

ORIGINAL ARTICLE

How likely is septic shock to develop in a patient with Fournier's gangrene? A risk prediction model based on a 7-year retrospective study

Yang Yang^{1,†}, Li-Chun Wang^{1,†}, Xin-Yang Yu², Xiao-Fei Zhang¹, Zhong-Qing Yang², Yang-Zi Zheng², Bin-Yan Jiang^{2,*} and Lei Chen^{1,*}

¹Department of Critical Care Medicine, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, P. R. China; ²Department of Applied Mathematics, The Hong Kong Polytechnic University, Hong Kong SAR, China

*Corresponding authors. Lei Chen, Department of Critical Care Medicine, the Sixth Affiliated Hospital, Sun Yat-sen University, 26 Yuancun Erheng Road, Guangzhou, Guangdong 510655, P. R. China. Tel: +86-13570236595; Email: chenlei6@mail.sysu.edu.cn and Bin-Yan Jiang, Department of Applied Mathematics, The Hong Kong Polytechnic University, Hong Kong SAR, China. Tel: +852-27666349; Email: by.jiang@polyu.edu.hk

[†]These authors contributed equally to this work.

Abstract

Background Fournier's gangrene (FG) is a rare life-threatening form of necrotizing fasciitis. The risk factors for septic shock in patients with FG are unclear. This study aimed to identify potential risk factors and develop a prediction model for septic shock in patients with FG.

Methods This retrospective cohort study included patients who were treated for FG between May 2013 and May 2020 at the Sixth Affiliated Hospital, Sun Yat-sen University (Guangzhou, China). The patients were divided into a septic shock group and a non-septic shock group. An L1-penalized logistic regression model was used to detect the main effect of important factors and a penalized Quadratic Discriminant Analysis method was used to identify possible interaction effects between different factors. The selected main factors and interactions were used to obtain a logistic regression model based on the Bayesian information criterion.

Results A total of 113 patients with FG were enrolled and allocated to the septic shock group ($n = 24$) or non-septic shock group ($n = 89$). The best model selected identified by backward logistic regression based on Bayesian information criterion selected temperature, platelets, total bilirubin (TBIL) level, and pneumatosis on pelvic computed tomography/magnetic resonance images as the main linear effect and $\text{Na}^+ \times \text{TBIL}$ as the interaction effect. The area under the ROC curve of the probability of FG with septic shock by our model was 0.84 (95% confidence interval, 0.78–0.95). The Harrell's concordance index for the nomogram was 0.864 (95% confidence interval, 0.78–0.95).

Conclusion We have developed a prediction model for evaluation of the risk of septic shock in patients with FG that could assist clinicians in identifying critically ill patients with FG and prevent them from reaching a crisis state.

Key words: Fournier's gangrene; sepsis; septic shock; nomogram; risk prediction

Submitted: 3 March 2022; Revised: 23 April 2022; Accepted: 1 June 2022

© The Author(s) 2022. Published by Oxford University Press and Sixth Affiliated Hospital of Sun Yat-sen University

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Introduction

Fournier's gangrene (FG), as a form of necrotizing fasciitis (NF), is a rare, rapidly progressing, and life-threatening subcutaneous infection of the external genitalia and/or perineum [1, 2]. FG can lead to septic shock and multiple organ dysfunction syndrome in a short time in the absence of prompt and adequate treatment [3]. Despite the advances made in understanding the etiology and pathophysiology of FG, the associated mortality rate does not appear to have reduced over the past 25 years [4].

Although FG is a rare disease with a reported incidence of only 1:7,500 to 1:750,000, its overall mortality is high, in the range of 3%–67% [5]. Moreover, sepsis accounts for substantial mortality in patients with FG [6, 7] and the mortality goes up to 78% in patients who develop sepsis [8]. Accurate assessment of the risk of developing septic shock, corresponding source control, and prompt aggressive treatment are essential for improving the outcomes in critically ill patients with FG [9, 10]. Identification of the risk factors for septic shock in patients with FG is of tremendous importance for early risk assessment and reduction of mortality.

The risk factors for development of septic shock in patients with FG have not been clearly identified [11–13]. Therefore, the aim of this study was to identify clinical characteristics that could be used to predict septic shock in these patients. Awareness and prevention of septic shock may potentially reduce the mortality of FG. Our findings will be helpful for clinical evaluation and risk assessment in patients with FG in the future.

Patients and methods

Study design and participants

We retrospectively reviewed 116 patients who were treated for FG between May 2013 and May 2020 at the Sixth Affiliated Hospital, Sun Yat-sen University (Guangzhou, China). The inclusion criteria were as follows: (i) a diagnosis of FG, defined as necrotizing soft tissue infection, where necrosis of the subcutaneous tissue involves part of the external genitalia and/or perineum without muscle involvement [2] and (ii) treated in our gastrointestinal surgery department. The exclusion criteria were incomplete case data and abandonment of treatment. Patients with FG who developed septic shock were allocated to a septic shock group and those who did not to a non-septic shock group. Septic shock was defined as sepsis that presented with hypotension and required vasopressors to maintain a mean arterial pressure of ≥ 65 mmHg and a serum lactate level of >2 mmol/L despite adequate volume resuscitation [14].

The study protocol was approved by our institutional ethics committee of the Sixth Affiliated Hospital, Sun Yat-sen University (2021ZSLYEC-111). A waiver for informed consent was allowed by the ethics committee in view of the retrospective nature of the research and the anonymity of the data.

Collection of clinical and biochemical data

All data for the study participants were collected from the electronic medical records in the hospital information system. The clinical and biochemical parameters on the day of admission were analysed. The patient demographics included sex, age, and body mass index. Co-morbidities, vital signs, smoking status, and alcohol consumption were recorded. Laboratory

variables and the presence of pneumatosis on computed tomography/magnetic resonance images (CT/MRI) were analysed. We also calculated the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score. The day of presentation, surgical procedure, time from admission to starting on antibiotic therapy, types of antibiotics administered, days of antibiotic use, and use of continuous renal replacement therapy were recorded. We also recorded the time from onset of symptoms to admission, time from admission to surgery, length of stay in the intensive care unit (ICU), and length of hospital stay, and calculated the mortality rate. In total, we recorded 35 features (i.e. independent variables) for each patient.

Statistical analysis

Numerical variables are expressed as the mean \pm standard deviation. The Shapiro–Wilk test was used to check for normality of distributions. Variables passing the normality test were compared using the two-sample t-test and those that were rejected by the Shapiro–Wilk test were compared using the nonparametric Mann–Whitney U test. Categorical variables are expressed as the percentage and were compared using the chi-squared test. Fisher's exact test was used for contingency tables to examine the significance of the association between two categorical variables. We used logistic regression analysis to assess the risk of patients with FG developing septic shock. To reduce the curse of dimensionality in our analysis, we first used an L1-penalized logistic regression model to detect the main (linear) effect of important factors. The optimal cut-off value for each selected factor was calculated using receiver-operating characteristic (ROC) curves with the Youden's J-statistic. The area under the ROC curve (AUROC) was also used to evaluate the predictive value of each selected factor. To allocate possible interaction effects between different factors, we used a penalized Quadratic Discriminant Analysis classifier to detect an interaction [15]. The predictive effect of the selected interaction term (sodium $[\text{Na}^+] \times$ total bilirubin [TBIL]) was further evaluated using an empirical probability/risk function. The selected factors and interactions were then used to obtain a final logistic regression model. The optimal model was selected by backward selection via the Bayesian information criterion (BIC). A lower BIC score indicated a better fit of the corresponding model to the data. Harrell's concordance index and the AUROC were used for internal validation, and a nomograph was generated based on the fitted model for manual prediction. All hypothesis tests were two-sided with a significance level of 0.05 at 95% confidence interval (CI). All statistical analyses were performed using IBM SPSS version 23.0 (IBM Corp., Armonk, NY, USA) or Microsoft R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 116 patients were treated for FG between May 2013 and May 2020 and enrolled. There were three exclusions, leaving 113 patients for inclusion in the analysis. These patients were divided into a septic shock group ($n = 24$) and a non-septic shock group ($n = 89$) (Figure 1).

There was no significant between-group difference in demographic characteristics (Table 1). Patients in the septic shock group were more severely ill than those in the non-septic shock group, with a lower platelet count ($179.8 \pm 103.8 \times 10^9/\text{L}$ vs

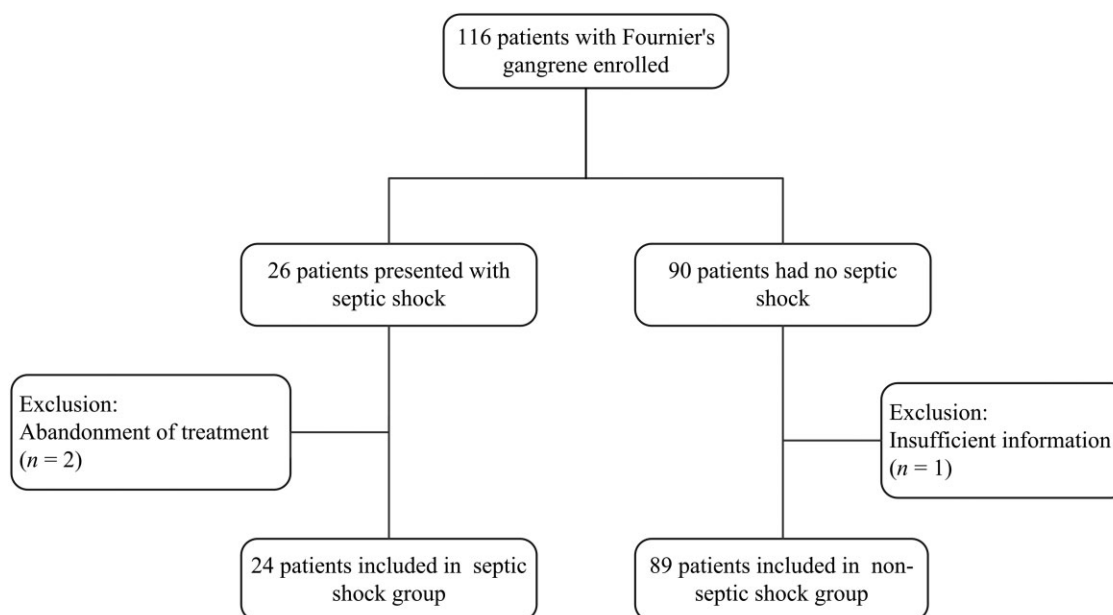


Figure 1. Flow chart showing the patient enrolment process

$286.4 \pm 140.5 \times 10^9/L$, $P = 0.001$), hematocrit (0.32 ± 0.07 vs 0.35 ± 0.06 , $P = 0.024$), and albumin (24.9 ± 7.3 vs 30.4 ± 6.9 g/L, $P = 0.001$), and a higher temperature (37.7 ± 1.2 vs $36.9 \pm 0.7^\circ\text{C}$, $P = 0.001$), longer prothrombin time (15.5 ± 3.7 vs 13.7 ± 2.0 s, $P = 0.026$), and higher TBIL (46.9 ± 67.5 vs 16.5 ± 14.5 $\mu\text{mol/L}$, $P = 0.030$). Pelvic CT/MRI was performed in all patients, and the presence of pneumatosis was more common in the septic shock group than in the non-septic shock group (83.3% vs 49.4%, $P = 0.003$). Overall, the mortality rate was higher in the septic shock group than in the non-septic shock group (25.0% vs 1.1%, $P < 0.001$) (Table 2).

There was no significant between-group difference in time from onset of symptoms to admission or in any of the other time intervals ($P > 0.05$) (Table 2). We also compared the time from admission to start of infusion of antibiotics and the types of antibiotics initially used between the groups and found no significant difference between the two groups ($P > 0.05$). Twenty-one patients in the septic shock group and 87 in the non-septic shock group underwent a surgical procedure; the between-group difference was not statistically significant ($P > 0.05$). Patients with septic shock were more likely to receive continuous renal replacement therapy (20.8% vs 1.1%, $P = 0.001$) and to require colostomy (37.5% vs 14.6%, $P = 0.013$) than those in the non-septic shock group. Median ICU stay was longer in the septic shock group (5.7 ± 7.0 vs 0.8 ± 1.9 days, $P < 0.001$).

Variable selection

Linear effect

We used L1-penalized logistic regression to detect factors with linear effects. The following features were chosen for further analysis: sex, temperature (T), pulse (P), systolic blood pressure (SBP), mean arterial pressure (MAP), Na^+ , platelet count (PLT), prothrombin time (PT), activated partial thromboplastin time (APTT), creatinine (Cr), albumin (ALB), TBIL, pneumatosis on CT/MRI, diabetes mellitus, heart disease, liver disease, smoking, and/or alcohol consumption, hyperlipidaemia, and malignancy. The AUROC for each selected factor was as follows: PLT 0.73

(95% CI, 0.62–0.84), T 0.72 (95% CI, 0.59–0.84), ALB 0.71 (95% CI, 0.59–0.83), PT 0.69 (95% CI, 0.57–0.82), pneumatosis on CT/MRI 0.67 (95% CI, 0.58–0.76), TBIL 0.65 (95% CI, 0.50–0.79), Na^+ 0.63 (95% CI, 0.48–0.78), MAP 0.62 (95% CI, 0.48–0.77), and SBP 0.61 (95% CI, 0.47–0.75). More details are shown in Figure 2.

Interactions

Interaction effects were selected via the penalized Quadratic Discriminant Analysis method. The selected interaction effect was $\text{Na}^+ \times \text{TBIL}$, and the corresponding AUROC was 0.65. The marginal distributions of Na^+ and TBIL in the two groups are presented in Figure 3A and B, respectively, while the joint distribution for samples in both groups is shown in Figure 3C. The two lines in Figure 3C are the log of the optimal cut-off values for Na^+ (138.95) and TBIL (17.36) obtained from the ROC curves of Na^+ and TBIL using the Youden's J-statistic. It can be seen that plots allocated in the first quadrant (meaning that the Na^+ and TBIL are higher than the optimal cut-off values) were mostly from the septic shock group, suggesting that patients with both high Na^+ and high TBIL values might have a higher risk of developing septic shock. To further evaluate this interaction effect on risk prediction, we computed the empirical risk of developing septic shock when $\log(\text{Na}^+ \times \text{TBIL})$ was larger than any given threshold. Specifically, for any threshold t , the empirical probability was defined as:

$$\frac{\text{Number of FG patients with septic shock and } \log(\text{Na}^+ \times \text{TBIL}) > t}{\text{Number of FG patients with } \log(\text{Na}^+ \times \text{TBIL}) > t}$$

The empirical probability of having septic shock is plotted in Figure 3D, in which we can observe that nearly half of all patients with FG and a $\log(\text{Na}^+ \times \text{TBIL})$ of >8 developed septic shock.

Logistic regression model

We combined all the selected factors with the linear effect and interaction effect identified in the previous subsections and fitted a logistic regression model with BIC-based backward

Table 1. Demographic and clinical characteristics of patients with Fournier's gangrene

Characteristic	Total (n = 113)	Septic shock group (n = 24)	Non-septic shock group (n = 89)	P-value
Age, years	49.6 ± 14.9	49.5 ± 16.5	49.6 ± 14.5	0.975
Male, n (%)	101 (89.4)	21 (87.5)	80 (89.9)	0.716
BMI, kg/m ²	24.7 ± 4.0	24.5 ± 3.3	24.7 ± 4.2	0.834
Co-morbidities, n (%)				
Pulmonary disease	1 (0.9)	0 (0)	1 (1.1)	0.619
Hypertension	25 (22.1)	5 (20.8)	20 (22.5)	0.868
Diabetes mellitus	63 (55.8)	12 (50.0)	51 (57.3)	0.527
Heart disease	5 (4.4)	2 (8.3)	3 (3.4)	0.301
Acute renal injury	6 (5.3)	2 (8.3)	4 (4.5)	0.464
Neurological disorder	3 (2.7)	0 (0)	3 (3.4)	0.371
Liver disease	9 (8.0)	1 (4.2)	8 (9.0)	0.445
Hyperlipidemia	2 (1.8)	1 (4.2)	1 (1.1)	0.325
Immunosuppression	4 (3.5)	1 (4.2)	3 (3.4)	0.861
Malignancy	8 (7.1)	3 (12.5)	5 (5.6)	0.249
Smoking and/or alcoholism, n (%)	11 (9.7)	1 (4.2)	10 (11.2)	0.305
Vital signs				
T, °C	37.1 ± 0.9	37.7 ± 1.2	36.9 ± 0.7	0.001
P, bpm	93.5 ± 18.0	99.5 ± 22.7	91.8 ± 16.3	0.063
RR, bpm	20.1 ± 3.5	20.7 ± 5.9	19.9 ± 2.5	0.551
SBP, mmHg	123.9 ± 18.5	117.5 ± 24.9	125.7 ± 16.1	0.056
DBP, mmHg	75.2 ± 11.5	70.1 ± 14.5	76.6 ± 10.2	0.050
MAP, mmHg	91.5 ± 12.7	85.9 ± 16.9	92.9 ± 11.0	0.064
Laboratory examinations				
WBC count, × 10 ⁹ /L	14.7 ± 6.8	14.0 ± 6.9	14.9 ± 6.8	0.582
Neutrophil percentage	0.80 ± 0.09	0.82 ± 0.08	0.79 ± 0.09	0.153
PLT, × 10 ⁹ /L	263.8 ± 140.2	179.8 ± 103.8	286.4 ± 140.5	0.001
Hb, g/L	117.3 ± 24.9	110.1 ± 29.0	119.3 ± 23.5	0.109
HCT	0.34 ± 0.06	0.32 ± 0.07	0.35 ± 0.06	0.024
Na ⁺ , mmol/L	136.6 ± 5.6	138.9 ± 9.4	136.0 ± 4.0	0.056
K ⁺ , mmol/L	3.8 ± 0.5	3.8 ± 0.5	3.9 ± 0.5	0.622
Lymphocyte, × 10 ⁹ /L	1.3 ± 0.7	1.2 ± 0.6	1.4 ± 0.7	0.287
PT, s	14.1 ± 2.5	15.5 ± 3.7	13.7 ± 2.0	0.026
APTT, s	32.0 ± 11.2	32.3 ± 6.6	31.9 ± 12.2	0.505
Glucose, mmol/L	11.3 ± 7.1	9.9 ± 6.0	11.7 ± 7.4	0.305
Cr, μmol/L	91.4 ± 57.4	98.8 ± 49.2	89.4 ± 59.5	0.446
ALB, g/L	29.3 ± 7.3	24.9 ± 7.3	30.4 ± 6.9	0.001
TBIL, μmol/L	23.0 ± 35.4	46.9 ± 67.5	16.5 ± 14.5	0.030
LRINEC score	4.5 ± 2.4	5.5 ± 1.9	4.2 ± 2.5	0.137
CT/MRI pneumatosis, n (%)	64 (56.6)	20 (83.3)	44 (49.4)	0.003

ALB, albumin; APTT, activated partial thromboplastin time; BMI, body mass index; Cr, creatinine; CT/MRI, computed tomography/magnetic resonance images; DBP, diastolic blood pressure; Hb, haemoglobin; HCT, hematocrit; LRINEC, Laboratory Risk Indicator for Necrotizing Fasciitis; MAP, mean arterial pressure; P, pulse; PLT, platelet count; PT, prothrombin time; RR, respiratory rate; SBP, systolic blood pressure; T, temperature; TBIL, total bilirubin; WBC, white blood cells.

selection. The best model selected by backward logistic regression with BIC was the one with the following features:

$$T + \text{PLT} + \text{TBIL} + \text{pneumatosis on CT/MRI} + \text{Na}^+ \times \text{TBIL}$$

Moreover, the AUROC of the fitted logistic regression model was 0.84 (95% CI, 0.78–0.95). The ROC curves for the selected variables and the logistic regression model are plotted in Figure 4. We also performed an in-sample validation via the leave-one-out cross-validation procedure for the logistic regression model with a probability of 0.5 as the cut-off point. Specifically, by selecting a sample from the 113 observations, we fitted a logistic regression model with the proposed factors using the rest of the samples and used the fitted model to classify the selected

sample. This was repeated for all the samples, and the resulting classification accuracy was 82.3%, indicating that the proposed model had promising performance. Based on the risk factors included in the logistic regression model, we further compared the numbers and proportions of patients in the two groups who had the following complications: fever ($T > 37.3^\circ\text{C}$), thrombocytopenia ($\text{PLT} < 100 \times 10^9/\text{L}$), hypernatremia ($\text{Na}^+ > 145 \text{ mmol/L}$), hyponatremia ($\text{Na}^+ < 135 \text{ mmol/L}$), and hyperbilirubinemia ($\text{TBIL} > 21 \mu\text{mol/L}$). A higher proportion of patients in the septic shock group developed fever, thrombocytopenia, hyperbilirubinemia, and hypernatremia. However, nearly half (49.4%) of the patients in the non-septic shock group had hyponatremia, whereas the proportion in the septic shock group was only 29.2% (Table 3).

Table 2. Clinical interventions and findings

Variable	Total (n = 113)	Septic shock group (n = 24)	Non-septic shock group (n = 89)	P-value
Admission time, n (%)				
Weekdays	69 (61.1)	14 (58.3)	55 (61.8)	0.757
Weeknights	21 (18.6)	3 (12.5)	18 (20.2)	0.570
Weekend days	16 (14.1)	6 (25.0)	10 (11.2)	0.166
Weekend nights	7 (6.2)	1 (4.2)	6 (6.7)	1.000
Surgery				
Number of receiving surgical service, n (%)	108 (95.6)	21 (87.5)	87 (97.8)	0.108
Number of surgical debridement	1.1 ± 0.5	1.1 ± 0.8	1.2 ± 0.4	0.534
Colostomy, n (%)	22 (19.5)	9 (37.5)	13 (14.6)	0.013
Vacuum-assisted closure, n (%)	6 (5.3)	1 (4.2)	5 (5.6)	0.786
Antibiotics				
Time from admission to antibiotics infusion, hours	2.4 ± 2.0	2.5 ± 2.5	2.4 ± 1.8	0.830
Types of antibiotics initially used, n (%)				
Second-generation cephalosporins	19 (16.8)	3 (12.5)	16 (18.0)	0.817
Third-generation cephalosporins	27 (23.9)	4 (16.7)	23 (25.8)	0.506
Third-generation cephalosporin plus enzyme inhibitor	42 (37.2)	9 (37.5)	33 (37.1)	0.970
Penicillin plus enzyme inhibitors	14 (12.3)	4 (16.7)	10 (11.2)	0.713
Carbapenem antibiotics	11 (9.7)	4 (16.7)	7 (7.9)	0.367
Antibiotic-days during hospital stay, days	11.5 ± 7.6	13.6 ± 9.2	10.9 ± 7.0	0.180
The use of CRRT, n (%)	6 (5.3)	5 (20.8)	1 (1.1)	0.001
Clinical findings				
Time from symptoms onset to admission, days	13.5 ± 18.1	9.3 ± 7.5	14.7 ± 19.8	0.193
Time from admission to surgery, hours	24.4 ± 35.4	21.4 ± 38.9	39.1 ± 62.0	0.225
ICU stay, days	1.8 ± 4.1	5.7 ± 7.0	0.8 ± 1.9	< 0.001
Hospital length of stay, days	22.8 ± 16.0	22.7 ± 12.3	22.8 ± 16.9	0.294
In-hospital mortality, n (%)	7 (6.2)	6 (25.0)	1 (1.1)	< 0.001

CRRT, continuous renal replacement therapy; ICU, intensive care unit.

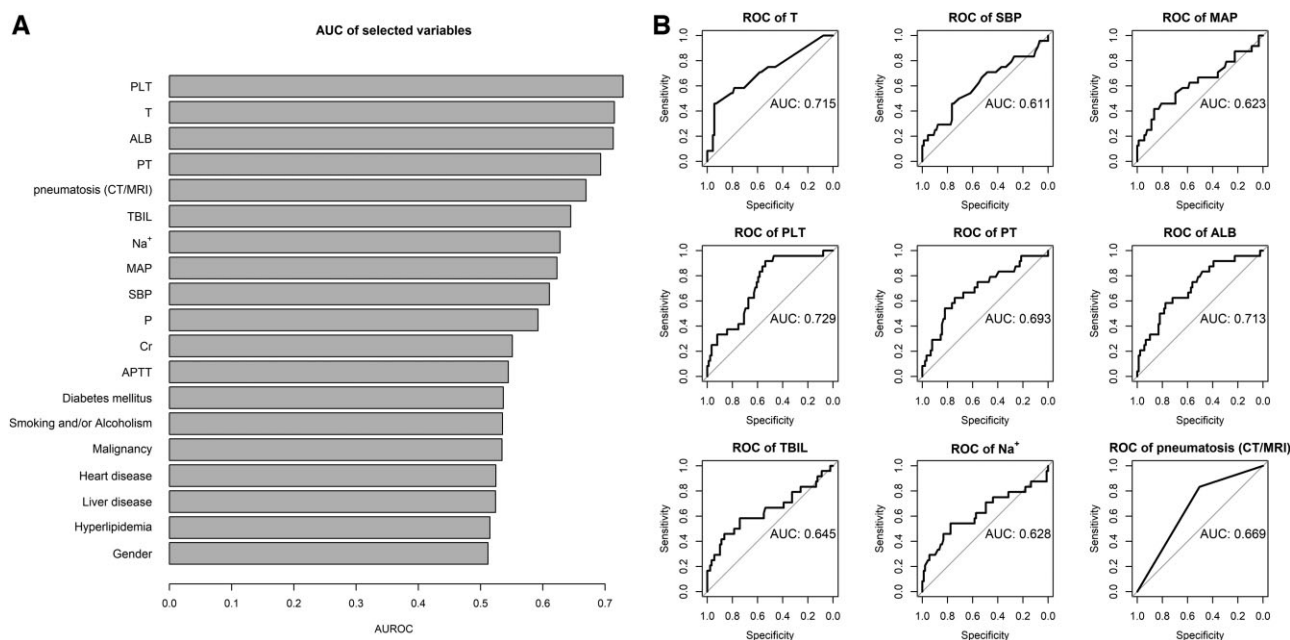


Figure 2. The AUROCs for selected factors and the ROCs for factors with an AUROC of >0.6. (A) The AUROCs for selected factors. (B) ROCs for selected factors with an AUROC of >0.6. ALB, albumin; APTT, activated partial thromboplastin time; AUROC, area under the receiver-operating characteristic curve; Cr, creatinine; CT/MRI, computed tomography/magnetic resonance images; MAP, mean arterial pressure; P, pulse; PLT, platelet count; PT, prothrombin time; ROC, receiver-operating characteristic curve; SBP, systolic blood pressure; T, temperature; TBIL, total bilirubin.

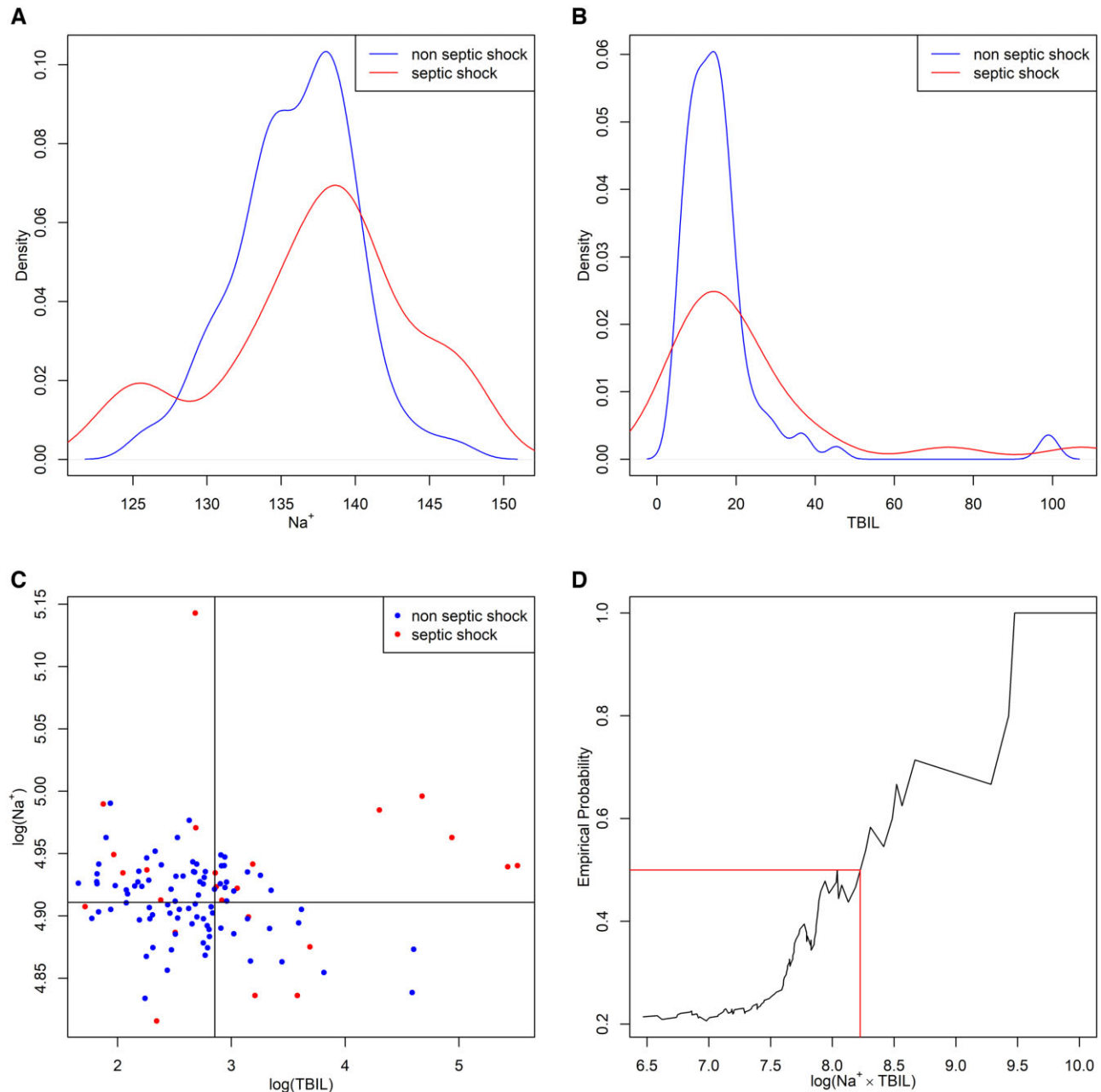


Figure 3. Sodium and total bilirubin (TBIL) distribution curves and the empirical probability of septic shock. (A) and (B) Marginal distribution of sodium and TBIL. (C) Joint distribution of TBIL and sodium. (D) Empirical probability of sepsis vs log (sodium \times TBIL).

A nomogram containing five predictors (T, PLT, TBIL, pneumatosis on CT/MRI, $\text{Na}^+ \times \text{TBIL}$) was developed by our logistic regression model (Figure 5). Note that TBIL not only appears in the logistic regression model as a linear effect but is also one of the main components for the interaction effect $\text{Na}^+ \times \text{TBIL}$. To reduce the confounding in the nomogram, we combined the two predictors (TBIL and $\text{Na}^+ \times \text{TBIL}$) and defined a new predictor:

$$\text{Na.TBIL} = (\text{Na}^+ - 135.74) \times \text{TBIL}$$

where -135.74 represents the ratio of the coefficients of TBIL and $\text{Na}^+ \times \text{TBIL}$ in the fitted logistic regression model (Table 4). Interestingly, the value of 135.74 is very close to the lower

reference range of blood Na^+ (135 mmol/L). A calibration curve of the nomogram is presented in Figure 6, which shows that the probability of septic shock in patients with FG predicted by the nomogram agreed well with the actual probability. The predictive accuracy of the nomogram quantified using Harrell's concordance index via 1,000 bootstrap resamples was 0.864 (95% CI, $0.78\text{--}0.95$).

Discussion

Our logistic regression model identified four factors (i.e. T, PLT, TBIL, and pneumatosis on CT/MRI) with linear effects and one interaction factor (i.e. the product of Na^+ and TBIL) that could be used to assess the risk of septic shock in patients with FG.

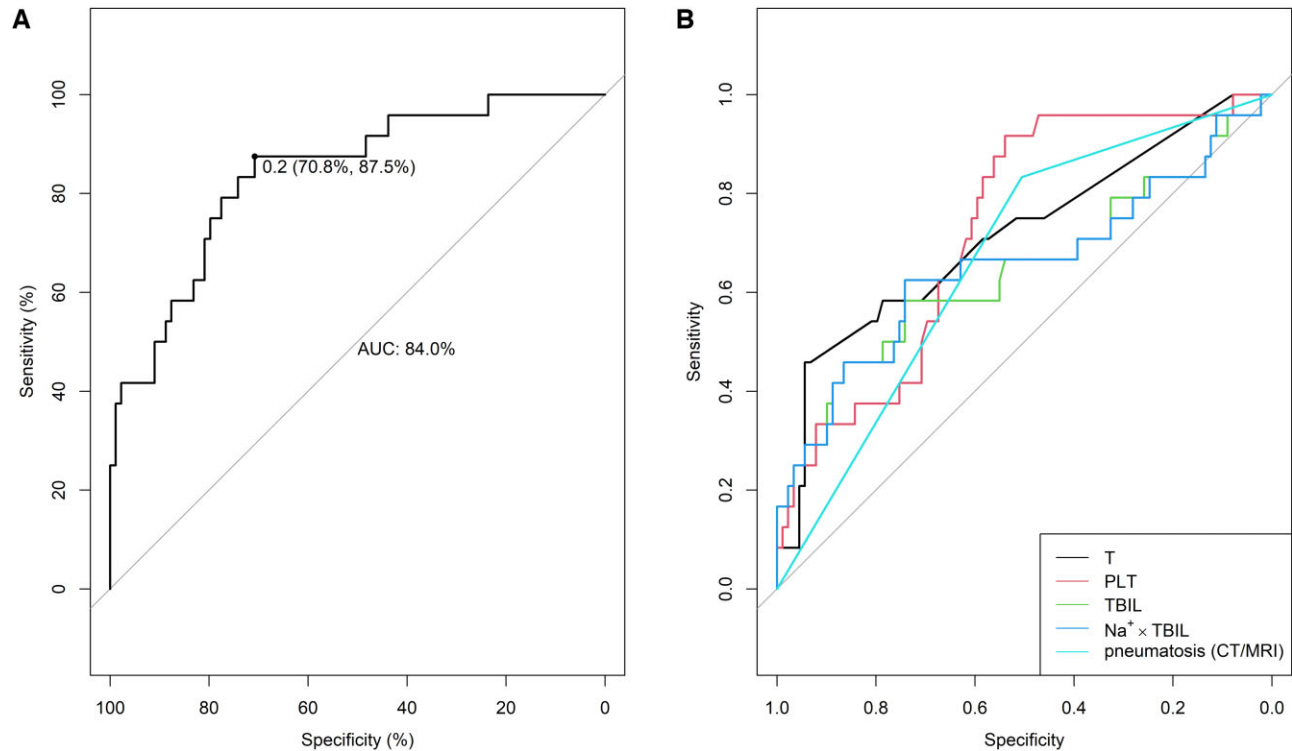


Figure 4. ROC for the fitted logistic regression model. (A) ROC of the fitted logistic regression model. (B) ROCs of selected variables. AUC, area under the receiver-operating characteristic curve; CT/MRI, computed tomography/magnetic resonance image; PLT, platelet count; ROC, receiver-operating characteristic curve; T, temperature; TBIL, total bilirubin.

Table 3. Numbers and proportions of patients who developed complications

Complication	Non-septic shock group (n = 89)	Septic shock group (n = 24)	P-value ^a
Fever	18 (20.2%)	13 (54.2%)	0.002
Thrombocytopenia	6 (6.7%)	6 (25.0%)	0.028
Hyperbilirubinemia	12 (13.5%)	11 (45.8%)	0.001
Hyponatremia	44 (49.4%)	7 (29.2%)	0.077
Hypernatremia	1 (1.1%)	4 (16.7%)	0.006
Hypernatremia and hyperbilirubinemia	0 (0%)	2 (8.3%)	0.044

^aP-value of chi-square test.

We also constructed a practical nomogram for prediction of the risk of septic shock in patients with FG that incorporated readily available clinical data. This nomogram had good optimal discrimination and internal validity (Figures 5 and 6).

Our FG-associated in-hospital mortality rate was 6.2%, which is far lower than those reported in most studies [4, 6] and may reflect early radical debridement and prompt aggressive treatment [16]. However, the mortality rate in our septic shock group was high at 25%. Our patients with FG who developed septic shock had a higher rate of organ dysfunction, including a lower PLT, longer PT, and a higher TBIL than patients without septic shock (Table 1). Moreover, patients with FG who developed septic shock had a longer ICU stay and a higher in-hospital mortality rate (Table 2). Therefore, it is essential for surgeons, especially intensivists, to be able to identify the specific characteristics of patients with FG who develop septic shock and

establish better management protocols to reduce complications and mortality.

Most of the previous studies have investigated risk factors for FG or predictors of mortality in patients with FG. However, we focused on identifying the risk factors for septic shock in patients with FG. The risk factors identified in our model have several implications.

Fever in this study was found to be an important risk factor for septic shock in patients with FG. In previous studies, fever in patients with FG was related to the progression of septic shock [17, 18]. In our study, fever was identified in a greater proportion of patients in the septic shock group (54.2% vs 20.2%). Temperature not only serves as an important component of the Fournier's Gangrene Severity Index score but also as a marker of disease severity in patients with FG [19]. Therefore, we should be more vigilant when treating patients with FG who develop a high temperature in view of their higher risk of developing septic shock.

We also found that a marked decrease in PLT was an independent risk factor for septic shock in patient with FG. This finding is consistent with other reports describing an association between a decline in PLT and occurrence of severe sepsis [20, 21]. A retrospective propensity-matched cohort study by Menard et al. [22] found a decline in PLT in 45% of patients with septic shock. A study by Demir et al. [23] in patients with FG suggested that PLT was negatively associated with the mortality rate. Multiple mechanisms contribute to a low PLT in patients with septic shock and are mediated mainly by an increase in consumption or destruction of platelets [21]. This should be a reminder to clinicians that a decreased PLT in patients with FG may indicate a higher risk of septic shock.

We also confirmed that the presence of pneumatosis on pelvic CT/MRI could be used as a predictor of septic shock in

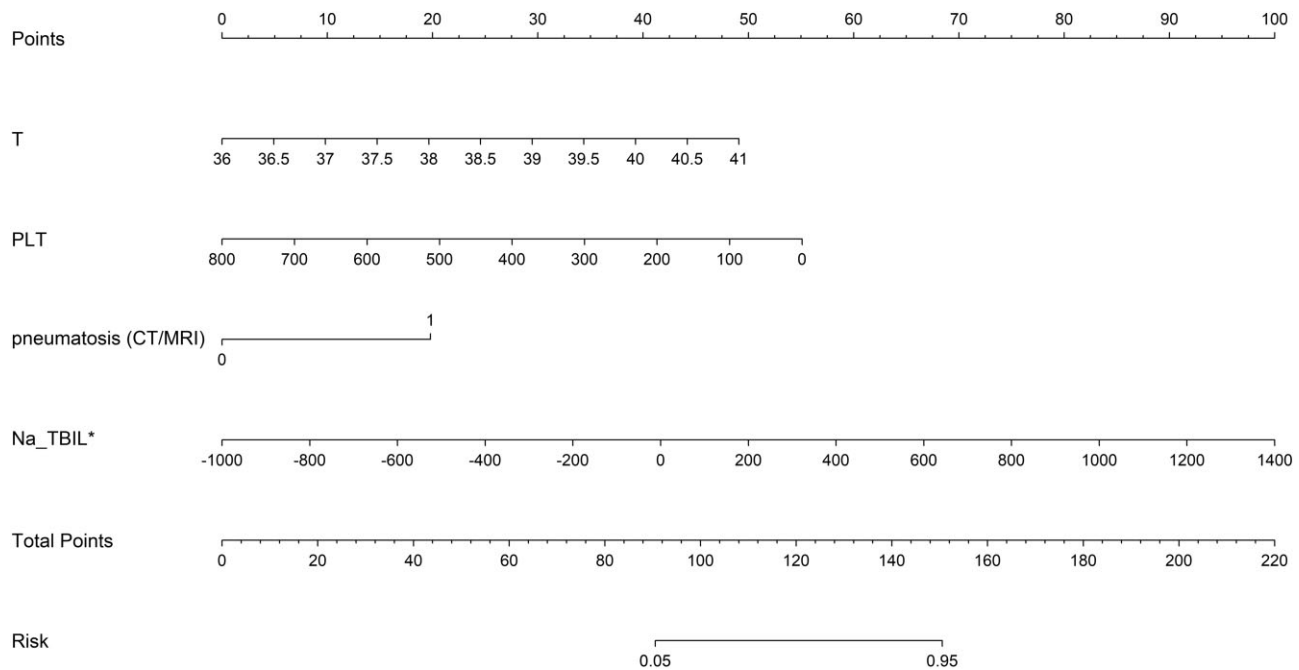


Figure 5. Nomogram established for predicting Fournier's gangrene with septic shock. CT/MRI, computed tomography/magnetic resonance image; PLT, platelet count; T, temperature; TBIL, total bilirubin; $\text{Na_TBIL}^* = (\text{Na}^+ - 135.74) \times \text{TBIL}$.

Table 4. Coefficients for the selected logistic regression model

Variable	Estimate	Standard error	z-value	Pr(> z)
(Intercept)	-37.04	13.06	-2.84	0.005
Temperature	0.96	0.35	2.75	0.006
Platelet count	-0.01	0.00	-2.24	0.025
Total bilirubin	-0.56	0.30	-1.84	0.066
CT/MRI pneumatosis	1.94	0.74	2.63	0.009
$\text{Na}^+ \times \text{TBIL}$	0.00	0.00	1.87	0.062

CT/MRI, computed tomography/magnetic resonance imaging; Na^+ , sodium; TBIL, total bilirubin. $\text{Na}^+ \times \text{TBIL}$, product of the total bilirubin value and the sodium value. Bayesian information criterion: 88.52.

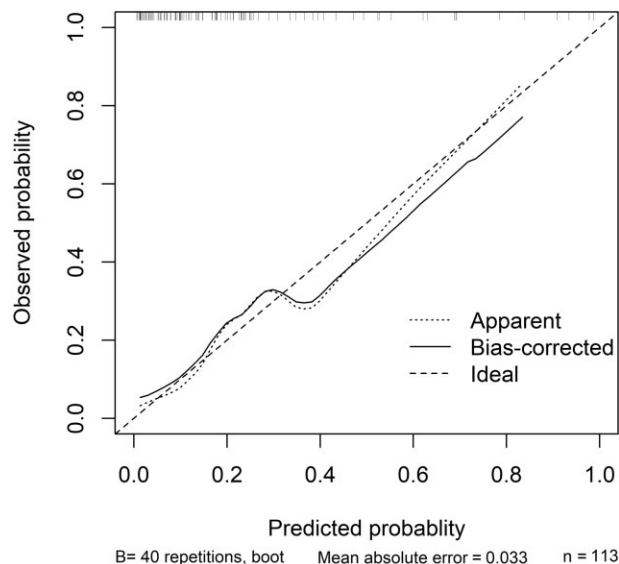


Figure 6. Calibration curve for our internal validation nomogram model

patients with FG. Fernando et al. [24] found that CT and MRI had strong accuracy in the diagnosis of NF, with a sensitivity of 88.5% and a specificity of 93.3%. Some researchers have pointed out that the appearance of gas on CT/MRI is a late phenomenon in NF [25]. It should be noted that pneumatosis is often absent in the earlier stages of the disease and manifests as the patient's condition deteriorates [10]. This may explain why the presence of pneumatosis on pelvic CT/MRI could be a predictor for occurrence of septic shock in patients with FG.

We found that elevated bilirubin was also suggestive of development of septic shock in patients with FG. Ertl et al. [26] reported that elevated bilirubin was a significant risk factor for a poor prognosis in patients with NF. Elevated bilirubin levels are typically encountered in patients with sepsis and are caused by hypoxemia/liver hypoperfusion, which may impair the steps in bile synthesis [27, 28].

In our study, the blood sodium level was 136.6 ± 5.6 mmol/L in patients with FG, which is very close to the lower reference range (135 mmol/L). Previous studies have reported that hyponatremia is a useful parameter for distinguishing NF from non-NF infection and that hyponatremia is more common in NF infection than in non-NF infection [29, 30]. However, in the present study, hyponatremia was found in 49.4% of patients with FG in the non-septic shock group but in only 29.2% of those in the septic shock group. We also observed that hypernatremia was significantly more common in our septic shock group (16.7% vs 1.1%, $P = 0.006$). A possible explanation for this finding is that fever and impaired renal function are more common in patients with septic shock [31]. In addition to the above linear effects, the product of $\text{Na}^+ \times \text{TBIL}$ was selected as an indicator for occurrence of septic shock in patients with FG. Such an interaction effect suggests that simultaneous occurrence of hypernatremia and hyperbilirubinemia is also a critical risk factor for developing septic shock; this finding has not been reported previously. We observed that none of the patients in our non-septic shock group developed both complications

simultaneously, while 8.3% of those in the septic shock group experienced both complications at the same time ($P=0.044$). Simultaneous occurrence of hypernatremia and hyperbilirubinemia might be caused by hypoxemia and hypoperfusion in these patients.

Our focus in this study was to establish a logistic regression model and develop a nomogram to predict occurrence of septic shock in patients with FG. The nomogram developed in this study had good internal validation and performed well in terms of discrimination and calibration. On the one hand, the nomogram could be used to assist clinicians in identifying critically ill patients as soon as possible and establish better management protocols, including prompt debridement, early use of advanced antibiotics, and close monitoring of vital signs, so as to prevent these patients from reaching a crisis state. On the other hand, patients at higher risk of developing septic shock (previously defined as severe sepsis) are usually treated more aggressively in clinical practice than other patients with sepsis. For example, according to the Surviving Sepsis Campaign guideline, broad-spectrum antibiotics should be used within 1 hour after diagnosis in patients with FG who develop septic shock but can be used within 3 hours of diagnosis in those without sepsis. The risk of developing septic shock when calculated by our method could be used further to help clinicians make a better decision on whether targeted therapy should be used earlier.

This study has some limitations. First, the nomogram developed for the purposes of this study was based on a small sample of patients from a single centre. Therefore, it is possible that some factors with relatively weak effects on the risk of developing septic shock were not identified owing to a relatively small signal-to-noise ratio. Second, although the nomogram model was found to have good performance in discrimination and calibration in internal validation, the predicting nomogram model still lacks external validation in other populations. Therefore, further research is needed to verify the accuracy and efficacy of our nomogram.

In conclusion, we have developed a prediction model to evaluate the risk of development of septic shock in patients with FG. The findings of this study could potentially provide new insights into the development of septic shock in patients with FG, assist clinicians in identifying critically ill patients, and help to establish better management protocols to reduce complications and mortality in these patients if they develop septic shock.

Authors' Contributions

Y.Y. collected the data and L.C.W. takes responsibility for its integrity. Y. Y. and L.C.W. contributed substantially to the study design and writing of the article. X.Y.Y., Z.Q.Y., and Y.Z.Z. contributed to the data analysis and drawing of the diagrams. X.F.Z. contributed to data interpretation. B.Y.J. and L.C. contributed substantially to the study design and revisions to the manuscript. All authors read and approved the final manuscript.

Funding

This work did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

None.

Conflict of Interest

The authors have declared no conflicts of interest for this article.

References

1. Corman ML. Classic articles in colonic and rectal surgery: Jean-Alfred Fournier. *Sem Med* 1888;3:984–8.
2. Hagedorn JC, Wessells H. A contemporary update on Fournier's gangrene. *Nat Rev Urol* 2017;14:205–14.
3. Singh A, Ahmed K, Aydin A et al. Archivio italiano di urologia e andrologia Arch ital urol androl = Archives of Italian urology and andrology. *Arch Italiano Urol Androl* 2016;88:157–64.
4. Radcliffe RS, Khan MA. Mortality associated with Fournier's gangrene remains unchanged over 25 years. *BJU Int* 2020;125:610–6.
5. Shyam DC, Rapsang AG. Fournier's gangrene. *Surgeon* 2013;11:222–32.
6. Benjelloun EB, Souiki T, Yakla N et al. Fournier's gangrene: our experience with 50 patients and analysis of factors affecting mortality. *World J Emerg Surg* 2013;8:1.
7. El-Qushayri AE, Khalaf KM, Dahy A et al. Fournier's gangrene mortality: a 17-year systematic review and meta-analysis. *Int J Infect Dis* 2020;92:218–25.
8. Yanar H, Taviloglu K, Ertekin C et al. Fournier's gangrene: risk factors and strategies for management. *World J Surg* 2006;30:1750–4.
9. Kabay S, Yucel M, Yaylak F et al. The clinical features of Fournier's gangrene and the predictivity of the Fournier's Gangrene Severity Index on the outcomes. *Int Urol Nephrol* 2008;40:997–1004.
10. Sartelli M, Guirao X, Hardcastle TC et al. 2018 WSES/SIS-E consensus conference: recommendations for the management of skin and soft-tissue infections. *World J Emerg Surg* 2018;13:1–24.
11. Lu G, Liu H, Li D et al. Fournier gangrene caused by *Escherichia coli* complicated with septic shock and sepsis-associated encephalopathy in an 8-month-old girl: a case report. *Minerva Med* 2020.
12. Vyas HG, Kumar A, Bhandari V et al. Prospective evaluation of risk factors for mortality in patients of Fournier's gangrene: a single center experience. *Indian J Urol* 2013;29:161–5.
13. Lukász P, Ecsedy G, Lovay Z et al. Our experience in Fournier's gangrene with severe septic shock. *Magyar Sebészet* 2014;67:113–22.
14. Singer M, Deutschman CS, Seymour C et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA—J Am Med Assoc*. 2016;315:801–10.
15. Jiang B, Wang X, Leng C. A direct approach for sparse quadratic discriminant analysis. *J Mach Learn Res* 2018;19:1–37.
16. Lin HC, Chen ZQ, Chen HX et al. Outcomes in patients with Fournier's gangrene originating from the anorectal region with a particular focus on those without perineal involvement. *Gastroenterol Rep* 2019;7:212–7.
17. Goh T, Goh LG, Ang CH, Wong CH. Early diagnosis of necrotizing fasciitis. *Br J Surg* 2014;101:119–25.
18. Yeh DD, Velmahos G. *Necrotizing Soft Tissue Infections: Geriatric Trauma and Critical Care*, 2nd edn. Springer Nature, Switzerland AG 2017;187–200.
19. Laor E, Palmer LS, Tolia BM et al. Outcome prediction in patients with Fournier's gangrene. *J Urol* 1995;154:89–92.
20. Iba T, Levy JH, Warkentin TE et al. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. *J Thromb Haemost* 2019;17:1989–94.

21. Iba T, Di Nisio M, Thachil J et al. A proposal of the modification of Japanese Society on Thrombosis and Hemostasis (JSTH) Disseminated Intravascular Coagulation (DIC) diagnostic criteria for sepsis-associated DIC. *Clin Appl Thromb/Hemost* 2018; **24**:439–45.
22. Menard CE, Kumar A, Houston DS et al. Evolution and impact of thrombocytopenia in septic shock: a retrospective cohort study. *Crit Care Med* 2019; **47**:558–65.
23. Demir CY, Yuzkat N, Ozsular Y et al. Fournier gangrene: association of mortality with the complete blood count parameters. *Plast Reconstruct Surg* 2018; **142**:68E–75E.
24. Fernando SM, Tran A, Cheng W et al. Necrotizing soft tissue infection: diagnostic accuracy of physical examination, imaging, and LRINEC score: a systematic review and meta-analysis. *Ann Surg* 2019; **269**:58–65.
25. Kwee RM, Kwee TC. Diagnostic performance of MRI and CT in diagnosing necrotizing soft tissue infection: a systematic review. *Skelet Radiol* 2022; **51**:727–36.
26. Ertl CW, Carpp NC, Johnson J et al. Evaluation of factors associated with death in patients with necrotizing fasciitis of the abdominal wall. *Surg Infect*. 2017; **18**:176–80.
27. Fuchs M, Sanyal AJ. Sepsis and cholestasis. *Clin Liver Dis* 2008; **12**:151–72.
28. Woznica EA, Inglot M, Woznica RK et al. Liver dysfunction in sepsis. *Adv Clin Exp Med* 2018; **27**:547–51.
29. Wall DB, Klein SR, Black S et al. A simple model to help distinguish necrotizing fasciitis from nonnecrotizing soft tissue infection. *J Am Coll Surg* 2000; **191**:227–31.
30. Wong CH, Khin LW, Heng KS et al. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. *Crit Care Med* 2004; **32**:1535–41.
31. Ni H-B, Hu X-X, Huang X-F et al. Risk factors and outcomes in patients with hypernatremia and sepsis. *Am J Med Sci* 2016; **351**:601–5.