4):564-573. https://doi.org/10.4187/respcare.02807

12. Ryu S, Oh SK, Cho SU, You Y, Park JS, Min JH, Jeong W, Cho YC, Ahn HJ, Kang C. **Utility of the blood urea nitrogen to serum albumin ratio as a prognostic factor of mortality in aspiration pneumonia patients**. *The American journal of emergency medicine.* 2020. https://doi.org/10.1016/j.ajem.2020.02.045

13. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. **A prediction rule to identify low-risk patients with community-acquired pneumonia**. *N Engl J Med.* 1997;**336**(4):243-250. https://doi.org/10.1056/nejm199701233360402

14. Aronson D, Mittleman MA, Burger AJ. **Elevated blood urea nitrogen level as a predictor of mortality in patients admitted for decompensated heart failure**. *The American journal of medicine.* 2004;**116**(7):466-473. https://doi.org/10.1016/j.amjmed.2003.11.014

15. Oh DH, Kim YC, Kim EJ, Jung IY, Jeong SJ, Kim SY, Park MS, Kim A, Lee JG, Paik HC. **Multidrug-resistant Acinetobacter baumannii infection in lung transplant recipients: risk factors and prognosis**. *Infectious diseases (London, England).* 2019;**51**(7):493-501. https://doi.org/10.1080/23744235.2018.1556400

16. Ugajin M, Yamaki K, Iwamura N, Yagi T, Asano T. **Blood urea nitrogen to serum albumin ratio independently predicts mortality and severity of community-acquired pneumonia**. *International journal of general medicine.* 2012;**5**:583-589. https://doi.org/10.2147/ijgm.s33628

17. Horwich TB, Kalantar-Zadeh K, MacLellan RW, Fonarow GC. **Albumin levels predict survival in patients with systolic heart failure**. *American heart journal.* 2008;**155**(5):883-889. https://doi.org/10.1016/j.ahj.2007.11.043

18. Xue P, Huang ZW, Li YH, Guo J, Wang ZC, Zhao JL, You Z. **Clinical study on severe acute pancreatitis associated with hypoalbuminemia in early stage**. *Journal of Chinese integrative medicine.* 2005;**3**(6):443-445.

19. Thalacker-Mercer AE, Johnson CA, Yarasheski KE, Carnell NS, Campbell WW. **Nutrient ingestion, protein intake, and sex, but not age, affect the albumin synthesis rate in humans**. *The Journal of nutrition.* 2007;**137**(7):1734-1740.

20. Weaving G, Batstone GF, Jones RG. **Age and sex variation in serum albumin concentration: an observational study**. *Annals of clinical biochemistry.* 2016;**53**(Pt 1):106-111. https://doi.org/10.1177/0004563215593561

1 Table 1: Comparison of baseline characteristics.

Variables	Total (n = 212)	U/A ≤ 0.2555 (n = 58)	U/A > 0.2555 (n = 154)	P-value
Demographic data				
Age(years)	73.0 (61.0, 82.8)	66.0 (53.8, 78.3)	78.5 (63.0, 84.0)	0.001
Sex(male)	150, 70.8%	34, 58.6%	116, 75.3%	0.017
HAP	34, 16.0%	8, 13.8%	26, 16.9%	0.585
Underlying diseases				
Hypertension	119, 56.1%	21, 36.2%	98, 63.6%	<0.001
Diabetes mellitus	53, 25.0%	10, 17.2%	43, 27.9%	0.109
CHD	25, 11.8%	4, 6.9%	21, 13.6%	0.175
Stroke	44, 20.8%	8, 13.8%	36, 23.4%	0.125
COPD	27, 12.7%	4, 6.9%	23, 14.9%	0.118
CKD	27, 12.7%	1, 1.7%	26, 16.9%	0.003
Radiological findings				
Bilateral pneumonia	175, 82.5%	50, 86.2%	125, 81.2%	0.389
Pleural effusion	66, 31.1%	16, 27.6%	50, 32.5%	0.494

Treatment				
Invasive Mechanical use	109, 51.4%	34, 58.6%	75, 48.7%	0.294
Vasopressor Use	73, 34.4%	14, 24.1%	59, 38.3%	0.053
CRRT	73, 34.4%	7, 12.1%	66, 42.9%	<0.001
Clinical data				
MAP	83.0 (69.5, 103.0)	85.0 (74.6, 108.5)	83.0 (66.9, 101.3)	0.153
Heart Rate	109.9 (83.8, 136.0)	104.5 (84.4, 124.6)	111.9 (84.1, 139.7)	0.035
Respiratory rate	27.0 (22.0, 34.8)	25.5 (20.0, 33.3)	27.0 (22.0, 35.0)	0.161
APACHE II score	20.0 (16.0, 26.0)	16.5 (12.0, 20.0)	22.0 (17.0, 27.3)	<0.001
Laboratory results				
ALT	34.5 (21.0, 65.8)	33.0 (21.0, 51.3)	34.8 (21.0, 76.8)	0.265
AST	44.5 (27.0, 82.0)	42.5 (24.5, 60.8)	44.5 (28.0, 97.0)	0.054
Creatinine	114.9 (72.8, 191.4)	65.2 (51.1, 85.6)	140.4 (98.0, 239.0)	<0.001
Urea	11.8 (6.9, 19.1)	5.5 (4.2, 6.5)	15.4 (11.1, 21.6)	<0.001
Albumin	29.0 (24.1, 33.9)	30.8 (26.5, 35.1)	28.3 (23.3, 33.3)	0.001

WBC	11.7 (8.0, 16.0)	12.9 (9.9, 16.8)	11.2 (6.8, 15.5)	0.035
Neutrophil count	10.0 (6.3, 13.9)	11.0 (8.4, 14.6)	9.7 (5.4, 13.8)	0.072
Lymphocyte count	0.6 (0.3, 1.0)	0.8 (0.4, 1.3)	0.6 (0.3, 0.9)	0.006
Monocyte count	0.5 (0.2, 0.8)	0.6 (0.3, 1.1)	0.5 (0.2,0.8)	0.008
Platelet count	205.0 (117.3, 280.5)	234.5 (176.8, 322.0)	186.5 (98.3, 256.0)	<0.001
RBC	3.6 (2.6, 4.6)	4.0 (3.1, 4.9)	3.4 (2.4, 4.4)	<0.001
Hemoglobin	102.9 (73.8, 132.0)	112.9 (89.2, 136.6)	99.1 (69.0, 129.2)	0.001
HCT	31.3 (22.7, 39.9)	33.9 (26.6, 41.2)	30.3 (21.4, 39.2)	0.004
Clinical Outcomes	12.0 (6.3, 21.0)			
ICU LOS	21.0 (11.3, 32.0)	14.0 (9.0, 24.3)	11.0 (5.0, 19.3)	0.020
Hospital LOS	101, 47.6%	25.0 (15.5, 36.3)	18.0 (10.0, 32.0)	0.040
In-hospital death		16, 27.6%	85, 55,2%	<0.001

1 Data are mean ± standard or medians （25th-75th percentile）or number and percentage.

2 U/A: urea to albumin ratio; HAP: hospital acquired pneumonia; CHD: coronary heart disease;

3 COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; CRRT: continuous

4 renal replacement therapy; MAP: mean arterial pressure; APACHE: acute physiology and chronic

health evaluation; ALT: alanine aminotransferase; AST: aspartate aminotransferase; WBC: white blood cell; RBC: red blood cell; HCT: hematocrit; LOS: length of stay.

Table 2: Independent predictors of in-hospital mortality by univariate and multivariate COX regression analysis.

Factors	HR□95%CI□	P
Univariate cox analysis		
Age	1.013 (1.001-1.026)	0.029
Mechanical ventilation	0.796 (0.641-0.990)	0.040
Vasopressor use	2.407 (1.619-3.578)	<0.001
CRRT	2.402 (1.607-3.592)	<0.001
ALT	1.001 (1.000-1.001)	0.006
Albumin	0.947 (0.908-0.988)	0.011
Urea	1.020 (1.003-1.037)	0.024
AST	1.001 (1.000-1.001)	<0.001
Creatinine	1.002 (1.000-1.003)	0.016
Multivariate cox analysis		
Vasopressor use	1.888 (1.226-2.907)	0.004
CRRT	1.679 (1.020-2.762)	0.041

Covariates included in multivariate analysis: age, sex, mechanical ventilation, vasopressor use, CRRT, ALT, albumin, urea, AST, creatinine.

CRRT: continuous renal replacement treatment; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HR: hazard ratio; CI: confidence interval.

Table 3: Relationship between U/A level and in-hospital mortality.

In-hospital mortality	U/A > 0.2555 group	
	HR (95%CI)	P
Unadjusted	2.788 (1.577-4.929)	<0.001
Model 1	2.724 (1.499-4.949)	0.001
Model 2	2.080 (1.100-3.934)	0.024
Model 3	2.234 (1.146-4.356)	0.018

Reference group is U/A ≤ 0.2555 group.

Model 1: age and sex

Model 2: Model1 plus treatment (mechanical ventilation, CRRT, vasopressor use)

Model 3: Model2 plus and laboratory test□Creatinine□ALT□A ST□

CRRT: continuous renal replacement treatment; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HR: hazard ratio; CI: confidence interval.

Table 4: Relationship between in-hospital mortality and U/A level by sex.

In-hospital	male		Female		Sex*U/A interaction	
Mortality	HR(95%CI)	P	HR(95%CI)	P	β	P
urea/albumin	0.520□0.232-1.165□	0.112	9.380□2.248-39.138□	0.002	4.290	0.004

Adjusted for age, Mechanical ventilation, CRRT, vasopressor use, ALT, AST, Creatinine.

CRRT: continuous renal replacement treatment; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HR: hazard ratio; CI: confidence interval.

Figure 1: study algorithm, including patient enrollment and outcomes.

Note: low group: U/A ≤ 0.2555; high group: U/A > 0.2555; SP: severe pneumonia; ROC: receiver operating characteristics curve.

Figure 2: ROC curve for predicting mortality in patients with SP.

U/A had a modest power for predicting in-hospital mortality as suggested by AUC of 0.63 (95%CI: 0.55-0.70, P = 0.001), with a sensitivity of 84.2% and a specificity of 37.8% at a cutoff of 0.2555.

Figure 3: Kaplan-Meier survival curve according to U/A level.

Compare to the lower group (U/A ≤ 0.2555), patients in the higher group (U/A > 0.2555) showed elevated in-hospital mortality.

Figures

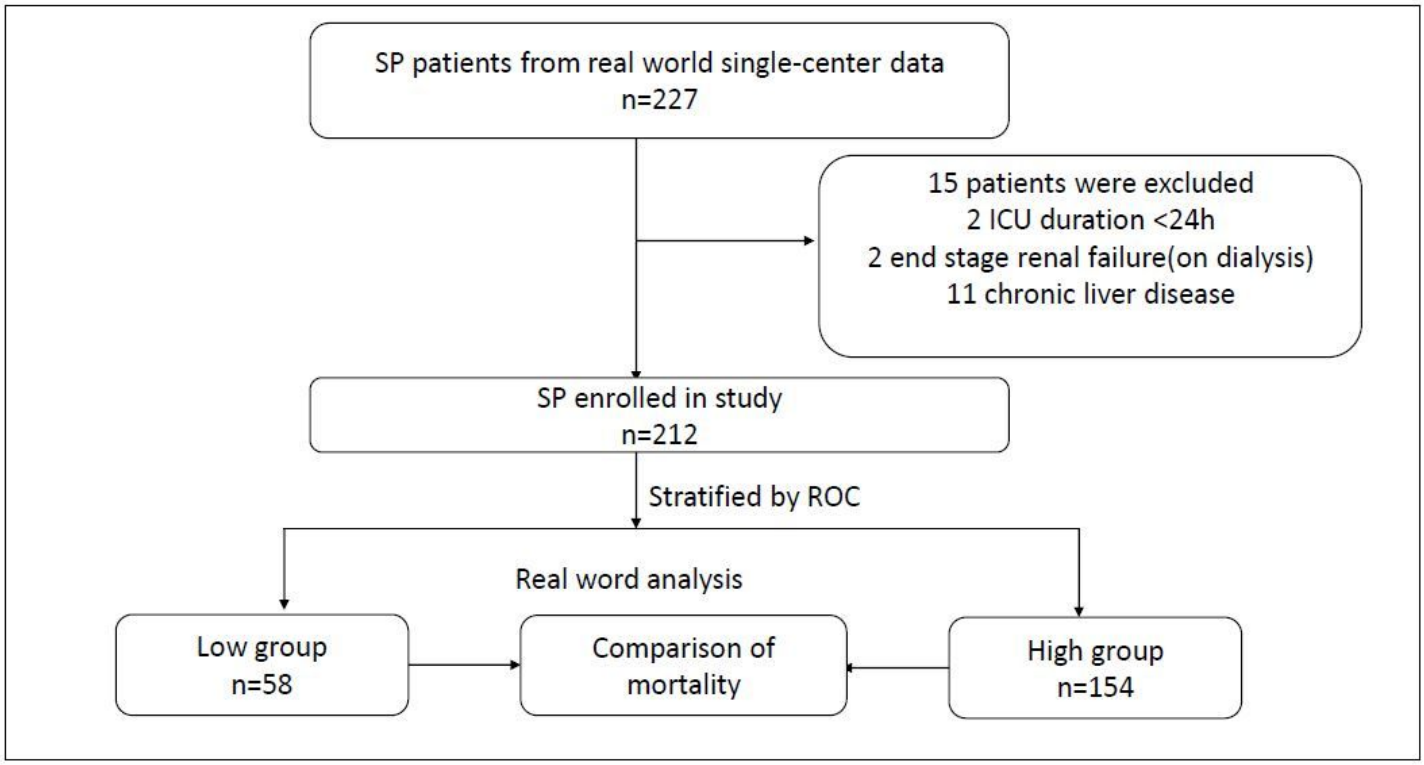

Figure 1

study algorithm, including patient enrollment and outcomes. Note: low group: U/A ≤ 0.2555; high group: U/A > 0.2555; SP: severe pneumonia; ROC: receiver operating characteristics curve.

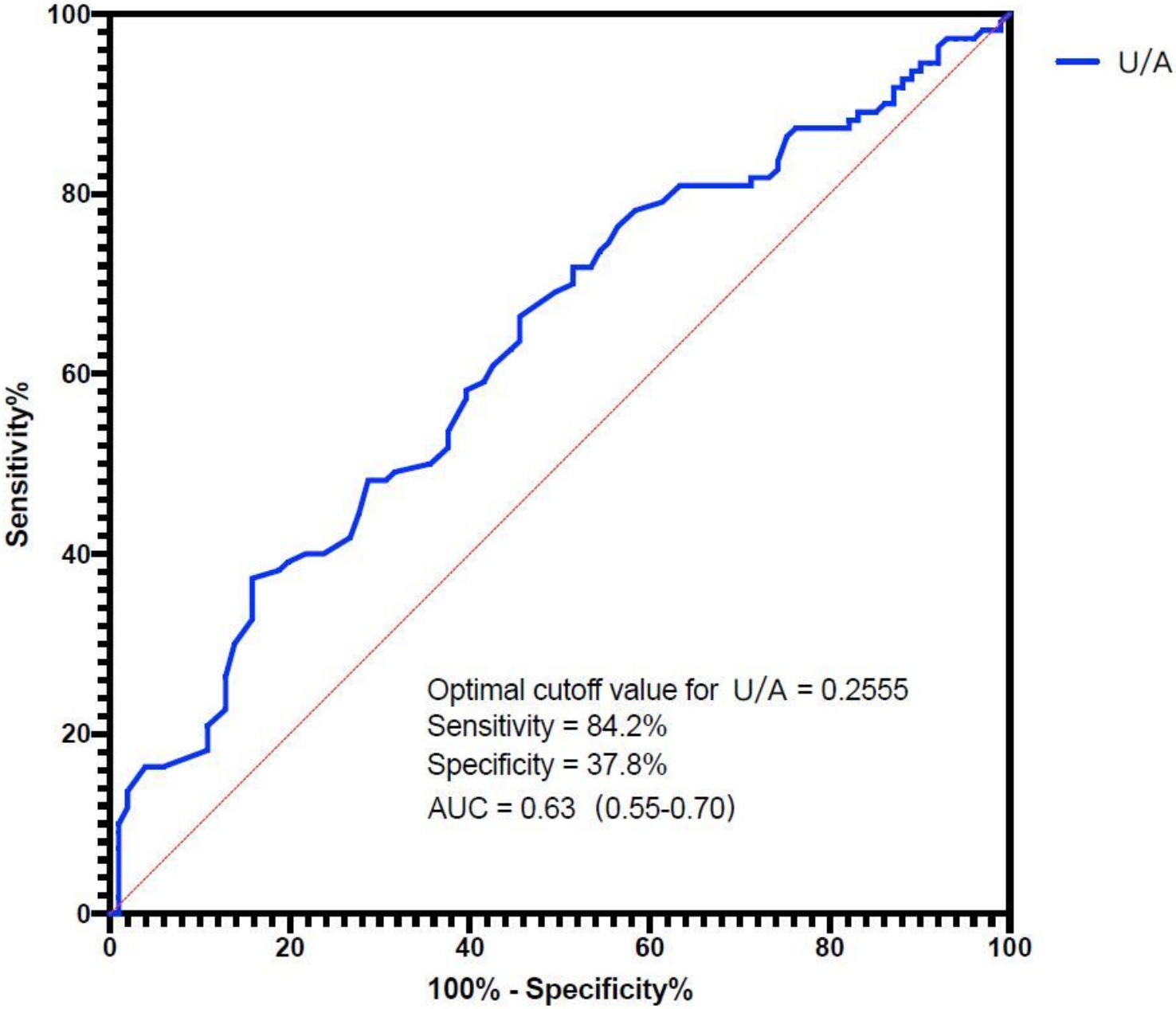

Figure 2

ROC curve for predicting mortality in patients with SP. U/A had a modest power for predicting in-hospital mortality as suggested by AUC of 0.63 (95%CI: 0.55-0.70, P = 0.001), with a sensitivity of 84.2% and a specificity of 37.8% at a cutoff of 0.2555.

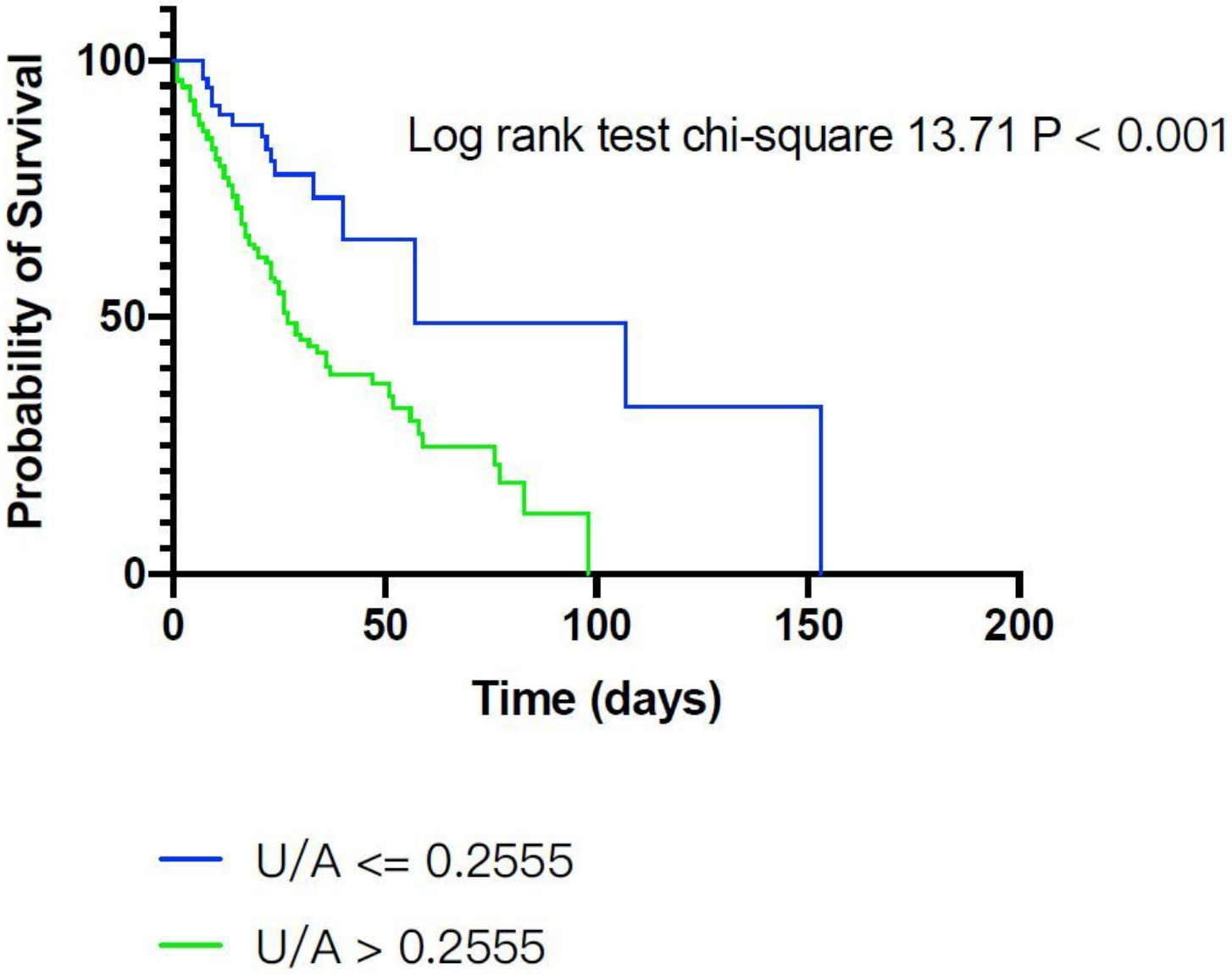

Figure 3

Kaplan-Meier survival curve according to U/A level. Compare to the lower group (U/A ≤ 0.2555), patients in the higher group (U/A > 0.2555) showed elevated in-hospital mortality.