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Diagnostic Performance of Initial Serum Albumin Level for Predicting in-Hospital Mortality Among Necrotizing Fasciitis Patients

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Abstract

Background:

Hypoalbuminemia is known to be associated with adverse outcome in critical illness. In this study, we attempted to identify if hypoalbuminemia on emergency department (ED) arrival a reliable predictor for in-hospital mortality in necrotizing fasciitis (NF). patients.

Method:

A retrospective cohort study of hospitalized patients with NF was conducted in a tertiary teaching hospital in Taiwan between March 2010 and March 2018. Blood samples were collected in the ED upon arrival, and serum albumin levels were determined. we evaluated the predictive value of serum albumin level at ED presentation for in-hospital mortality. All collected data were statistically analyzed.

Result:

Of the 707 NF patients, 40 (5.66%) died in the hospital. The mean serum albumin level was 3.1 ± 0.9 g/dL and serum albumin levels were significantly lower in the non-survivor group than in the survivor group (2.8± 0.7 g/dL vs. 3.5 ± 0.8 g/dL). In the multivariable logistic regression model, albumin was associated with in-hospital mortality significantly (odds ratio[OR] 0.92, 95% confidential interval (CI) 0.88–0.96, *P* <0.001). The area under-the-receiver-operating-characteristic curve (AUC) for in-hospital survival was 0.77 (95% CI 0.72–0.82) and corresponding sensitivity, specificity, positive predictive value, negative predictive value, positive and negative likelihood ratio were 66%, 74%, 33%, 88%, 2.25 and 0.48, respectively. High sensitivity (96%) was shown at albumin level of 4.0 g/dL and high specificity (91%) was shown at level of 2.5 g/dL.

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Conclusion:

Initial serum albumin levels were independently associated with in-hospital mortality among adult patients with necrotizing fasciitis and demonstrated fair discriminative performance in the prediction of in-hospital mortality. NF patients with hypoalbuminemia on ED arrival should be closely monitored for signs of deterioration and consider early and aggressive intervention to prevent mortality.

Key words: albumin, mortality, necrotizing fasciitis

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Introduction

Necrotizing fasciitis (NF) is a serious form of infection involving rapidly spreading inflammation and extensive necrosis of the skin, subcutaneous tissue, and superficial fascia [1]. The treatment of choice for NF is rapid surgical debridement and broad-spectrum antibiotic therapy [2]. Even with aggressive treatment, patients may suffer mortality and significant morbidity such as amputation and organ failure [3-5].

Various factors have been shown to be associated with mortality among patients with necrotizing fasciitis. Most of the identified factors have been patient characteristics such as older age, liver cirrhosis, cancer and peripheral vascular disease. Among widely used laboratory markers, band polymorphonuclear neutrophils >10 %, serum creatinine level >2 mg/dL, hyperlactatemia, Laboratory Risk Indicator of Necrotizing Fasciitis (LRINEC) score > 8 and serum albumin levels have been identified in association with mortality [6-8]. Serum albumin levels may also serve as a prognostic factor for critical patients, and the diagnostic performance of this parameter in critical care is well-known [9-11]. However, the diagnostic performance of serum albumin levels has not yet been reported among patients with necrotizing fasciitis.

In the present study, we determined the association between in-hospital mortality and serum albumin levels at the presentation to the emergency department (ED) among patients with necrotizing fasciitis. Additionally, the diagnostic performance of serum albumin levels was investigated.

Material and Methods

Patient selection

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The institutional review board of our hospital approved this prospective study. In all, 707 patients were enrolled based on two criteria, 1) surgically proven diagnosis of NF and 2) treatment received between March 2010 and March 2018 in our hospital. All patients were assessed by emergency physicians as soon as they were admitted. They received broad-spectrum antibiotic treatment for anaerobic and aerobic bacteria as well as early surgical debridement including fasciotomy or primary amputation post-diagnosis. Each patient's medical record was screened for documentation of NF to confirm the diagnosis. Blood samples were collected in the ED upon arrival, and the serum albumin levels were determined. Baseline demographic characteristics, laboratory findings, serum albumin, clinical presentation were compared between survivors and non-survivors groups.

Data analysis

We reviewed charts and recorded variables including age, systolic and diastolic blood pressure at triage, comorbidities, discharge diagnosis and mortality or survival on discharge. Patients with in-hospital mortality was defined as a death occurring in the hospital after admission, also known as 'non-survivors group', otherwise as 'survivors group'. We defined these variables as follows: episodes of hypotension, episodes of systolic blood pressure less than 90 mmHg at the ED; hypothermia, body temperature less than 36 degrees Celcius at the ED; hyperthermia, body temperature >= 38 degrees Celcius at the ED ; acidosis, pH less than 7.35 in arterial blood gas test at the ED; coagulopathy, a prolonged prothrombin time test (international normalized ratio) result greater than 1.5 at the ED; thrombocytopenia, platelet counts less than 100 x 10^3 uL at the ED ; anemia, hemoglobin less than 10 mg/dL at the ED; episodes of SpO2<90%, oxygen saturation less than 90% at the ED. Prothrombin time test,

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hemoglobin, platelet counts, blood gas test, serum lactate, albumin, sodium, creatinine, CRP (C-reactive protein) were assessed by first laboratory analyses in ED.

Statistical analyses were done by using SPSS 20.0. Assumptions of normality and homogeneity of variance were first checked. For continuous variables with a skewed distribution, descriptive results were expressed as medians and interquartile ranges. The Mann–Whitney U test was used to determine the differences between two groups, and the Kruskal-Wallis H test was used to analyze the differences among groups. Univariate binary and multivariate logistic regression analyses were performed to investigate whether serum albumin was independently associated with in-hospital mortality. The model fit was assessed with the Hosmer–Lemeshow goodness-of-fit test. A non-significant value for the Hosmer-Lemeshow Chi-square test suggests an absence of biased fit. Analysis of the area under the curve (AUC) of the Receiver Operating Characteristic (ROC) curve was constructed to assess the predictive strength. The nonparametric method of Delong was used to compare significant difference between AUCs. Sensitivity, specificity, and positive and negative likelihood ratios and predictive values were calculated at different cut-off values. Optimal cut-off points to maximize both sensitivity and specificity were also determined. Differences with P values <0.05 were considered to be statistically significant. We additionally compared the baseline characteristics of groups categorized by the presence or absence of hypoalbuminemia (hypoalbuminemia vs. non-hypoalbuminemia). A logistic regression analysis was performed to examine the association between baseline characteristics and the occurrence of hypoalbuminemia.

Results

Patient characteristics

Of the total 707 NF patients, 40 (5.66%) died in the hospital. Patients who were discharged to home were considered to have a favorable outcome. The demographic and clinical characteristics and laboratory findings on the ED arrival are compared between survivors and non-survivors in Table 1. The level of serum albumin upon ED arrival in non-survivors was significantly lower than in survivors ($p < 0.001$). SOFA scores in non-survivors was significantly higher than in survivors, which calculated during the first 24 hours after admission. In the analysis of initial variables recorded at ED, there were statistically significant differences with acidosis (16.04% vs. 25.0%, $P < 0.001$), coagulopathy (14.24% vs. 27.5%, $P < 0.001$), blood lactate (2.8 vs. 6.6 mmol/l, $P < 0.001$), serum creatinine (1.7 vs. 2.4 mg/dl, $P < 0.01$), and CRP level (124.1 vs. 161.7 mg/dl, $P < 0.01$). Age was similar in both groups.

Comparison of data in NF patients with different levels of serum albumin

Serum albumin was detectable with a range of 0.8 - 6.3 g/dL in 707 samples. The median serum albumin level measured upon ED arrival was 2.9 g/dL. A comparison of the demographic, clinical characteristics and the laboratory findings collected upon ED arrival and SOFA score among NF patients with different levels of serum albumin is shown in Table 2. The incidence of in-hospital mortality was significantly associated with decreased serum albumin levels ($P < 0.001$). A significant increase in the SOFA scores ($P < 0.001$), incidence of acidosis, episodes of hypotension, thrombocytopenia, and the CRP concentrations were associated with decreases in the serum albumin levels. In contrast, the serum albumin levels ($P < 0.001$) was significantly decreased with increases in the blood lactate levels.

Association of serum albumin level with in-hospital mortality

Univariate binary and multivariate logistic regression analyses were performed to investigate whether the serum albumin level upon ED arrival was independently associated with in-hospital mortality (Table 3). Age, SOFA score, laboratory findings collected on the ED arrival, clinical conditions and comorbidities that were potentially associated with in-hospital mortality were included in the analyses. The following factors were significantly associated with in-hospital mortality in the unadjusted binary logistic regression analysis: SOFA score, acidosis, coagulopathy, episode of hypotension, blood lactate, albumin, creatinine, and CRP value, and comorbidity with chronic kidney disease. The odds for in-hospital mortality decreased by 14%, for every 1 g/dL increase in serum albumin (OR = 0.86; 95% CI, 0.83-0.89; *P* <0.001). The association of serum albumin levels with in-hospital mortality remained significant after adjusting for age and SOFA score (OR = 0.89; 95% CI, 0.85-0.96; *P* <0.001). Multivariate logistic regression analysis identified blood lactate (OR = 1.17; 95% CI, 1.07-1.29; *P* < 0.001), serum albumin (OR per 1 g/dl increase = 0.92; 95% CI, 0.88- 0.96; *P* <0.001), and SOFA score (OR per 1-point increase = 1.15; 95% CI, 1.11-1.20; *P* <0.001) as independent factors that were significantly associated with in-hospital mortality in NF. The Hosmer- Lemeshow goodness-of-fit test for the multivariate logistic regression model was not significant (*P* = 0.611), indicating that the model adequately fits the data. Furthermore, the association between serum albumin levels and in-hospital mortality remained significant after adjusting for SOFA score and serum albumin (OR = 0.95; 95% CI, 0.90-0.98; *P* <0.001).

Ability of blood lactate level to predict in-hospital mortality

The predictive ability of serum albumin levels from NF patients upon ED arrival (n = 707) for in-hospital mortality (n = 40) was assessed (Table 4). The level of serum albumin was predictive of in-hospital mortality and achieved AUC of 0.77 (95% CI,

0.72-0.82; *P* <0.001). This AUC is similar to SOFA score (AUC = 0.82; 95% CI, 0.78-0.86; *P* <0.001) for predicting the in-hospital mortality. The *P*-value for comparison of both AUCs was 0.324. Combining serum albumin levels with SOFA score improved the predictive performance (AUC = 0.84; 95% CI 0.76-0.92; *P* <0.001), which is better than serum albumin alone (*P* = 0.013), but not significantly better than SOFA score alone (*P* = 0.274). Figure 1 shows the ROC curves and the AUC of the serum albumin level at ED arrival, SOFA score, and the combination of the serum albumin with SOFA score for predicting the in-hospital mortality of NF patients. The sensitivity and specificity of the serum albumin levels and SOFA scores at the optimal cut-off value to predict in-hospital mortality are shown in Table 4. Serum albumin displayed a sensitivity of 66% and a specificity of 74% at the optimal cut-off value of 3.2 g/dL. The positive and negative likelihood ratios were 2.25 and 0.48, respectively. SOFA score displayed a sensitivity of 67% and a specificity of 83% for predicting in-hospital mortality at the optimal cut-off score of 7.2, and the positive and negative likelihood ratios were 3.8 and 0.39, respectively. We also calculated the sensitivity and specificity of differing levels of serum albumin to predict in-hospital mortality in NF patients (Table 5). At the cut-off value of ≤ 4.0 of 96% and a specificity of 25% for predicting in-hospital mortality, and the positive and negative likelihood ratios were 1.24 and 0.12, respectively. The specificity increased to 91%, and the positive likelihood ratio increased to 4.18 at the cut-off value of ≤ 2.5 g/dL, although the sensitivity decreased to 26%. The OR values of serum albumin at the levels above the set cut-off points are shown in Table 5.

Discussion

This study provides data on serum albumin levels and demonstrates that the serum albumin level upon ED arrival is significantly associated with in-hospital mortality in

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NF patients. A low serum albumin level at ED arrival is predictive of in-hospital mortality in NF patients. Some studies have demonstrated that albumin levels is associated with mortality in adults with NF [12-15]. To our knowledge, no studies verified the use of serum albumin as a prognostic index in NF patients who are admitted via ED. The observation that the extent of serum albumin levels is strongly linked with mortality independent of illness severity indicates that serum albumin is a useful early predictor in identifying. Discriminatory value for predicting in-hospital mortality was fair at cut-off value (3.2 g/dL), and sensitivity and specificity were low at 66% and 74%, respectively. However, the use of a relatively high level of albumin (4.0 g/dL)was associated with high sensitivity (96%), and the use of a low level of albumin (2.5 g/dL) was associated with high specificity (91%). These findings seem to have meaningful clinical significance. One contribution of this study is the use of SOFA score to control for the severity of the illness. Previous studies suggest that SOFA score is an important tool in predicting mortality and clinical outcomes in critically ill patients [16-19]. The association of ED serum albumin with in-hospital mortality in this study was independent of age and the severity of illness as assessed by SOFA score. The ROC curve analysis in the present study showed that the prognostic accuracy of serum albumin for in-hospital mortality (AUC = 0.77) was similar to that of SOFA score (AUC = 0.82). Because serum albumin at ED and SOFA score obtained within the first 24 hours after admission are comparable in predicting mortality, we recommend assessing mortality risk with serum albumin at ED because it is simple to use. Some theories exit regarding the reasons why lower serum albumin levels, or hypoalbuminemia, may be associated with poor outcomes. Because synthesis and distribution of albumin may be directly associated with serum albumin level, factors that could affect albumin synthesis, distribution, or both need to

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be considered. Theoretically, decreased liver function or insufficient amino-acids intake may result in the hypoalbuminemia. In the present study, malnutrition was more frequently identified in the hypoalbuminemia group. A distribution disturbance between intravascular albumin levels and extravascular albumin levels may also exist. Certain conditions may decrease serum albumin levels such as pleural effusion, ascites, edema, or nephrosis. There was no significant difference was identified in the rates of liver cirrhosis or chronic kidney disease between the hypoalbuminemia group and non-hypoalbuminemia group. (Table 6.) In addition to aforementioned effect of hypoalbuminemia in association with other pathological conditions, hypoalbuminemia may be directly linked to opposing treatment effects. Nearly all drugs, including antibiotics can bind with plasma protein and form protein-drug complexes. Because the unbound fraction of drugs exhibits a pharmacologic effect [20], lower serum protein levels would be beneficial. However, protein-drug complexes can escape via renal tubular secretion or hepatic metabolism [21] and may serve as a reservoir, resulting in a slow release of the drug in an active unbound form. These effects may be associated with an increased biological half-life of drug; thus, contrary to the prior mechanism, higher serum protein levels would be beneficial in this case. In addition, it is not certain whether higher serum albumin levels are more beneficial or if a specific threshold of serum albumin level exists. Therefore, further investigations regarding this issue are needed. We cautiously suggest that the strategy in which serum albumin levels are maintained at the highest level as possible may be beneficial based on this study. This finding implies that higher serum albumin level were associated with greater chance of survival. Based on this result, the authors thought that potential role of albumin administration would exist in NF. Although the study

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result was obtained using data at initial presentation and not after treatment, it could be representative of one-point in the patients' course of illness.

There were several limitations of this study. First, there was a temporal mismatch in evaluating mortality indicators. We compared the prognostic performance of an albumin value obtained on ED arrival to a SOFA score, which considers a range of values and includes the worst values obtained in the first 24 hours of admission. The prognostic accuracy of the combination of serum albumin level and SOFA score was not significantly better than the use of SOFA score alone ($p = 0.274$), which might be explained by the discrepancy in the timescales for these two methods. Notably, the primary aim of the study was to evaluate the predictive value of serum albumin, when measured as a screening method at ED arrival, to predict mortality in patients with NF. Thus, serial changes in the lactate levels during the first 24 hours of admission or post surgical intervention were not evaluated. Second, we could not collect long-term mortality data. Third, this was a retrospective observational single center study. Whether the results of the present study are replicable in the other regions is of question, because of potential differences in treatment quality and hospital resources. Further studies are needed to investigate the trends in the changes of albumin values and explore whether the addition of the albumin value in the first 24 hours to the SOFA score evaluation improves the prediction of mortality in NF patients.

Conclusion

Our study indicates that the serum albumin levels upon ED arrival were significantly associated with mortality in NF, even after adjusting for age, blood lactate, and SOFA score. A low level of serum albumin upon ED arrival was independently predictive of in-hospital mortality in the NF patients. These findings extend the knowledge of serum albumin as a clinical biomarker of mortality in critical illness.

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Abbreviations

AUC, area under the receiver-operating-characteristic curve

CI, confidence interval

CKD, chronic kidney disease

CRP, C-reactive protein

DBP, diastolic blood pressure

ED, emergency department

LR+, likelihood ratio positive; LR-, likelihood ratio negative

NF, necrotizing fasciitis

OR, odds ratio

PV+, positive predictive value; PV-, negative predictive value

SBP, systolic blood pressure

SOFA, sequential organ failure assessment

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

CP Chang conceived of the study, and participated in its design and coordination and helped to draft the manuscript. CN Lin participated in drafted the manuscript and statistical analysis. CT Hsiao participated in the design of the study and statistical analysis. WC Fann participated in the design of study and drafted the manuscript. SR Wu and IC Chen participated in statistical analysis.All authors read and approved the final manuscript.

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Ethical approval and consent to participate

The institutional review board of Chia-yi Chang Gung Memorial Hospital approved this retrospective study (100-4178B). Consent to participate was not applicable.

Consent for publication

Not applicable

Availability of supporting data

Please contact author for data requests

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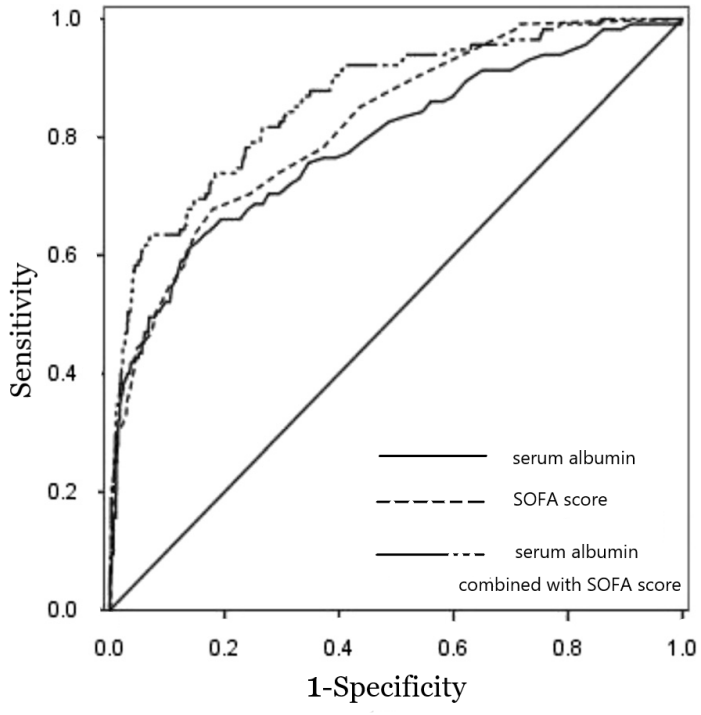

Figure 1. Receiver operating characteristic curves for the ability of serum albumin, SOFA score, and serum albumin combined with SOFA score to predict in-hospital mortality in NF patients (n = 707)

The area under the receiver operating characteristic curve for serum albumin, SOFA score, and serum albumin combined with SOFA score were 0.77, 0.82 and 0.84, respectively, with a Hosmer-Lemeshow goodness-of-fit p value >0.05.

Table 1. Comparison of demographic and clinical characteristics and laboratory findings on ED arrival between survival and non-survival NF patients

Characteristics	Survivors(n=667)	Non-survivors(n=40)	*P* Value
Age, years, mean	57.2 (35.7-69.8)	60.7 (39.3-82.6)	0.09
SBP at triage, mmHg	146.5 (124.6-189.9)	141.4 (104.6-198.5)	0.93
DBP at triage, mmHg	85.1 (55.6-101.7)	78.7 (44.1-99.5)	079
SOFA score	4 (0-6)	9 (5-23)	<0.001
episodes of hypotension, n (%)	86(12.90)	19(47.50)	<0.01
hypothermia (BT<36), n (%)	78(11.70)	10(25.0)	0.56
hyperthermia (BT>=38), n (%)	150(22.49)	9(22.50)	0.94
Acidosis, n(%)	106(16.04)	10(25.0)	<0.001
Coagulopathy, n (%)	95(14.24)	11(27.5)	<0.001
Thrombocytopenia, n (%)	69(10.34)	7(17.5)	0.23
Anemia, n (%)	88(13.19)	11(27.50)	0.08
episode of SpO2<90% , n (%)	65(9.75)	6(15.0)	0.07
blood lactate (mmol/l)	2.8 (0.5-5.6)	6.6 (1.2-11.8)	<0.001
serum albumin (g/dl)	3.1 (2.1-4.8)	2.6 (1.9-3.6)	<0.001
serum creatinine (mg/dl)	1.7 (0.5-3.8)	2.4 (0.9-6.6)	<0.01
serum glucose (mg/dl)	163 (121.5-188.9)	192 (128.6-246.5)	<0.01
CRP (mg/dl)	124.1 (56.1-174.5)	161.7 (65.8-205.6)	<0.01
Heart failure, n (%)	163 (24.43)	11 (27.5)	0.24
Diabetes mellitus, n (%)	193 (28.94)	14 (35.0)	0.26
Liver cirrhosis, n (%)	141 (21.14)	13 (32.5)	0.15
Chronic kidney disease, n (%)	207 (31.03)	14 (35.0)	0.34

Values are median [interquartile range]. Numbers in parentheses denote percentages.

CRP, C-reactive protein; DBP, diastolic blood pressure; SBP, systolic blood pressure; SOFA, sequential organ failure assessment

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Table 2. Comparison of demographic and clinical characteristics and laboratory findings on ED arrival among NF patients with different levels of serum albumin

Admission serum albumin, g/dL	**<2.5**	**2.5-3.0**	**3.0-3.5**	**3.5-4.0**	**>4.0**	***P* value**
n	95	286	187	86	53	
Age, years	60.1 (40.5-78.6)	57.6 (42.3-70.8)	54.8 (39.8-72.5)	52.3 (43.7-78.1)	51.1 (32.3-65.6)	<0.001
SBP at triage, mmHg	141.2 (121.4-167.9)	137.5 (105.7-174.6)	132.9 (111.2-164.7)	133.7 (108.1-174.2)	132.5 (109.6-178.5)	0.58
DBP at triage, mmHg	65.2 (45.6-105.5)	70.1 (55.8-101.6)	68.4 (54.6-93.4)	69.2 (49.5-94.8)	64.9 (38.6-90.4)	0.23
Episode of hypotension, n (%)	25(21.1)	43(18.5)	32(17.1)	11(12.6)	6(8.9)	<0.001
SOFA score	8 (3-11)	7 (2-8)	6 (1-8)	4 (0-7)	3 (0-6)	<0.001
Hypothermia (BT<36), n (%)	12(12.5)	33(15.4)	26(13.8)	12(14.2)	8(11.5)	0.43
hyperthermia (BT>=38), n (%)	27(28.6)	73(25.6)	42(22.3)	21(24.9)	11(20.5)	0.56
Acidosis, n(%)	34(35.6)	59(20.5)	33(17.8)	13(15.6)	3(6.5)	<0.001
Coagulopathy, n (%)	26(27.1)	61(21.3)	39(20.6)	16(18.4)	10(18.3)	0.12

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Admission serum albumin, g/dL	**<2.5**	**2.5-3.0**	**3.0-3.5**	**3.5-4.0**	**>4.0**	***P* value**
Thrombocytopenia, n (%)	38(40.3)	93(32.6)	34(18.3)	14(15.9)	3(6.3)	<0.001
Anemia, n (%)	24(25.4)	61(21.2)	37(19.8)	14(16.8)	8(15.5)	0.45
Episode of SpO2<90%, n (%)	14(15.2)	35(12.4)	26(13.9)	9(10.7)	5(9.5)	0.28
In-hospital mortality, n(%)	17(17.9)	11(3.8)	7(3.7)	3(3.5)	2(3.8)	<0.001
blood lactate (mmol/l)	4.1 (2.9-5.6)	3.8 (2.6-5.1)	3.6 (2.3-4.5)	3.2 (2.4-4.1)	2.7 (1.5-3.9)	<0.001
serum creatinine (mg/dl)	2.4 (1.5-3.6)	2.2 (1.6-3.3)	2.2 (1.2-2.9)	1.8 (1.3-2.8)	1.6 (0.8-2.7)	0.08
serum glucose (mg/dl)	174 (124-298)	166 (126-254)	168 (117-249)	149 (115-224)	147 (107-226)	0.54
serum CRP (mg/dl)	174 (56-225)	158 (39-203)	142 (31-195)	129 (28-174)	78 (25-151)	<0.001
Diabetes mellitus, n(%)	32(34.1)	84(29.7)	58(31.2)	24(28.3)	12(23.3)	0.06
Liver cirrhosis, n(%)	39(41.5)	95(33.2)	57(30.8)	22(25.4)	6(11.3)	<0.001

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Admission serum albumin, g/dL	**<2.5**	**2.5-3.0**	**3.0-3.5**	**3.5-4.0**	**>4.0**	***P* value**
Heart failure, n(%)	17(18.6)	61(21.3)	29(15.4)	15(17.8)	6(10.9)	0.49
Chronic kidney disease, n(%)	32(33.8)	75(26.1)	46(24.9)	16(18.4)	5(9.5)	0.23

Values are median [interquartile range]. Numbers in parentheses denote percentages.

CRP, C-reactive protein; DBP, diastolic blood pressure; SBP, systolic blood pressure; SOFA, sequential organ failure assessment

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Table 3. Univariate and multivariate logistic regression analyses of variables potentially associated with in-hospital mortality in NF

	Univariate binary logistic regression		Multivariate logistic regression	
	OR(95% CI)	***P* value**	**OR(95% CI)**	***P* value**
Age	1.02(0.96-1.08)	0.542	1.06(0.96-1.16)	0.249
SOFA score	1.28(1.06-1.51)	<0.001	1.15(1.11-1.20)	<0.001[d]
Episode of hypotension	1.03(1.01-1.05)	0.001	1.11(0.63-1.97)	0.715
Episode of SpO2<90%	1.58(1.07-2.33)	0.325	1.14(1.02-1.18)	0.459
Acidosis	1.05(1.01-1.08)	<0.001	1.03(0.94-1.12)	0.217
Coagulopathy	1.01(1.00-1.01)	0.001	1.02(1.01-1.08)	0.428
Thrombocytopenia	1.03(0.98-1.08)	0.556	1.01(0.93-1.03)	0.829
Anemia	1.05(1.02-1.10)	0.065	0.99(0.98-1.01)	0.913
Hypothermia	1.01(1.00-1.01)	0.213	1.03(0.98-1.07)	0.541
Hyperthermia	1.12(1.02-1.15)	0.968	1.02(1.01-1.12)	0.280
Blood lactate	1.35(1.30-1.46)	<0.001	1.17(1.07-1.29)	<0.001
Serum glucose	1.09(1.01-1.23)	<0.01	1.94(0.76-4.75)	0.580
Serum albumin	0.86(0.83-0.89)	<0.001[a]	0.92(0.88-0.96)	<0.001[b,c]
Serum CRP	1.11(1.08-1.13)	<0.001	1.24(1.18-3.27)	0.086
Serum creatinine	1.01(1.00-1.01)	<0.001	1.12(0.89-2.35)	0.306

	Univariate binary logistic regression		Multivariate logistic regression	
Diabetes mellitus	1.05(1.02-1.06)	0.133	1.18(1.02-1.29)	0.102
Liver cirrhosis	1.02(1.00-1.03)	0.506	1.05(1.01-1.09)	0.020
Chronic kidney disease	1.02(1.00-1.02)	<0.01	1.14(1.05-1.18)	0.061

The p value of the Hosmer-Lemeshow goodness-of-fit test for the multivariate logistic regression model was 0.611

[a]The association of serum albumin with in-hospital mortality remained significant after adjustment for age, and SOFA score (OR = 0.89; 95% CI, 0.85-0.96; p <0.001). [b]The association of the serum albumin level with in-hospital mortality remained significant after adjustment for blood lactate and SOFA score (OR = 0.95; 95% CI, 0.90-0.98; p <0.001). [c]Odds ratio per 1 g/dl increase in albumin level. [d]Odds ratio per 1-point increase in SOFA score.

CI, confidence interval; CRP, C-reactive protein; DBP, diastolic blood pressure; OR, odds ratio; SBP, systolic blood pressure; SOFA, sequential organ failure assessment

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Table 4. Predicting performance of ED serum albumin and SOFA score for in-hospital mortality of NF

	AUC	95% CI	*P* value	Optimal cut-off value	Sensitivity	Specificity
Serum albumin	0.77	0.72-0.82	<0.001	3.2 g/dL	66%	74%
SOFA score	0.82	0.78-0.86	<0.001	7.2	67%	83%
Serum albumin combined with SOFA score	0.84	0.76-0.92	<0.001		68%	86%

P value (comparison of the difference between AUCs)

$p = 0.342$ (between serum albumin and SOFA score)

$p = 0.274$ (between serum albumin lactate combined with SOFA score and SOFA score alone)

$p = 0.013$ (between serum albumin combined with SOFA score and serum albumin alone)

AUC, area under the receiver-operating-characteristic curve; CI, confidence interval; SOFA, sequential organ failure assessment

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Table 5. Odds ratio, sensitivity, specificity for ED serum albumin at different levels to predict in-hospital mortality of NF

ED albumin, g/dL	OR[a] (95% CI)	P Value	Sensitivity	Specificity	LR+	LR-	PV+	PV-
≤ 2.5	8.32 (4.46-16.35)	<0.001	26%	91%	4.18	0.76	0.56	0.83
≤ 3.0	4.88 (3.45-8.62)	<0.001	45%	76%	2.14	0.68	0.35	0.85
≤ 3.5	3.02 (1.95-8.39)	<0.001	79%	48%	1.61	0.37	0.29	0.91
≤ 4.0	1.98 (1.33-6.52)	<0.001	96%	25%	1.24	0.12	0.21	0.98

CI, confidence interval; LR+, likelihood ratio positive; LR-, likelihood ratio negative; OR, odds ratio; PV+, positive predictive value; PV-, negative predictive value.

[a]Odds ratios of serum albumin at the levels above the set cut-off points.

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Table 6. Comparison between the non-hypoalbuminemia group and hypoalbuminemia group (serum albumin < 3.2 g/dL)

Characteristics	Non-hypoalbuminemia	Hypoalbuminemia	*P* Value
Age, years, mean	68.7 (41.7-78.2)	71.8 (45.3-89.6)	0.15
SOFA score	3 (0-5)	8 (4-18)	<0.001
episodes of hypotension, n (%)	33(9.6)	134(38.5)	<0.001
hypothermia (BT<36), n (%)	55(15.8)	50(14.2)	0.48
hyperthermia (BT>=38), n (%)	103(29.6)	96(27.5)	0.53
Acidosis, n(%)	40(11.4)	69(19.8)	<0.01
Coagulopathy, n (%)	48(13.8)	61(17.6)	0.29
Thrombocytopenia, n (%)	43(12.3)	100(28.7)	<0.01
Anemia, n (%)	53(15.1)	72(20.6)	0.18
blood lactate (mmol/l)	2.2 (0.2-4.8)	5.8 (1.4-15.7)	<0.001
CRP (mg/dl)	54.9 (14.1-113.7)	124.3 (42.8-166.6)	<0.01
Heart failure, n (%)	51(14.7)	58 (16.5)	0.41
Diabetes mellitus, n (%)	89 (25.1)	104 (29.7)	0.63
Liver cirrhosis, n (%)	99 (28.3)	126 (35.9)	0.08
Chronic kidney disease, n (%)	76 (21.8)	99 (28.4)	0.14

Values are median [interquartile range]. Numbers in parentheses denote percentages.

CRP, C-reactive protein; SOFA, sequential organ failure assessment