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ORIGINAL RESEARCH

Association Between Blood Urea Nitrogen Levels and Length of Stay in Patients with Pneumonic Chronic Obstructive Pulmonary Disease Exacerbation: A Secondary Analysis Based on a Multicentre, Retrospective Cohort Study

Jie Du[1], Jing Niu[1], Lanxiang Ma[2], Yongjie Sui[1], Shuili Wang[3]

[1]Department of Health Examination Center, Shaanxi Provincial People Hospital, Xi'an, People's Republic of China; [2]Department of Cardiology, Shaanxi Provincial Corps Hospital, Chinese People's Armed Police Forces, Xi'an, People's Republic of China; [3]Department of Respiratory Medicine, Shaanxi Provincial People Hospital, Xi'an, People's Republic of China

Correspondence: Lanxiang Ma, Department of Cardiology, Shaanxi Provincial Corps Hospital, Chinese People's Armed Police Forces, Xi'an, People's Republic of China, Tel +86-15991765901, Email mztjzx2250@163.com

Purpose: High blood urea nitrogen (BUN) is associated with an elevated risk of mortality in various diseases, such as heart failure and pneumonia. Heart failure and pneumonia are common comorbidities of chronic obstructive pulmonary disease (COPD) exacerbation. However, data on the relationship of BUN levels with length of stay (LOS) in patients with pneumonic COPD exacerbation are sparse. The purpose of this study was to evaluate the correlation between BUN levels and LOS in a cohort of patients with pneumonic COPD exacerbation.

Patients and Methods: The present study was a multicentre, retrospective cohort study. A total of 1226 patients with pneumonic COPD exacerbation were included through a validated algorithm derived from the 10th revision of the International Classification of Diseases and Related Health Problems (ICD-10). It should be noted that the entire study was completed by Shiroshita et al, who uploaded the data to the DATADRYAD website. The author only used these data for secondary analysis.

Results: After adjusting for potential confounders (age, gender), a nonlinear relationship was detected between BUN levels less than 40 mg/dl and LOS. The effect sizes and the confidence intervals on the left and right sides of the inflection point were 0.27 (0.16, 0.39) and −0.17 (−0.34, 0.01), respectively.

Conclusion: High levels of BUN in the hospital may be associated with increased LOS. BUN was positively related to LOS when BUN was less than 40 mg/dl.

Keywords: pneumonia, chronic obstructive pulmonary disease, exacerbation, blood urea nitrogen, length of stay

Introduction

AECOPD affects long-term outcomes and is associated with substantial in-hospital mortality.[1] The disease course is chronic and progressive, often with "worsening" caused by respiratory infections, multiple organ dysfunction, and comorbidities.[2,3] High levels of BUN, suggestive of impaired heart and kidney function and poor neurohormonal activation, are often considered an ominous sign of various diseases.[4] Studies have confirmed that in critically ill patients, elevated BUN levels are associated with increased mortality.[5]

Patients with AECOPD frequently experience hypoxia, carbon dioxide retention, and systemic inflammation that may affect cardiac function, renal function, and neurohumoural regulation.[6] In addition, heart failure and pneumonia are common comorbidities in AECOPD, so high BUN levels may be associated with poor prognosis in AECOPD. However, to date, no studies have assessed the relationship between BUN levels at admission for pneumonic COPD exacerbation

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and LOS. Therefore, this study was based on a cohort of 1226 participants to further investigate the effect of BUN levels on LOS in patients with pneumonic COPD exacerbation.

This report is a secondary analysis based on existing published data.[7] The BUN level was used as the independent variable in this secondary analysis, and most of the covariates were consistent with the original text.

Methods

Study Design and Participants

The study population was derived from a previously reported retrospective cohort study[7] carried out across a secondary analysis in five acute general hospitals in Japan (Kameda Medical Center, Hyogo Prefectural Amagasaki General Medical Center, Awa Regional Medical Center, Saiseikai Yokohamashi Tobu Hospital, and Ichinomiyanishi Hospital). A total of 1226 patients with pneumonic COPD exacerbation (excluding 11 patients with missing breath levels) were included in this analysis. The inclusion criteria were hospitalized patients with pneumonic COPD exacerbation of age ≥40 years. As described in a previous article,[8] we used a modified version of the patient selection algorithm based on the International Statistical Classification of Diseases and Related Health Problems (ICD-10) 10th edition. Inclusion criteria were as follows: (1) Diagnosis of initial pneumonia (ICD-10 codes: J12, J13, J14, J15, J16, J18, J69, and P23) at the time of admission with comorbid COPD (ICD-10 codes: J44.1 and J44.9); (2) Initial admission diagnosis of COPD exacerbation (ICD-10 code; J44.1) with comorbid pneumonia on admission (ICD-10 code; J12, J13, J14, J15, J18, J69 and P23). Exclusion criteria were as follows: diagnosis with other respiratory diseases and complicated pneumonia (asthma attack, pneumothorax or heart failure, obstructive pneumonia or empyema), diagnosis with severe cardiopulmonary disease (patients requiring tracheal intubation, tracheotomy or use of vasopressors on the day of admission).

The research protocol complied with the Declaration of Helsinki. In addition, the project was approved by the various hospital institutional review boards, and due to the retrospective nature of the study (approval number, 19-076), the Kameda Medical Center Institutional Review Board waived the need for written informed consent. Access to patient data was anonymous and confidential.

Since this paper is a secondary analysis of a retrospective study, it has been approved by the Ethics Committee of Shaanxi Provincial People's Hospital.

Data Source

We retrieved data information from the "DATADRYAD" database. The study cites the Dryad packet from Shiroshita et al 2020. The variables analysed included age, gender, use of steroid treatment, activity of daily living (full assistance or not), BUN levels, respiratory rate (rr), altered mental status(AMS), heart rate (hr), information regarding wheezing lung sounds, fever, clinical stability, hospital discharge, and tracheal intubation.

Statistical Analysis

Data were analysed in this study using R statistical software (https://www.r-project.org) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc. Boston MA). Continuous variables are presented as the mean±standard deviation or median (interquartile range, 25th-75th percentile), and categorical variables are presented as numbers and percentages. Statistical differences were determined using the chi-square test, one-way ANOVA, and Kruskal–Wallis *H*-test. In addition, a generalized additive model (GAM) was used to analyse the nonlinear relationship between BUN levels and LOS in pneumonic COPD exacerbation patients. A P value <0.05 was considered statistically significant.

Results

Patients' Baseline Characteristics

A total of 1226 hospitalized patients with pneumonic COPD exacerbation were included in this study (Table 1). BUN-stratified groups defined by quartiles were Q1 group (<13.80), Q2 group (14.00–17.70), Q3 group (18.00–24.80) and Q4 group (25.00–152.00). Compared with subjects in the highest quartile of BUN levels (Q4), patients in the other three groups (Q1-Q3) had significantly lower changes in age, rr, LOS, and AMS (p<0.05).

Table 1 Baseline Characteristics of Participants

Bun Quartile	Q1 (<13.8)	Q2 (14.00–17.70)	Q3 (18.00–24.80)	Q4 (25.00–152.00)	*P*-value
Number of patients	290	283	342	311	
Age (mean ±sd)	75.66±8.84	78.02±7.80	79.94±7.76	82.84±7.38	<0.001
RR (mean ±sd)	23.38±5.62	24.27±7.15	24.55±6.10	25.37±6.27	0.003
HR (mean ±sd)	102.77±19.74	101.80±18.39	101.65±19.39	99.01±19.33	0.098
LOS (mean ±sd)	14.69±11.86	15.42±16.02	17.08±16.03	20.42±19.05	<0.001
Time to stability (mean ±sd)	3.97±4.35	3.40±3.66	4.31±4.87	3.72±4.56	0.069
Gender (n, %)					0.049
Male	249 (85.86%)	258 (91.17%)	314 (91.81%)	284 (91.32%)	
Female	41 (14.14%)	25 (8.83%)	28 (8.19%)	27 (8.68%)	
Steroid (n, %)					0.627
No	135 (46.55%)	142 (50.18%)	158 (46.20%)	140 (45.02%)	
Yes	155 (53.45%)	141 (49.82%)	184 (53.80%)	171 (54.98%)	
Hospital (n, %)					<0.001
1	150 (51.72%)	148 (52.30%)	122 (35.67%)	110 (35.37%)	
2	76 (26.21%)	85 (30.04%)	134 (39.18%)	141 (45.34%)	
3	18 (6.21%)	12 (4.24%)	19 (5.56%)	13 (4.18%)	
4	18 (6.21%)	15 (5.30%)	33 (9.65%)	21 (6.75%)	
5	28 (9.66%)	23 (8.13%)	34 (9.94%)	26 (8.36%)	
Full assisting in daily activities (n, %)					<0.001
No	264 (91.03%)	246 (86.93%)	302 (88.30%)	236 (75.88%)	
Yes	26 (8.97%)	37 (13.07%)	40 (11.70%)	75 (24.12%)	
Wheezing lung sound (n, %)					0.119
No	186 (64.14%)	199 (70.32%)	249 (72.81%)	212 (68.17%)	
Yes	104 (35.86%)	84 (29.68%)	93 (27.19%)	99 (31.83%)	
AMS (n, %)					<0.001
No	261 (90.31%)	250 (88.34%)	293 (85.67%)	224 (72.73%)	
Yes	28 (9.69%)	33 (11.66%)	49 (14.33%)	84 (27.27%)	
Fever (n, %)					0.389
No	213 (73.45%)	216 (76.33%)	263 (76.90%)	247 (79.42%)	
Yes	77 (26.55%)	67 (23.67%)	79 (23.10%)	64 (20.58%)	
Stability (n, %)					0.013
No	41 (14.14%)	46 (16.25%)	46 (13.45%)	69 (22.19%)	
Yes	249 (85.86%)	237 (83.75%)	296 (86.55%)	242 (77.81%)	
Discharge (n, %)					0.003
No	17 (5.86%)	15 (5.30%)	19 (5.56%)	37 (11.90%)	
Yes	273 (94.14%)	268 (94.70%)	323 (94.44%)	274 (88.10%)	
Intubation (n, %)					0.243
No	287 (98.97%)	281 (99.29%)	341 (100.00%)	307 (98.71%)	
Yes	3 (1.03%)	2 (0.71%)	0 (0.00%)	4 (1.29%)	

Abbreviations: RR, respiratory rate; HR, heart rate; LOS, length of stay; AMS, altered mental status; 1, Kameda Medical Center; 2, Hyogo Prefectural Amagasaki General Medical Center; 3, Awa Regional Medical Center; 4, Saiseikai Yokohamashi Tobu Hospital; 5, Ichinomiyanishi Hospital.

Table 2 The Results of Univariate Analysis

Characteristics	Statistics	β (95% CI)	*P*-value
Age	79.27±8.35	0.11 (0.01, 0.22)	0.0403
Gender			
Male	1105 (90.13%)	Ref	
Female	121 (9.87%)	−2.67 (−5.67, 0.33)	0.0811
Steroid			
No	575 (46.90%)	Ref	
Yes	651 (53.10%)	1.07 (−0.73, 2.87)	0.2452
Hospital			
1	530 (43.23%)	Ref	
2	436 (35.56%)	0.95 (−1.07, 2.98)	0.3570
3	62 (5.06%)	−5.00 (−9.17, −0.84)	0.0187
4	87 (7.10%)	3.28 (−0.34, 6.91)	0.0757
5	111 (9.05%)	1.40 (−1.88, 4.69)	0.4024
Full assisting in daily activities			
No	1048 (85.48%)	Ref	
Yes	178 (14.52%)	−6.59 (−9.05, −4.03)	<0.0001
Wheezing lung sound			
No	846 (60.00%)	Ref	
Yes	380 (31.00%)	−3.43 (−5.36, −1.50)	0.0005
RR	24.42±6.31	0.25 (0.10, 0.40)	0.0009
AMS			
No	1028 (84.12%)	Ref	
Yes	194 (15.88%)	3.36 (0.91, 5.82)	0.0073
HR	101.28±19.26	−0.00 (−0.05, 0.04)	0.8779
Fever			
No	939 (76.59%)	Ref	
Yes	287 (23.41%)	0.18 (−1.94, 2.31)	0.8651
Stability			
No	202 (16.48%)	Ref	
Yes	1024 (83.52%)	−4.09 (−6.50, −1.69)	0.0009
Discharge			
No	88 (7.18%)	Ref	
Yes	1138 (92.82%)	−3.38 (−6.87, 0.11)	0.0577
Intubation			
No	1216 (99.27%)	Ref	
Yes	9 (0.73%)	39.10 (28.76, 49.44)	<0.0001
Bun	21.39 ± 12.53	0.14 (0.07, 0.21)	0.0002
Bun quartile			
Q1	290 (23.65%)	Ref	
Q2	283 (23.08%)	0.73 (−1.89, 3.35)	0.5849
Q3	342 (27.90%)	2.39 (−0.12, 4.89)	0.0621
Q4	311 (25.37%)	5.73 (3.17, 8.29)	<0.0001

Abbreviations: RR, respiratory rate; HR, heart rate; LOS, length of stay; AMS, altered mental status; 1, Kameda Medical Center; 2, Hyogo Prefectural Amagasaki General Medical Center; 3, Awa Regional Medical Center; 4, Saiseikai Yokohamashi Tobu Hospital; 5, Ichinomiyanishi Hospital.

Univariate Analysis of All Variables

The results of univariate analysis showed that age, BUN, rr, AMS, and intubation were positively related to LOS. Full assistance in daily activities, wheezing lung sounds and stability were negatively correlated with LOS. However, gender was not associated with LOS (Table 2).

Relationship Between BUN Levels and LOS

As shown in Table 3, in the crude model, every 1 mg/dl increase in BUN extended LOS by 0.1 days (95% CI 0.1 to 0.2, p<0.001). In Model I (adjusted for age and gender) and model II (further adjusted for steroids, full assistance in daily activities, wheezing lung sounds, rr, AMS, hr, fever stability, discharge and intubation), the correlations were similar to those in the crude model. To confirm the stability of the results, this study performed a sensitivity analysis of BUN levels by categorical variables (quartiles). The results showed that BUN levels were positively correlated with LOS (Table 3).

Nonlinear Relationship Analysis

As shown in Figure 1, after adjusting for age, gender, steroid use, full assistance in daily activities, wheezing lung sounds, rr, AMS, hr, fever, stability, discharge and intubation, our analysis found a nonlinear relationship between BUN levels and LOS. Through the analysis of the two-segment regression model, it was found that the inflection point was 40. The effect size and confidence interval to the left of this inflection point were 0.27 (0.16–0.39, P<0.0001). However, to the right of the inflection point, we did not observe an association between BUN levels and LOS (P=0.0632) (Table 4).

Subgroup Analysis

To further analyse the impact of other risk factors associated with BUN levels and LOS, this study performed subgroup analyses on the following stratified variables: age, gender, steroid use, full assistance in daily activities, wheezing lung sounds, rr, AMS, hr, fever, stability, discharge and intubation (Table 5). Additive interactions between BUN levels and LOS were observed for gender, AMS, fever, stability and discharge. (P value for interaction<0.05). Stronger correlations were found in participants with gender, AMS, fever, stability and discharge (Figure 2). However, significant interactions were not found for age, steroid use, rr, hr, intubation, full assistance in daily activities, or wheezing lung sounds.

Discussion

Based on the current research literature, this is the first study to investigate the association between BUN levels and LOS in patients with pneumonic COPD exacerbation. It is well known that the level of BUN is a biomarker that is widely used in clinical practice and that can be quickly obtained as a test result. Our study demonstrated a nonlinear association between BUN levels and LOS in patients with pneumonic COPD exacerbation; namely, when the BUN level was below the inflection point of 40 mg/dl, LOS was positively correlated with the BUN level. Furthermore, to reduce the likelihood of bias and overestimation of

Table 3 Association Between BUN Levels and LOS

	Crude Model	Model I	Model II
	β (95% CI) *P*-value	**β (95% CI) *P*-value**	**β (95% CI) *P*-value**
Bun	0.1 (0.1, 0.2) <0.001	0.1 (0.1, 0.2) <0.001	0.1 (0.0, 0.2) 0.011
Bun quartile			
Q1	Ref	Ref	Ref
Q2	0.7 (−1.9, 3.4) 0.585	0.5 (−2.1, 3.2) 0.702	0.3 (−2.3, 3.0) 0.793
Q3	2.4 (−0.1, 4.9) 0.062	2.1 (−0.5, 4.6) 0.111	1.6 (−0.9, 4.1) 0.213
Q4	5.7 (3.2, 8.3) <0.001	5.3 (2.6, 8.0) <0.001	4.6 (1.9, 7.3) <0.001
p for trend	1.9 (1.1, 2.7) <0.001	1.8 (0.9, 2.6) <0.001	1.5 (0.6, 2.3) <0.001

Notes: Crude model adjust for: None. Model I adjust for: age; gender. Model II adjust for: age; gender; steroid; full assisting in daily activities; wheezing lung sound; rr; AMS; hr; fever; stability; discharge; intubation.

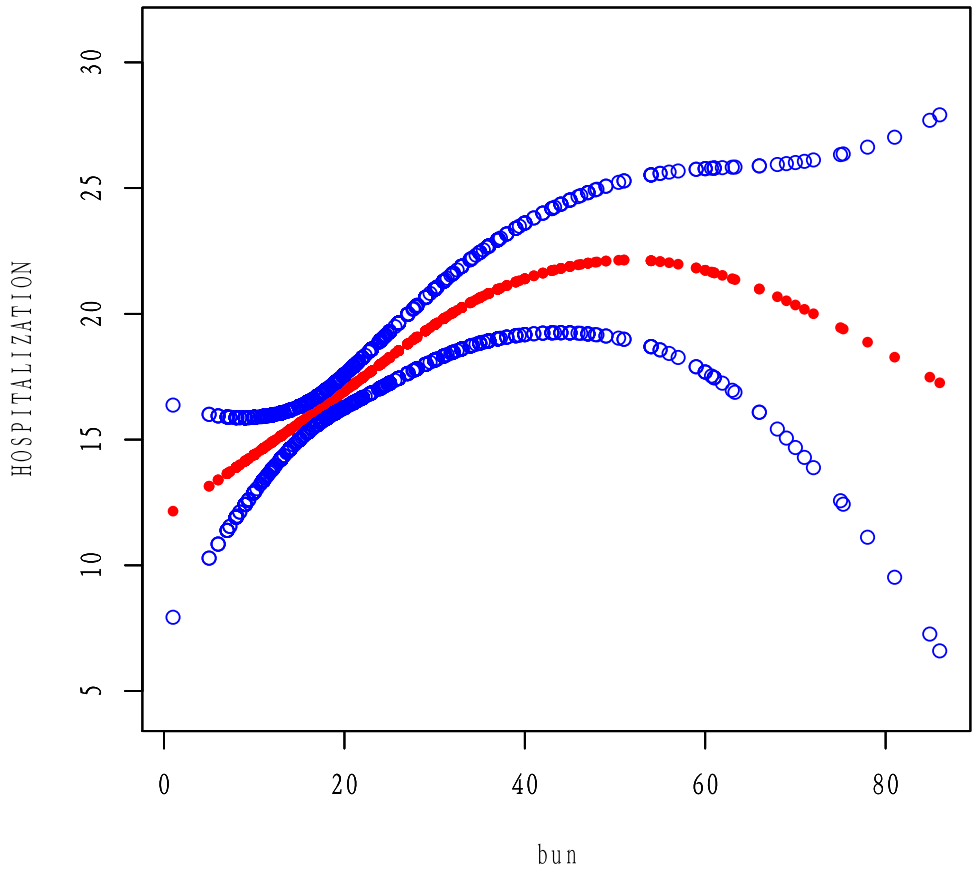

Figure 1 A non-linear relationship of BUN levels with LOS.

correlations, we adjusted for a range of potential confounders. In multivariate logistic regression analyses, BUN as a categorical or continuous variable was significantly associated with LOS, and consistent results were observed in stratified analyses. The relationship between BUN levels and LOS in patients with pneumonic COPD exacerbation was further confirmed. The findings of this study may be helpful to clinicians. At the time of emergency admission, appropriate interventions can be selected according to the BUN level.

In patients with other lung disease types, BUN levels have also been shown to correlate with poor prognosis. A retrospective study of patients with acute pulmonary embolism showed that patients with higher BUN levels had adverse hospital outcomes at a significantly higher rate than those with lower BUN levels.[9] In patients with aspiration pneumonia and community-acquired pneumonia, BUN levels were significantly different between the surviving and nonsurviving groups.[10] BUN levels were also identified as a major risk factor associated with poor COVID-19 outcomes.[11] In a study of elderly emergency patients and critically ill patients, BUN levels were also shown to be associated with poor outcomes.[12] Therefore, BUN may contribute to increased LOS in patients with pneumonic COPD exacerbation. Possible explanations are as follows: BUN levels are considered to be markers of neurohumoural activity, cardiorenal function, and catabolic conditions. Cardiovascular disease, although often undetected, is prevalent in COPD

Table 4 The Results of Two-Piecewise Linear Regression Model

Inflection Point of BUN Levels (mg/dl)	(β) 95% CI	*P*-value
<40	0.27 (0.16, 0.39)	<0.0001
≥40	−0.17 (−0.34, 0.01)	0.0632

Notes: Effect: LOS. Cause: BUN levels. Adjusted: age; gender; steroid; full assisting in daily activities; wheezing lung sound; rr; AMS; hr; fever; stability; discharge; intubation.

Table 5 Effect of BUN Levels on LOS by Subgroups

Characteristics	N	(β) 95% CI	*P*-value	*P* (Interaction)
Age				0.7690
47–75	388	0.12 (−0.02, 0.26)	0.0846	
76–82	390	0.16 (0.00, 0.32)	0.0460	
83–105	448	0.10 (−0.00, 0.20)	0.0601	
Gender				0.0104
Male	1105	0.18 (0.10, 0.27)	<0.0001	
Female	121	−0.05 (−0.15, 0.04)	0.2916	
Steroid				0.5770
No	575	0.12 (0.02, 0.21)	0.0163	
Yes	651	0.16 (0.05, 0.26)	0.0036	
RR group				0.2809
0–21	372	0.25 (0.10, 0.40)	0.0008	
22–25	338	0.10 (−0.03, 0.23)	0.1396	
26–81	408	0.13 (0.00, 0.25)	0.0485	
AMS				0.0288
No	1028	0.18 (0.10, 0.27)	<0.0001	
Yes	194	0.01 (−0.14, 0.16)	0.9253	
HR group				0.7309
30–91	390	0.16 (0.04, 0.29)	0.0119	
92–108	403	0.15 (0.05, 0.26)	0.0035	
109–200	419	0.09 (−0.07, 0.25)	0.2625	
Fever				0.0248
No	939	0.18 (0.10, 0.26)	<0.0001	
Yes	287	−0.04 (−0.20, 0.12)	0.6096	
Stability				<0.0001
No	202	−0.092 (−0.252, 0.069)	0.2626	
Yes	1024	0.235 (0.154, 0.317)	<0.0001	
Discharge				<0.0001
No	88	−0.357 (−0.643, −0.072)	0.0162	
Yes	1138	0.208 (0.134, 0.281)	<0.0001	
Intubation				0.9303
No	1216	0.125 (0.055, 0.195)	0.0005	
Yes	9	0.15 (−0.30, 0.59)	0.5188	
Full assisting in daily activities				0.8599
No	1048	0.110 (0.031, 0.188)	0.0061	
Yes	178	0.125 (−0.061, 0.310)	0.1907	
Wheezing lung sound				0.3701
No	846	0.158 (0.064, 0.251)	0.001	
Yse	380	0.086 (−0.010, 0.183)	0.0793	

patients and activates the SNS and RAS, which in turn reduces eGFR and increases urea reabsorption. Respiratory infections are the main cause of "exacerbations" in COPD patients. Patients with pneumonia often have a state of hydration that results in increased renal reabsorption of urea, and elevated BUN levels are frequently observed. It has been reported that in patients with pulmonary infection, higher BUN levels are generally associated with a worse prognosis,[13] which may be due to catabolic abnormalities caused by the inflammatory response and dehydration state in

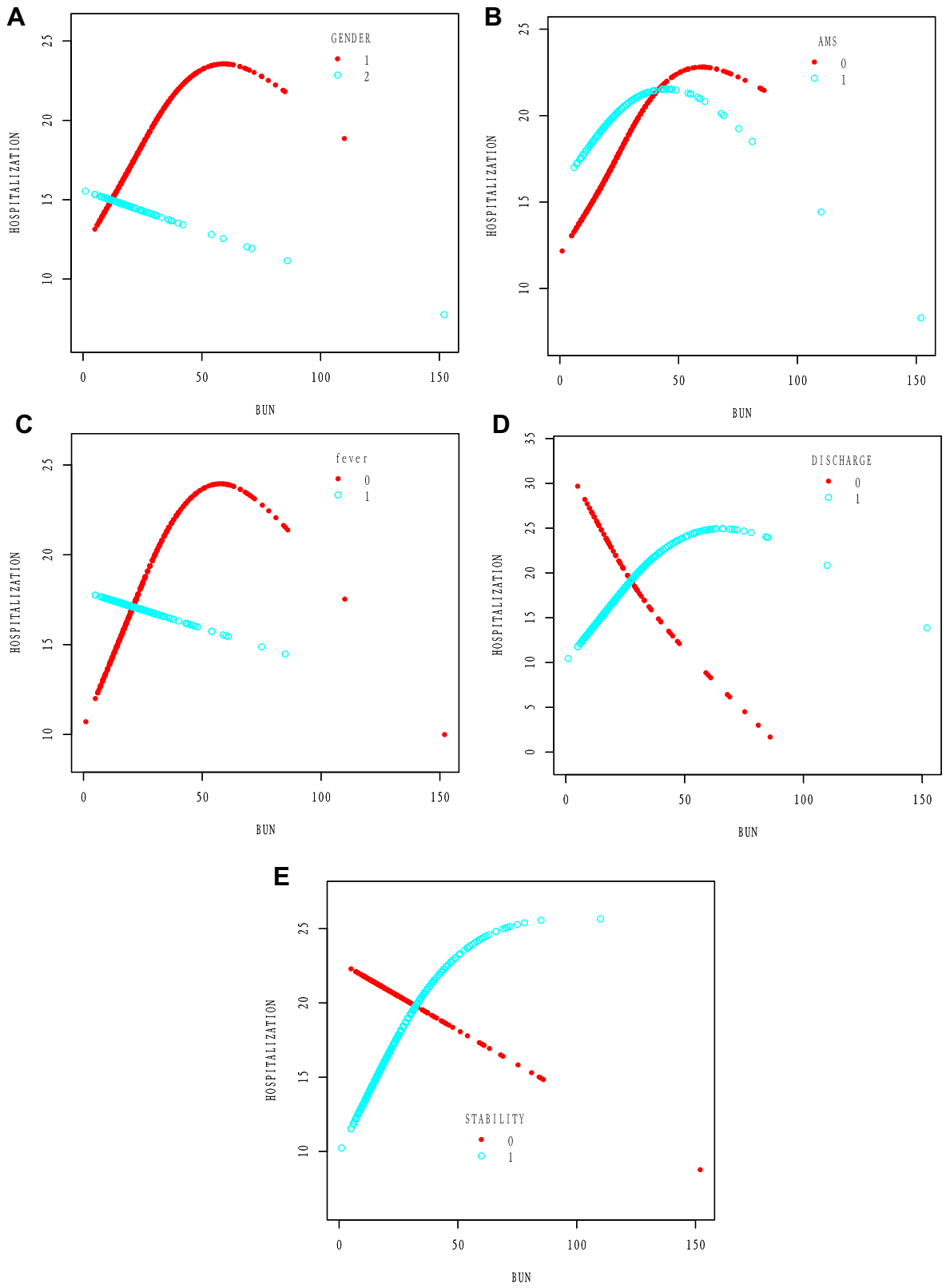

Figure 2 Effect of BUN levels on LOS by subgroups of gender, AMS, fever, discharge and stability (**A**–**E**).

patients with pneumonia. However, the impact of these mechanisms should be assessed through further studies.[14,15] In this study, all patients with pneumonic COPD exacerbation contributed to the correlation of BUN levels with LOS.

Furthermore, our study has certain limitations. First, the study was a retrospective cohort study, so some bias may have inevitably been introduced. Excluded patients may have influenced the study results, and we were unable to assess this. Second, due to the limitations of the raw data, we were unable to obtain detailed information on the baseline characteristics and experimental parameters of all patients, such as patient BMI, smoking history, disease history, pulmonary function (FEV1), and blood oxygen saturation. Third, we performed a secondary analysis of limited raw data. The target population consisted of relatively elderly Japanese patients with pneumonic COPD exacerbation. Ninety percent of the population was male, which may be related to the higher incidence in males and strict exclusion criteria, which of course also causes a certain gender bias.

Conclusion

In our cohort study, the BUN concentration on admission was closely related to LOS in pneumonic COPD exacerbation patients, showing a nonlinear relationship, and when the BUN level was less than 40 mg/dl, LOS was positively correlated with BUN level. As an inexpensive and readily determined parameter, elevated BUN levels on admission should be a red flag to alert physicians regarding early intervention.

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Disclosure

The authors report no conflicts of interest in this work.

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