Clinical characteristics and predictors of burn complicated with smoke inhalation injury: A retrospective analysis

ZHIFANG NIU1,2*, ZILING DING1*, YION CHAN3, LI YAN4, WENYU ZHANG4, HONGYU WANG5, JIE SHI1, QI LV1, SHIKE HOU1, XIAOQIN GUO1 and HAOJUN FAN1

1Institute of Disaster and Emergency Medicine, Tianjin University, Tianjin 300072; 2Department of Emergency, Tianjin Medical University General Hospital, Tianjin 300052; 3Institute of Adolescent Safety Emergency Education, Institute of Disaster and Emergency Medicine, Tianjin University, Tianjin 300072; 4Department of Burns and Plastic Surgery, Characteristic Medical Center of Chinese People's Armed Police Force, Tianjin 300163; 5Department of Burns and Plastic Surgery, 983 Hospital of The Joint Logistics Support Force of The Chinese People's Liberation Army, Tianjin 300162, P.R. China

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Correspondence to:
Professor Haojun Fan or Professor Xiaoxin Guo, Institute of Disaster and Emergency Medicine, Tianjin University, 92 Weijin Road, Nan Kai, Tianjin 300072, P.R. China
E-mail: fanhaojun999@126.com
E-mail: guoxiaoqinlet@163.com

*Contributed equally

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Abstract. Fire smoke enters the human lungs through the respiratory tract. The damage to the respiratory tract and lung tissue is known as smoke inhalation injury (SII). Fire smoke can irritate airway epithelium cells, weaken endothelial cell adhesion and lyse alveolar type II epithelia cells, leading to emphysema, decreased lung function, pneumonia and risk of acute lung injury/acute respiratory distress syndrome (ARDS). The purpose of the present study was to analyze the clinical characteristics of patients with SII and the risk factors affecting their prognosis. A total of 103 patients with SII admitted between January 2016 to December 2021 to the Burns Unit of the Characteristic Medical Center of Chinese People's Armed Police Force and 983 Hospital of the Joint Logistics Support Force of the Chinese People's Liberation Army were selected for the present study. The demographics and clinical features between different severities of SII were analyzed. Univariate/multivariate logistic regression was used to analyze the potential predictors for severity, ARDS and mortality of patients with SII. Receiver operating characteristic (ROC) curves were used to screen independent risk factors and identify their prediction accuracy. It was concluded that total body surface area (TBSA), III burn area (of total %TBSA), cases of respiratory infections, ARDS morbidity, mortality, acute physiology and chronic health evaluation II, lung injury prediction score, lactic acid, white blood cells (WBC), alanine transaminase, blood urea nitrogen, serum creatinine and uric acid were indicators that were raised with increasing severity of SII. However red blood cells, hemoglobin, platelet count, total protein, albumin, and albumin/globulin were decreased with the increasing severity of SII (P<0.05). WBC >20.91 (10⁹/l) was a reliable indicator for severe SII. Lactic acid >9.60 (mmol/l) demonstrated a high degree of accuracy in predicting ARDS development in patients with SII. Hemoglobin <83.00 (g/l) showed a high degree of accuracy in predicting mortality. In summary, the highlighted assessment parameters could be used to contribute to devising improved treatment plans to preempt worsening conditions (such as shock, ARDS, multiple organ dysfunction syndrome and death).

Introduction

Smoke inhalation injury (SII) is the most common cause of mortality in patients with fire burn injuries (1). Most hospitalized patients with burns usually have accompanying inhalation injury, and the incidence rate of SII is positively correlated with mortality rates (2). Fires produce a large quantity of smoke that contains dust particles, poisonous chemical gases and heat coupled with a near anoxic environment, which can result in inhalation injuries that are difficult to treat and pose risks to the preservation of patient life (3). Burns injury patients may undergo endotracheal intubation and invasive ventilation as the majority of damage is inflicted to the upper respiratory tract tissue, prior to the smoke reaching the tracheal carina (4,5). Supraglottic edema and airway blockage, or lower airway damage and subsequent respiratory failure can result due to chemical injury (6).

The chemical poisons within fire smoke are directly absorbed into the human body through the lung-blood exchange interface, resulting in systemic damage (7). The combined action of particulate matter, toxic gases and exposure to anoxic environments often results in lung injury...
with rapid deterioration, bringing great difficulties to timely treatment (8). The clinical signs of SII include severe airway obstruction and decreased pulmonary gas exchange function, which further limits treatments in patients with SII (7). Therefore, the early detection of high-risk SII sufferers and prevention of injury progression are of significant importance in SII management and healthcare.

According to data gathered in the United States during 2016-2017 (6), the incidence rate of SII is ~10% (9) of burn injury patients, which positively correlates with the increase of burns to total body surface area (TBSA) (10). The highest recorded incidence of SII (14%) was shown in patients with 80-89% TBSA affected by burn injury (11). The accurate definition of SII is frequently challenged. In a number of burn treatment centers, diagnoses rely on evidence consistent with lung injuries, clinical records and investigations associated with flame burns and prolonged smoke exposure (12). At the same time, burns to the neck and face, difficulty in pronunciation/speech, burnt nose hairs, presence of carbon powder on extension of the tongue, a cough producing black phlegm, congestion and edema of the pharynx should also be taken into consideration when diagnosing SII (7,10).

It has been reported that severe SII is an independent risk factor for burn-related death (13). Airway obstruction and severe pneumonia are the main causes of mortality associated with SII (14). Identifying and diagnosing the degree of SII presents an important clinical problem. Bronchoscopy can observe the severity of airway injury in the intensive care management of patients with SII (9). The use of biochemical and pathological markers, and imaging examination can also be used to judge the severity and prognosis of SII (15). The relationship between SII and acute respiratory distress syndrome (ARDS) has not yet been confirmed, but ARDS caused by burns has been demonstrated to increase mortality (16). Studies have shown that there are numerous risk factors for ARDS, including age, shock, acute physiological response in hospital, inappropriate mechanical ventilation (MV) methods, acute physiology and chronic health evaluation (APACHE II) score, lung injury score, serum fibrinogen and positive end-expiratory pressure (17,18). Therefore, although challenging, it is practical for clinicians to identify and diagnose the severity of SII to implement corresponding treatment methods.

The objective of the present study was to investigate the characteristics and risk factors for severe SII, and the relationship with ARDS and mortality in patients with burns complicated by SII. The current study aimed to assist in the formulation of improved treatment modalities to promote patient survival. To achieve this, each indicator was analyzed to observe whether it could serve as a strong predictor to influence the prognosis of SII.

Materials and methods

Participants. The selected patients were affected by flame injury and were from the Department of Burns and Plastic Surgery of Characteristic Medical Center of Chinese People’s Armed Police Force and 983 Hospital of the Joint Logistics Support Force of the Chinese People’s Liberation Army (Tianjin, China). Patients’ medical records were collected between the dates of January 2016 and December 2021. Before case collection an appropriate inclusion/exclusion criteria was developed where the exclusion criteria considered underlying diseases that affected the clinical data, including: i) Long-term and heavy smoking; ii) immunosuppressed status (treatment with immune inhibitors, chemotherapy, radiation therapy, high-dose glucocorticoids) or diseases affecting immune function (malignant lymphoma, leukemia, acquired immunodeficiency syndrome, systemic lupus erythematosus, multiplie myeloma); iii) hematologic disorders (anemia, hemophilia, myelodysplasiasyndromes, primary thrombocytosis, erythroblastosis); iv) coronary heart disease, serious arrhythmia or acute myocardial ischemia; v) single or multiorgan dysfunction (kidney, liver failure, upper gastrointestinal bleeding, stress ulcers, cardiac failure, disseminated intravascular coagulation); vi) pregnancy or nursing; and vii) severe allergy history. The inclusion criteria was the admission diagnosis was burn injury combined with inhalation injury. As shown in Fig. 1, the study collected a total of 141 cases.

Admission diagnosis was burn combined with inhalation injury, and further exclusion criteria were: i) Age <16 years old; ii) automatic discharge; and iii) the cause of injury was not caused by flames (for example hot steam, electric arc, chemical reagents). A total of 38 cases were excluded, and a total of 103 cases were included in the final study. The maximum age was 91 years, the minimum age was 17 years, and the average age was 46.70±14.21 years. The percentage of female patients was 30.1%. General data of SII patients' medical records were recorded, including: Age, sex, weight, time of admission, TBSA afflicted by burn, II burn area (of total %TBSA) and III burn area (of total %TBSA).

The extent of SII was divided into mild, moderate and severe. Determination of the extent of SII included the combination of hospital records, physical manifestations (burnt facial hair, carbon deposits in the oropharynx or sputum and facial burns), blood gas analyses, bronchoscopies and chest radiographies and pulmonary function (13,19): i) Mild, dry throat and pain, mild congestion, edema of pharynx, X-Ray and blood gas analysis without hypoxemia and airway stenosis, the patients were outside of anoxic environments, and the condition could be alleviated; (ii) Moderate, airway obstruction, wheezing, dry rale, throat mucosa, vocal cord mucosa, tracheal mucosa, congestion, edema and X-Ray analysis revealing tracheal stenosis; and iii) severe, extensive edema, hemorrhage, ulceration, necrosis and shedding of trachea and bronchial mucosa, chest imaging examination showing extensive pulmonary patchy shadows, bullae, bilateral pleural effusion, progressive aggravation between days 2-15 and blood gas analysis showing mild hypoxemia.

Oxygenation index: PaO2/FiO2, PaO2 is the partial pressure of arterial blood oxygen and FiO2 is the percentage of inhaled oxygen concentration (20). The normal value is 400-500 mmHg, and an oxygenation index of <300 mmHg indicates pulmonary respiratory dysfunction (16). SII patients with ARDS were defined according to the Berlin Definition: i) The mean of all PaO2/FiO2 were measured for each 24 h period within 1 week by arterial blood gas analysis. If the PaO2/FiO2 values were <300 mmHg, and positive end-expiratory pressure or continuous positive airway pressure were >5 cm H2O; ii) chest imaging, bilateral opaque infiltrates by radiography of chest; and iii) Origins of oedema, respiratory failure excluding
cardiac failure, or fluid hyperload as shown by echocardiography (21).

The present study was approved by the Ethics Committees of Characteristic Medical Center of Chinese People's Armed Police Force and 983 Hospital of the Joint Logistics Support Force of the Chinese People's Liberation Army. Written informed consents were obtained from the patients. This was a retrospective study and this study did not affect the treatment of patients received.

Study design. In the present study, the following independent steps were used for comparative analysis: i) Patients were classified as three categories (mild, moderate and severe) and comparisons of demographics, clinical biochemical indices and prognostic characteristics of the patients with SII were performed to explore the relationship between the severity of SII, burn area, mortality, degree of lung injury, biochemical indices and analysis of risk factors; ii) patients were divided into with or without ARDS groups and the relevant risk factors of ARDS in SII were analyzed; and iii) patients were divided into survival and mortality groups and analysis of related risk factors was performed in relation to SII-induced death.

Clinical and laboratory measurements and recordings. From medical records, patients with SII symptoms, general data, arterial blood gas analyses and blood biochemical parameters and in-hospital outcomes for patients with SII were recorded. Body mass index (BMI) is a commonly used measure of body weight and health and was also collected (22). BMI=weight (kg) divided by height (m) squared. APACHE II and lung injury prediction score (LIPS) were used to assess disease severity upon patients’ admission. APACHE II included three portions: Score of acute physiological temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation index, arterial pH, Na, K, HCO3, blood creatinine, hematocrit, white blood cells (WBC), Glasgow Coma Score (23), age and chronic health. It was employed to objectively assess the patient severity, formulate detection and treatment plans, evaluate the treatment effect and predict the mortality of group and individual patients (24). LIPS was used to identify patients at risk of developing acute lung injury early in the analysis and provided an opportunity to implement secondary prevention strategies. LIPS was composed of 4 formations: i) Predisposing circumstances, including shock, aspiration, septicemia and pneumonia; ii) high risk surgical procedures; iii) high risk of trauma; and iv) risk indicators covering alcohol abuse (BMI >30; hypoalbuminemia; chemotherapy; FiO2 >35%; respiratory rate >30 bpm; SpO2 <95%; pH <7.35; and diabetes mellitus) (25).

Statistical analysis. SPSS 25 (IBM Corp.) software package was used for data processing and analyses. The measurement data were conformed to normal distribution [age, BMI, total protein, albumin and uric acid (UA)], which were expressed as the mean ± standard deviation. One-way ANOVA and Bonferroni correction was used to determine the significance of each individual test. For measures with non-normal distribution [Admission time (h), TBSA, II burn area (of total %TBSA), III burn area (of total %TBSA), APACHE II, LIPS, pH, PaO2/FiO2, PaO2, PaCO2, lactic acid, WBC, neutrophils, red blood cell (RBC), hemoglobin, platelet, alanine transaminase (ALT), aspartate aminotransferase (AST), albumin/globulin (A/G), blood urea nitrogen (BUN), serum creatinine (SCr)], were expressed as [M(P25, P75)], and the Kruskal-Wallis H Test followed by Dunn’s post hoc was used for comparison between the three groups. Counting data (such as percentage of sex, respiratory infection rate, ARDS rate and mortality rate, the cause of death rate of ARDS, MODS and shock), were expressed as frequency (n) and percentage (%) values, and Fisher and chi-square (χ²) tests were used for comparison among the three groups. Univariate logistic regression with unadjusted odds ratio (OR) and 95% confidence interval (CI) was performed to identify potential parameters for severity, ARDS and mortality of patients with SII. Subsequently, the significant predictors from the univariate logistic regression model were verified by multiple logistic regression, and the independent risk factors were screened (P<0.05). The severity of SII was analyzed by ordered logistic regression. Patients with SII that developed ARDS and mortality was analyzed by binary logistic regression, which was further described in the receiver-operating characteristic (ROC) curve to calculate the area under the curve (AUC) and evaluate its accuracy in the distinction between severe SII, ARDS and mortality. The criteria for judging the quality of predictive models from AUC was a follows: i) Perfect, AUC=1; ii) good, 0.85<AUC<1; iii) fair, 0.7<AUC≤0.85; iv) low, 0.5<AUC≤0.7; and v) no predictive value ≤0.5. The cut-off point was determined as the maximum value of Youden index (=sensitivity + specificity -1), and the sensitivity and specificity were calculated respectively. P<0.05 was considered to indicate a statistically significant difference.

Results

General epidemiological data. From January 2016 to December 2021, a total of 141 patients were admitted with flame injury and were diagnosed with burn combined with SII.
| Characteristics                          | Total (n=103) | Mild (n=26) | Moderate (n=41) | Severe (n=36) | Test value | P-value |
|-----------------------------------------|--------------|------------|----------------|---------------|------------|---------|
| Demographics                            |              |            |                |               | F=1.258    | 0.289   |
| Age (years, $\bar{x} \pm sd$)           | 46.70±14.21  | 45.08±14.65| 45.07±13.89    | 49.72±14.16   |            |         |
| Female sex, n (%)                       | 31 (30.1%)   | 10 (38.5%) | 9 (22.0%)      | 12 (33.3%)    |            |         |
| BMI ($\bar{x} \pm sd$)                  | 22.40±2.39   | 22.23±2.42 | 22.81±2.50     | 22.07±2.22    |            |         |
| Admission time [h, M (P25‑P75)]         | 3.00 (2.00‑4.00) | 3.00 (2.00‑4.00) | 2.00 (1.00‑4.00) | 3.00 (2.00‑4.00) |            |         |
| Burn area                               |              |            |                |               |            |         |
| Total body surface area [%TBSA, M (P25‑P75)] | 50.00 (29.00‑70.00) | 26.00 (14.50‑46.00) | 55.00 (30.00‑60.00) | 70.00 (46.50‑85.00) | $X^2=24.184$ | 6.00x10^-6 |
| II burn area [%TBSA, M (P25‑P75)]       | 15.00 (8.00‑25.00) | 10.50 (5.00‑25.00) | 15.00 (10.00‑25.00) | 17.00 (8.50‑24.50) | $X^2=0.797$ | 0.671   |
| III burns area [%TBSA, M (P25‑P75)]     | 30.00 (10.00‑50.00) | 10.50 (4.75‑22.75) | 30.00 (11.00‑47.50) | 42.50 (30.00‑70.00) | $X^2=23.150$ | 9.00x10^-6 |
| Disease severity                        |              |            |                |               |            |         |
| Respiratory tract infection, n (%)      | 41 (39.81%)  | 5 (19.23%) | 15 (36.59%)    | 21 (58.33%)   |            |         |
| ARDS, n (%)                             | 20 (19.41%)  | 3 (11.53%) | 5 (12.19%)     | 12 (33.33%)   |            |         |
| APACHE II, M (P25‑P75)                  | 6.00 (3.00‑11.00) | 4.00 (2.00‑6.50) | 6.00 (2.00‑9.00) | 10.5 (3.25‑14.00) | $X^2=18.384$ | 4.00x10^-6 |
| LIPS, M (P25‑P75)                       | 6.50 (5.50‑7.50) | 5.25 (4.00‑6.00) | 7.00 (5.50‑7.50) | 7.50 (6.00‑8.75) | $X^2=23.559$ | 8.00x10^-6 |
| Mortality, n (%)                        | 15 (14.6%)   | 1 (3.8%)   | 3 (7.3%)       | 11 (30.6%)    |            |         |
| Cause of death                          |              |            |                |               |            |         |
| ARDS, n (%)                             | 6 (5.82%)    | -          | 1 (2.43%)      | 5 (13.89%)    |            |         |
| MODS, n (%)                             | 7 (6.80%)    | -          | 2 (4.88%)      | 5 (13.89%)    |            |         |
| Shock, n (%)                            | 2 (1.94%)    | 1 (3.84%)  | -              | 1 (2.77%)     |            |         |
| Laboratory analysis                     |              |            |                |               |            |         |
| Arterial blood gas                      |              |            |                |               |            |         |
| pH, M (P25‑P75)                         | 7.38 (7.34‑7.42) | 7.39 (7.32‑7.43) | 7.36 (7.33‑7.41) | 7.39 (7.35‑7.42) | $X^2=3.927$ | 0.140   |
| PaO2/FiO2 [mmHg, M (P25‑P75)]           | 293.94 (235.14‑402.74) | 320.01 (274.12‑413.79) | 300 (247.78‑390.86) | 251.57 (215.04‑332.67) | $X^2=5.147$ | 0.076   |
| PaO2 [mmHg, M (P25‑P75)]                | 110.00 (86.00‑151.00) | 145.50 (95.85‑159.75) | 110.00 (94.80‑140.00) | 90.50 (80.25‑128.25) | $X^2=8.282$ | 0.016   |
| PaCO2 [mmHg, M (P25‑P75)]               | 37.50 (32.20‑41.00) | 36.50 (30.43‑39.18) | 37.40 (32.60‑39.95) | 38.80 (34.35‑42.08) | $X^2=1.894$ | 0.475   |
| Lactic acid [mmol/l, M (P25‑P75)]       | 4.70 (2.70‑8.10) | 4.60 (3.03‑6.20) | 3.90 (2.20‑5.05) | 8.15 (4.38‑10.35) | $X^2=18.069$ | 1.20x10^-4 |
| Blood cell analysis                     |              |            |                |               |            |         |
| WBC [10^9/l, M (P25‑P75)]               | 18.70 (13.65‑27.25) | 13.92 (12.19‑18.49) | 16.83 (11.99‑24.02) | 26.06 (20.21‑30.64) | $X^2=22.507$ | 1.30x10^-5 |
| Neutrophils [%, M (P25‑P75)]            | 87.20 (82.60‑90.60) | 86.40 (83.88‑90.58) | 86.20 (81.00‑89.65) | 88.2 (84.40‑91.25) | $X^2=1.777$ | 0.411   |
| RBC [10^12/l, M (P25‑P75)]              | 5.03 (3.52‑5.58) | 5.39 (4.96‑6.71) | 5.03 (4.32‑5.39) | 3.85 (2.23‑5.35) | $X^2=13.059$ | 0.001   |
| Hemoglobin [g/l, M (P25‑P75)]           | 159.00 (5.52‑5.58) | 168.00 (157.75‑177.50) | 160.00 (143.00‑176.00) | 114.50 (79.75‑165.75) | $X^2=13.293$ | 0.001   |
| Platelet [10^12/l, M (P25‑P75)]         | 254.00 (195.00‑335.00) | 301.00 (227.50‑420.25) | 276.00 (206.00‑330.00) | 205.5 (129.00‑281.50) | $X^2=11.059$ | 0.004   |
| Biochemical analysis                    |              |            |                |               |            |         |
| ALT [IU/l, M (P25‑P75)]                 | 36.00 (24.00‑62.00) | 33.00 (19.00‑40.75) | 49.00 (24.50‑54.50) | 53.00 (27.50‑77.50) | $X^2=8.085$ | 0.018   |
| AST [U/l, M (P25‑P75)]                  | 47.00 (30.00‑74.00) | 47.00 (30.00‑66.25) | 59.00 (35.00‑69.00) | 45.00 (28.00‑85.00) | $X^2=0.108$ | 0.947   |
Following the exclusion criteria presented in Fig. 1, a study population of 103 subjects remained, with a maximum age of 91 and minimum age of 17 years. The average age amongst total SII patients was 46.70±14.21. The average age of SII patients with mild, moderate and severe were: 45.08±14.65, 45.07±13.89 and 49.72±14.16, respectively. There were no significant differences in the age of patients with SII with mild to moderate and severe (F=1.258; P=0.289). A proportion of 30.1% were female patients. Female patients showed little difference in mild to moderate and severe SII, with no significance determined (χ²=2.219; P=0.315). The average BMI was 22.40±2.39, and there were no significant differences in BMI between patients with mild, moderate and severe SII (F=1.003; P=0.371). Time of patients with SII from burn to admission was 3.00 h (2.00-4.00 h), there was also no significant difference in the time of previous admission between patients with mild, moderate and severe SII (χ²=2.073; P=0.355). Among these patients, 15 died and the fatality rate was 14.6%. Causes of death included: Multiple organ dysfunction syndrome (MODS) in seven cases, ARDS in six cases and shock in two cases. The TBSA (%) was 50.00 (29.00-70.00), and the Ⅱ burn area (of total TBSA %) was 15.00 (8.00-25.00). The larger the TBSA and Ⅲ burns area the more severe the extent of SII (χ²=24.184, P=6.00x10⁻⁶, χ²=23.150, P=9.00x10⁻⁶). With the SII from mild to severe, the number of patients with respiratory tract infection or that developed ARDS, patient mortalities and the levels of APACHE II, LIPS, lactic acid, WBC, ALT, BUN, SCr and UA were all also significantly increased (P<0.05). Whereas PaO₂/FiO₂, PaO₂, RBC, hemoglobin, platelet count, total protein, albumin and A/G were significantly decreased with the increasing severity of SII (P<0.05) (Table I).

### Predictors and risk factors for severity in patients with SII.

First, the present study revealed that TBSA, Ⅲ burns area (of total TBSA %), respiratory tract infection, APACHE II, LIPS, lactic acid, WBC, ALT, BUN, SCr and UA were associated with severity of SII (P<0.05), as determined by univariate ordered logistic regression analysis. There was no association between female sex, BMI, admission time, Ⅱ burn area (of total TBSA %), pH, PaO₂/FiO₂, PaCO₂, neutrophils, or AST with the severity of SII ranging from mild to severe (P>0.05) (Table II). Multivariate ordered logistic regression was performed for these variables with P<0.05 in the univariate ordered logistic regression analysis. The result (parallelism test P>0.05) revealed that APACHE II (OR=1.105, 95% CI 1.013-1.206, P=0.025), LIPS (OR=1.517, 95% CI 1.191-1.931, P=0.021), lactic acid (OR=1.174, 95% CI 1.052-1.310, P=0.004), WBC (OR=1.120, 95% CI 1.062-1.182, P=5.00x10⁻⁵), SCr (OR=1.018, 95% CI 1.007-1.028, P=0.001) and UA (OR=1.005, 95% CI 1.001-1.008, P=0.012) were independent risk factors for severity of patients with SII (Table II). The higher the level of APACHE II, LIPS, Lactic acid, WBC, SCr and UA, the higher the severity of SII. A clear discrimination of severe SII from moderate and mild SII groups was demonstrated based on the ROC curves, which showed that APACHE II, LIPS, lactic acid, WBC, SCr and UA had sensitivities of 55.6, 38.9, 61.1, 75.0, 72.2 and 58.3%; specificities of 83.6, 91.0, 80.6, 76.1, 71.6 and 76.4%; and AUC: 0.710.
0.704, 0.743, 0.774, 0.765 and 0.680 respectively (Table III) (Fig. 2). The results showed that WBC had the highest AUC (0.774) and sensitivity (75.0%), thus the reliability of WBC at the cutoff point of 20.91 (10^9/l) indicated a strong possibility of severe SII.

**Predictors and risk factors for patients with SII and ARDS development.** The potential factors in relation to patients with SII and ARDS development as calculated by univariate logistic regression were TBSA, Ⅲ burns area (of total TBSA %), respiratory tract infection, APACHE II, LIPS, PaO2/FiO2, PaO2, lactic acid, WBC, RBC, hemoglobin, platelet count, ALT, BUN, and UA (P<0.05). There was no relationship between age, female sex, BMI, admission time, Ⅱ burn area (of total %TBSA), pH, PaCO2, neutrophils, AST, total protein, albumin, A/G and SCr associated with patients with SII development of ARDS (P>0.05) (Table IV). Multivariate logistic regression revealed that APACHE II (OR=1.881, 95% CI 1.040-3.404, P=0.037), LIPS (OR=2.889, 95% CI 1.025-8.139, P=0.045), lactic acid (OR=2.095, 95% CI 1.130-3.882,
P=0.019) and WBC (OR=1.281, 95% CI 1.017‑1.613, P=0.036) were independent risk factors for patients with SII with ARDS development. However, PaO2/FiO2 (OR=0.979, 95% CI 0.966‑0.993, P=0.003) was a protective factor (Table IV). Further ROC curves demonstrated that APACHE II, LIPS, lactic acid, WBC and UA had sensitivities of 100, 87.5, 100, 100 and 100; specificities of 83.3, 85.4, 89.6, 86.5 and 52.1%; and AUC of 0.934, 0.923, 0.938, 0.966 and 0.760, respectively (Table V) (Fig. 3). The most accurate parameters for predicting development of ARDS in patients with SII were APACHE II, LIPS, lactic acid, WBC and UA (AUC>0.85). Lactic acid's highest AUC (0.966) and sensitivity (100%), with the highest reliability of lactic acid having a cut-off point of 9.6 (mmol/l), suggested that lactic acid was a strong predictor that patients with SII had developed ARDS.

Predictors and risk factors for mortality of patients with SII. The univariate logistic regression results showed that TBSA, II TBSA (of total TBSA %), III TBSA (of total TBSA %), severity of SII, respiratory tract infection, APACHE II, LIPS, lactic acid, WBC, PaO2/FiO2, PaO2, RBC, hemoglobin, platelet count, AST, A/G, BUN and SCr were associated with mortality of patients with SII (P<0.05). There was no relationship between female sex, BMI, admission time moderate of SII, ARDS, pH, neutrophils, ALT, total protein, albumin, UA and mortality of SII patients (P>0.05) (Table VI). Further multivariate logistic regression revealed that respiratory tract infection (OR=4.964, 95% CI 1.179‑20.905, P=0.029), lactic acid (OR=1.219, 95% CI 1.044‑1.423, P=0.012), WBC (OR=1.157, 95% CI 1.010‑1.325, P=0.036) and SCr (OR=1.023, 95% CI 1.004‑1.043, P=0.017) were independent risk factors for mortalities of patients with SII, whereas hemoglobin (OR=0.979, 95% CI 0.916‑0.983, P=0.003) and A/G (OR=0.401, 95% CI 0.102‑0.931, P=0.020) were protective factors. ROC curves showed that when lactic acid, WBC, hemoglobin, A/G and SCr had sensitivities of 60.0, 93.3, 100, 80.0 and 100%; specificities of 83.0, 67.0, 90.9, 79.5 and 62.5%; and AUC of 0.741, 0.801, 0.953, 0.854 and 0.852, respectively (Table VII). The results suggested that hemoglobin had the highest reliability (AUC=0.953) at a cutoff point of 83.00 (g/l) for predicting mortality in patients with SII (Fig. 4). A/G and SCr (AUC>0.85) were also reliable predictors for mortality of patients with SII.

Discussion

According to the American Burn Association (ABA), from the total number of patients admitted to 128 burn centers in the United States in 2016, 3,275 fatalities were associated with burns from smoke inhalation; a total of 2,745 deaths were from residential fires, 310 from car accident‑related fires and 220 from other causes (16). Similar to the present retrospective study, among the 103 patients with burn combined with inhalation injury, the main causes of injury were residential-associated (44.8%), with factory accidents (23.0%) and car accidents (16.1%) accounting for less. The majority of the fires occurred indoors, causing an abundance of hot air and pernicious smoke, which is more conducive to SII (26). In the present study, the average age of injured adults were 46.70±14.21 years and female patients accounted for 30.1%. In addition, the total SII patients' average BMI was 22.40±2.39, the average BMI of patients with SII in mild to severe categories were within the normal healthy range. The time interval from burn to admission was 3.00 h (2.00‑4.00 h), there were no significant difference in sex and the time of
admission between mild, moderate and severe SII. After regression statistical analysis, sex, BMI and the time of patient admission were not considered risk factors for patients with severe SII for developing ARDS or risk of mortality. However, statistical results suggested that the severity of SII was positively associated with the TBSA. With increasing SII severity, incidence of respiratory tract infections, ARDS and mortality also significantly increased. Accompanying pathologies of burn injuries include MODS, sepsis, pneumonia and cellulitis. Overall, >60% of deaths from burn injuries were attributed to MODS (27).

Despite extensive investigations, the etiology of MODS remains unclear. All cases seem to show uncontrolled systemic inflammatory response syndrome (SIRS) (28). The causes of post-burn infection include sepsis, bacteremia after wound treatment, small repetitive infection and bacterial translocation in the intestines (28). In the present study’s results on mortality of SII, the more serious the inhalation injury was, the higher

Table IV. Univariate and multivariate logistic regression analysis of risk factors for SII patients with acute respiratory distress syndrome development.

| Parameters                                      | Univariate logistic regression | Multivariate logistic regression |
|-------------------------------------------------|-------------------------------|---------------------------------|
|                                                  | OR (95% CI)                   | P-value                         | OR (95% CI)                   | P-value                         |
| Age, yearsa                                      | 1.033 (0.981-1.087)           | 0.219                           | -                              | -                               |
| Female sex, n (%)a                               | 0.924 (0.169-5.042)           | 0.927                           | -                              | -                               |
| Admission time (h)a                              | 1.292 (0.827-2.020)           | 0.260                           | -                              | -                               |
| BMIb                                            | 0.991 (0.716-1.371)           | 0.955                           | -                              | -                               |
| Burn area                                        |                                |                                 |                                |                                 |
| Total body surface area (%TBSA)y                | 1.036 (1.000-1.073)           | 0.048                           | -                              | -                               |
| II burn area (%TBSA)y                            | 0.999 (0.941-1.061)           | 0.978                           | -                              | -                               |
| III burns area (%TBSA)yx                         | 1.031 (1.001-1.061)           | 0.039                           | -                              | -                               |
| Respiratory tract infection, n (%)yx             | 10.457 (1.209-90.441)         | 0.033                           | -                              | -                               |
| Disease severity                                |                                |                                 |                                |                                 |
| APACHE IIy                                      | 1.799 (1.186-2.728)           | 0.006                           | 1.881 (1.040-3.404)            | 0.037                           |
| LIPSyx                                          | 3.844 (1.682-8.784)           | 0.001                           | 2.889 (1.025-8.139)            | 0.045                           |
| Laboratory analysis                             |                                |                                 |                                |                                 |
| Arterial blood gas                               |                                |                                 |                                |                                 |
| pHy                                             | 0.178 (0.000-489.389)         | 0.088                           | -                              | -                               |
| PaO2/FiO2 (mmHg)yx                              | 0.971 (0.953-0.989)           | 0.002                           | 0.979 (0.966-0.993)            | 0.003                           |
| PaO2 (mmHg)yx                                   | 0.947 (0.909-0.988)           | 0.011                           | -                              | -                               |
| PaCO2 (mmHg)yx                                  | 1.015 (0.975-1.056)           | 0.477                           | -                              | -                               |
| Lactic acid (mmol/l)yx                          | 2.093 (1.301-3.367)           | 0.002                           | 2.095 (1.130-3.882)            | 0.019                           |
| Blood cell analysis                             |                                |                                 |                                |                                 |
| WBC (10⁹/l)yx                                   | 1.115 (1.023-1.215)           | 0.013                           | 1.281 (1.017-1.613)            | 0.036                           |
| Neutrophils (%)a                                | 0.974 (0.928-1.023)           | 0.294                           | -                              | -                               |
| RBC (10⁵/l)yx                                   | 0.413 (0.229-0.746)           | 0.003                           | -                              | -                               |
| Hemoglobin (g/l)yx                              | 0.968 (0.948-0.989)           | 0.003                           | -                              | -                               |
| Platelet (10⁹/l)yx                              | 0.985 (0.974-0.996)           | 0.008                           | -                              | -                               |
| Biochemical analysis                            |                                |                                 |                                |                                 |
| ALT (IU/l)yx                                    | 1.023 (1.005-1.040)           | 0.011                           | -                              | -                               |
| AST (IU/l)yx                                    | 1.003 (0.997-1.009)           | 0.365                           | -                              | -                               |
| Total protein (g/l)y                            | 0.992 (0.929-1.059)           | 0.807                           | -                              | -                               |
| Albumin (g/l)y                                  | 0.953 (0.880-1.031)           | 0.228                           | -                              | -                               |
| A/Gyx                                          | 0.196 (0.027-1.432)           | 0.108                           | -                              | -                               |
| BUN (mmol/l)yx                                  | 1.254 (1.004-1.566)           | 0.046                           | -                              | -                               |
| SCr (µmol/l)yx                                  | 1.012 (1.000-1.025)           | 0.059                           | -                              | -                               |
| UA (mmol/l)yx                                   | 1.010 (1.004-1.015)           | 0.001                           | -                              | -                               |

*aUnivariate logistic regression of binary logistic regression; bMultivariate logistic regression of binary logistic regression. OR, odds ratio; CI, confidence intervals; TBSA, total body surface area; APACHE, acute physiology and chronic health evaluation; LIPS, lung injury prediction score; WBC, white blood cells; RBC, red blood cells; ALT, alanine transaminase; AST, aspartate aminotransferase; A/G, Albumin/Globulin; BUN, blood urea nitrogen; SCr, serum creatinine; UA, uric acid.
the rate of mortality; 15 of the 103 patients died (case fatality rate of 14.56%). MODS, ARDS and shock are still considered the main causes of death in burns patients (29). Patients mortalities within 48 h after SII predominantly result from obstruction and asphyxia (1). Septic shock caused by exacerbated inflammatory reaction, rapid and extensive fluid transfer in burn and non-burn tissues leading to progressive hypovolemic shock forms an important cause of burn shock-related mortality (12). In the current dataset, patients who died within 3-7 days were predominantly afflicted with ARDS, and those who died after 7 days were predominantly afflicted with sepsis or wound sepsis complicated with MODS. The serum marker levels at admission, routine evaluation and associated parameters (laboratory, clinical examination) provided important information such as the grade of SII, tendency to develop into ARDS, mortality and prognosis. Risk stratification for clinicians will be an extremely important consideration (30). The present study demonstrated that APACHE II, LIPS, PaO2/FiO2, lactic acid and WBC were also positively raised with the increasing severity of SII, whereas PaO2/FiO2, PaO2, RBC, hemoglobin, platelet count, total protein, albumin and A/G were decreased with the increasing severity of SII.

The pathophysiology of SII includes direct protein denaturation and a complex systemic inflammatory response accompanied by the flow of protein-rich plasma and cellular contents into the interstitial space, alveoli and bronchial system, leading to the development of pulmonary oedema, increased airway resistance and the subsequent formation of fibrin clots and loss of surface active substances (31,32). Combined, these events further limit the air flow to the alveoli, which increases the probability of respiratory infection (15,33). In the present patient dataset, the number of respiratory infections was directly proportional to the severity of SII, patients SII and ARDS and mortality. APACHE II is a reliable, convenient and commonly utilized scoring system for clinicians to evaluate disease severity in critically ill patients (24). The higher the score, the worse the pathological condition and prognosis (18). As a novel system for predicting lung injury, a higher LIPS score is associated with more serious lung injury (34). In the present study data, the increase of the severity of SII was associated with increases in APACHE II and LIPS, which could be performed as independent risk factors for severity of SII and ARDS development of patients with SII. Comparisons of the AUC of the two groups demonstrated that APACHE II and LIPS had relatively higher AUC (AUC>0.9) in patients with SII and ARDS group. APACHE II >11.5 and LIPS >7.75 indicated the possibility that patients with SII had ARDS.

Fires rapidly consume oxygen, resulting in low oxygen content in the environment (anoxic). Moreover, the extreme heat of the smoke passing through the respiratory tract results in edema and mucosal detachment, which are prone to drive upper respiratory tract obstructions, severe hypoxemia and decreased PaO2/FiO2 in patients with inhalation injury (16). The normal range of PaO2/FiO2 is 400-500 (mmHg) (21). The average PaO2/FiO2 of patients with mild and moderate SII was shown to be between 300-400 (mmHg), but the average PaO2/FiO2 of patients with severe SII was lower than 300 (mmHg), indicating that patients with severe SII were likely to have respiratory disorders. In the present study, PaO2/FiO2 was a protective factor in determining ARDS development of SII patients. With the AUC=0.938, PaO2/FiO2<215.07 (mmHg) was accurate to indicate possibility that patients with SII developed ARDS.

In the stress state of large-area burns, pathophysiological changes such as microcirculation disturbance, tissue ischemia and hypoxia lead to insufficient oxygenated blood perfusion to important organs, and subsequent increases in level of lactic acid (35). It has been demonstrated that base deficit and serum

Table V. Receiver operating characteristic curve analysis of APACHE II, LIPS, PaO2/FiO2, lactic acid and WBC in predicting SII patients with acute respiratory distress syndrome development.

| Parameters          | AUC     | 95% CI          | Cut-off | Sensitivity (%) | Specificity (%) | Youden index (%) | P-value          |
|---------------------|---------|-----------------|---------|-----------------|-----------------|-----------------|------------------|
| APACHE II           | 0.934   | 0.883-0.985     | 11.50   | 100             | 83.3            | 83.3            | 1.34x10⁻⁴       |
| LIPS                | 0.923   | 0.856-0.991     | 7.75    | 0.875           | 85.4            | 71.1            | 1.93x10⁻⁴       |
| PaO2/FiO2           | 0.938   | 0.889-0.986     | 215.07  | 100             | 89.6            | 89.6            | 1.17x10⁻⁴       |
| Lactic acid (mmol/l)| 0.966   | 0.925-1.000     | 9.60    | 100             | 86.5            | 86.5            | 4.10x10⁻⁵       |
| WBC (10⁹/l)         | 0.760   | 0.634-0.885     | 18.50   | 100             | 52.1            | 52.1            | 0.022            |

AUC, area under curve; CI, confidence intervals; APACHE, acute physiology and chronic health evaluation; LIPS, lung injury prediction score; WBC, white blood cells; RBC, red blood cells; SCr, serum creatinine; UA, uric acid.
lactic acid have well-known associations with mortality in burn patients (36). The present study showed that the average value of lactic acid in patients with SII was higher compared with the normal range (0.5-2.2 mmol/l), especially in patients with moderate and severe SII. Lactic acid is an intermediate product of anaerobic metabolism of glucose, which can be excreted through normal metabolic pathways. In the present study, while lactic acid was suggested to be an independent risk factor for determining the severity of SII, patients with ARDS and SII and SII mortality. Compared with other groups,

| Parameters | Univariate logistic regression | Multivariate logistic regression |
|------------|-------------------------------|---------------------------------|
| Age, years* | 1.015 (1.019-1.110) 0.437 | - - |
| Female sex, n (%)* | 0.313 (0.066-1.480) 0.143 | - - |
| BMI* | 0.927 (0.730-1.177) 0.535 | - - |
| Admission time (h) | 1.104 (0.788-1.547) 0.565 | - - |
| Burn area | Total body surface area (%TBSA)* 1.042 (1.015-1.071) 0.002 | - - |
| | II burn area (%TBSA)* 0.935 (0.877-0.997) 0.040 | - - |
| | III burns area (%TBSA)* 1.058 (1.029-1.088) 6.60x10^-5 | - - |
| Degree of lung injury | Moderate of SII, n (%)* 1.974 (0.194-20.059) 0.565 | - - |
| | Severe of SII, n (%)* 11.000 (1.319-91.720) 0.027 | - - |
| Disease severity | Respiratory tract infection, n (%)* 8.138 (2.129-31.109) 0.002 | 4.964 (1.179-20.905) 0.029 |
| | ARDS, n (%)* 2.554 (0.448-14.564) 0.291 | - - |
| | APACHE II* 1.170 (1.040-1.317) 0.009 | - - |
| | LIPS* 1.583 (1.098-2.282) 0.014 | - - |
| Laboratory analysis | Arterial blood gas | | |
| | pH* 0.103 (0.000-234.287) 0.564 | - - |
| | PaO2/FiO2 (mmHg)* 0.994 (0.988-1.000) 0.048 | - - |
| | PaO2 (mmHg)* 0.981 (0.964-0.999) 0.036 | - - |
| | PaCO2 (mmHg)* 0.978 (0.917-1.043) 0.502 | - - |
| | Lactic acid (mmol/l)* 1.243 (1.083-1.427) 0.002 | 1.219 (1.044-1.423) 0.012 |
| Blood cell analysis | WBC (10^9/l)* 1.107 (1.033-1.186) 0.004 | 1.157 (1.010-1.325) 0.036 |
| | Neutrophils (%)* 1.008 (0.956-1.063) 0.765 | - - |
| | RBC (10^12/l)* 0.366 (0.230-0.582) 2.10x10^-5 | - - |
| | Hemoglobin (g/l)* 0.941 (0.914-0.968) 3.20x10^-5 | 0.949 (0.916-0.983) 0.003 |
| | Platelet (10^9/l)* 0.993 (0.988-0.999) 0.024 | - - |
| Biochemical analysis | ALT (IU/l)* 1.011 (0.998-1.023) 0.099 | - - |
| | AST (IU/l)* 1.013 (1.003-1.023) 0.010 | - - |
| | Total protein (g/l)* 0.998 (0.952-1.047) 0.945 | - - |
| | Albumin (g/l)* 0.949 (0.897-1.005) 0.075 | - - |
| | A/G* 0.029 (0.004-0.209) 4.34x10^-4 | 0.401 (0.102-0.931) 0.020 |
| | BUN (mmol/l)* 1.250 (1.053-1.483) 0.011 | - - |
| | SCr (µmol/l)* 1.027 (1.012-1.042) 3.83x10^-4 | 1.023 (1.004-1.043) 0.017 |
| | UA (mmol/l)* 1.003 (1.000-1.007) 0.067 | - - |

*Univariate logistic regression of ordered logistic regression; *Multivariate logistic regression of ordered logistic regression. OR, odds ratio; CI, confidence intervals; TBSA, total body surface area; ARDS, acute respiratory distress syndrome; APACHE, acute physiology and chronic health evaluation; LIPS, lung injury prediction score; ALT, alanine transaminase; AST, aspartate aminotransferase; WBC, white blood cells; RBC, red blood cells; A/G, Albumin/Globulin; BUN, blood urea nitrogen; SCr, serum creatinine; UA, uric acid.
Lactic acid had the highest AUC (0.966) in ARDS group. When lactic acid >9.60 (mmol/l), it indicated the relative possibility that patients with SII developed ARDS. The present data also showed that there were no significant difference in pH measurements between the mild, moderate and severe patient groups. Therefore, after regression statistical analysis confirmed the finding, pH was not considered a risk factor for patients with severe SII for developing ARDS or risk of mortality.

Infections are the most common complications in hospitalized patients with severe burns (37). WBC is an effective predictor for early bloodstream infection in burn patients (38). The average increase of WBC at admission may be due to the initialization of systemic inflammation causing WBC mobilization (39). In the present study, WBC average values in mild, moderate and severe SII were significantly higher compared with normal patients. Yet the normal range of WBC was 4‑10 (10^9/l). The results suggested that SII caused a large leukocyte recruitment response. WBC was raised with the increased severity of SII. Moreover, in the current research, WBC was suggested to form an independent risk factor for determining the severity of SII, ARDS development in patients with SII and SII mortality. Consistent with our previous study that the severity of thermal burn injury is associated with WBC activation, WBC and neutrophil counts were significantly increased on admission day (40). Compared with the other indicators in severity of SII group, the highest AUC and sensitivity were 0.774 and 75.0%, respectively. Thus, WBC had reliable prediction at a cut‑off point of 20.91 (10^9/l) for indicating the possibility of severe SII.

In trauma bleeding after burns, hemolysis of red blood cells in the burn area occurs under the direct influence of heat (41,42). A variety of injury mechanisms cause red blood cell rupture, resulting in a reduction in the amount of red blood cells and a decrease in hemoglobin values (43). Early thrombocytopenia in burns is caused by the destruction of platelets or their accumulation in the skin near the burn scabs (44). The present study showed that RBC, hemoglobin and platelet count decreased with increasing severity of SII. Furthermore, hemoglobin was a protective factor for mortality of patients with SII, and the normal hemoglobin range was 110‑150 (g/l). The ROC curve showed that the AUC and sensitivity of hemoglobin were 0.953 and 100%, respectively. These data indicated that hemoglobin, at a cut‑off of 83.00 (g/l), was a highly reliable predictor for mortality of patients with SII.

Total protein, albumin and A/G also decreased with increasing severity of SII. Due to severe massive burns, plasma proteins can be lost through traumatic massive protein leakage and tissue breakdown, with a decrease in albumin and more loss of albumin than globulin, reversing the A/G ratio (normal A/G range is 1.5‑2.5) (45). The present study revealed A/G as a protective factor for SII mortality and that A/G had great accuracy in predicting mortality (AUC=0.854). Conversely ALT, BUN, SCr and UA were positively raised with increasing severity of SII. Elevated ALT in the early phase of injury can be due to shock or hypovolemia, resulting in ischemia and hypoxia in the liver, and leading to liver damage (46). Reduced effective circulating blood volume due to various causes after burns leads to reduced renal blood flow and decreased glomerular filtration rate, resulting in increased BUN, SCr and UA stasis (47). In the present study, SCr was an independent risk factor for predicting the severity of SII and SII mortality. The ROC curve results showed that SCr had accuracy in predicting mortality (AUC=0.852). UA was also shown to be an independent risk factors for the severity of SII, but the AUC was 0.680, which was relatively low compared with the other indicators within the same group.

In conclusion, SII remains a major cause of morbidity and mortality in burn patients worldwide. The current study concluded that combined serum, blood gas markers and

| Parameters       | AUC     | 95% CI       | Cut-off | Sensitivity (%) | Specificity (%) | Youden index (%) | P-value |
|------------------|---------|--------------|---------|-----------------|-----------------|------------------|---------|
| Lactic acid (mmol/l) | 0.741   | 0.883‑0.985  | 8.70    | 60.0            | 83.0            | 43.0             | 0.003   |
| WBC (10^9/l)     | 0.801   | 0.856‑0.991  | 20.91   | 93.3            | 67.0            | 60.4             | 2.06x10^-4 |
| Hemoglobin (g/l) | 0.953   | 0.889‑0.986  | 83.00   | 100             | 90.9            | 90.9             | 2.20x10^-5 |
| A/G              | 0.854   | 0.925‑1.000  | 0.94    | 80.0            | 79.5            | 59.5             | 1.30x10^-5 |
| SCr (µmol/l)     | 0.852   | 0.634‑0.885  | 95.00   | 100             | 62.5            | 62.5             | 1.40x10^-3 |

AUC, area under the curve; CI, confidence intervals; WBC, white blood cells; A/G, Albumin/Globulin; SCr, serum creatinine.
clinical indicators could predict severity SII, the probability to develop ARDS combined with SII and the mortality of SII. The present findings suggested that APACHE II, LIPS, lactic acid, WBC, UA and SCr were risk factors for severity of SII in patients, and WBC >20.91 (10⁹/l) could be a reliable indicator for severe SII. APACHE II, LIPS, lactic acid and WBC were risk factors for patients with SII to develop ARDS, whereas PaO₂/FiO₂ was protective factor against patients with SII developing ARDS. Lactic acid >9.60 (mmol/l) had the greatest accuracy in predicting patients with SII developing ARDS. Lactic acid, WBC and SCr were risk factors for mortality, whereas hemoglobin and A/G were protective factors against mortality. Hemoglobin <83.00 (g/l) had the greatest accuracy in predicting mortality. These patients had no indications of previous medical histories. The present study proposed that these indices could be convenient assessment parameters to devise better treatment plans to preempt worsening conditions. However, the small number of cases in the present study may have affected the results of the statistical analyses. In addition, the present study did not evaluate long-term results, thus it is necessary to analyze the risk factors in larger patient numbers and in long-term accumulation of datasets.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions

SH, HF and QL contributed to the study design and provided the funding acquisition. ZN, ZD, XG and LY contributed to data collection and wrote the manuscript. ZN, ZD, WZ, HW, JS and YC provided resources and participated in the data analysis. ZN and ZD performed data validation, and retouched the manuscript. ZN, ZD and GX confirmed the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committees of Characteristic Medical Center of Chinese People’s Armed Police Force and 983 Hospital of the Joint Logistics Support Force of the Chinese People's Liberation Army. Written informed consents were obtained from the patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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