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Correlation Between Pulmonary Vascular Permeability Index, Shock Index, and Severity of Septic Shock and Their Evaluation Values for Prognosis

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Abstract

Background: The changes before and after fluid resuscitation in patients with septic shock and their relationship with prognosis have rarely been reported.

Objectives: We aimed to observe the correlation between pulmonary vascular permeability index (PVPI), shock index (SI), and severity of septic shock.

Methods: This case-control study retrospectively analyzed the clinical data of 154 patients with septic shock treated at our hospital (Weifang, China) from October 2016 to October 2018. They were divided into a survival group or a death group according to the 28-day prognosis. Univariate analysis was performed for vital signs, the acute physiology and chronic health evaluation II (APACHE-II) score, the sequential organ failure assessment (SOFA) score at admission, SI at admission (SI1), SI at 3 h after fluid resuscitation (SI2), PVPI at admission (PVPI1), PVPI at 3 h after fluid resuscitation (PVPI2), and lactate clearance rate (LCR). The correlations of PVPI and SI with the APACHE-II score, SOFA score, and LCR were analyzed by plotting the receiver operating characteristic curves.

Results: Among the 154 cases, 70 survived after 28 days and 84 died. We observed that SI1, SI2, PVPI1, PVPI2, APACHE-II score, and SOFA score were significantly lower in the survival group than in the death group, while LCR was significantly higher ($P < 0.05$). Also, SI1, SI2, PVPI1, and PVPI2 were positively correlated with APSCHE-II and SOFA scores of patients with septic shock, but negatively correlated with LCR ($P < 0.05$). Moreover, SI2 predicted the prognosis of patients with septic shock significantly better than SI1, PVPI1, and PVPI2 did. When SI2 was 1.22, the Youden index was 0.822, the sensitivity was 91.23%, the specificity was 89.47%, the positive predictive value was 0.912, and the negative predictive value was 0.924. The positive and negative likelihood ratios were 0.897 and 0.375, respectively.

Conclusions: Based on the study, SI after fluid resuscitation was more valuable for evaluating the prognosis of patients with septic shock than SI at admission, as well as PVPI values at admission and after fluid resuscitation.

Keywords: Pulmonary Veins, Vascular Permeability, Index, Sepsis, Shock

1. Background

Septic shock is a common clinical syndrome resulting from tissue perfusion deficiency caused by severe systemic infection, leading to tissue hypoxia, vital organ damage, and even multiple organ failure (1, 2). Septic shock refers to persistent low blood pressure in patients with severe sepsis that cannot be corrected after adequate fluid replacement, accompanied by tissue hypoperfusion (3). With the mortality rate of as high as over 40 - 70%, septic shock has become one of the main causes of death for critically ill patients (4). Sepsis or septic shock cannot be easily diagnosed in the early stages and the severity or prognosis cannot be well assessed. Therefore, the early diagnosis is now mainly based on some easily measurable biological indices that benefit the design of appropriate treatment regimens and the reduction of mortality rate (5).

Acute respiratory distress syndrome caused by increased pulmonary vascular permeability is the main cause of high septic shock mortality (6). Recently, with the application of Pulse-indicated continuous cardiac output (PiCCO) in clinical practice, the Pulmonary Vascular Permeability index (PVPI) has become an early diagnostic marker for septic shock (7). At present, septic shock is often treated by early-goal directed therapy (EGDT), in which initial fluid resuscitation plays a key role, maintaining systemic organ perfusion as much as possible (8). Patients who well re-

spond to initial fluid resuscitation have significantly better short- and long-term prognoses than those with poor responses (9). Shock index (SI) can indirectly reflect the effect of fluid resuscitation, as a classic and easily detectable index for the severity of shock (5). Until now, most studies have focused on preliminary determination of the degree of shock in SI patients. However, the changes before and after fluid resuscitation and its relationship with prognosis have rarely been reported.

2. Objectives

Therefore, we herein aimed to investigate the values of PVPI and SI changes before and after fluid resuscitation for the prognosis of patients with septic shock to provide a basis for improving clinical diagnosis and treatment.

3. Methods

3.1. Baseline Clinical Data

We retrospectively analyzed the clinical data of 154 patients with septic shock treated at our hospital (Weifang, China) from October 2016 to October 2018 in a case-control study. The inclusion criteria were defined in accordance with the diagnostic criteria for septic shock and included patients aged 18-75-years-old admitted no longer than 72 h from the onset. The exclusion criteria were severe heart, liver, and kidney dysfunction, death 72 h within admission, tumors, immune system and hematological diseases, atrial fibrillation, the positive result of immunodeficiency virus infection, pregnancy or breast-feeding status, and incomplete clinical data. According to the criteria, 154 out of 170 cases were included and 16 were excluded.

This study was approved by the Ethics Committee of our hospital (approval no.: YXLL201609281145) and conducted following the Declaration of Helsinki principles. Written consent was obtained from all patients.

3.2. Treatment Methods

After admission, the vital signs together with biochemical, routine blood test, coagulation, inflammation, and blood gas indices of all patients were detected. According to their conditions, oxygen therapy, mechanical ventilation, phlegm reduction, acid suppression, liver protection, or nutritional support were performed. Meanwhile, EGDT implementing sepsis bundles was conducted immediately.

3.3. Grouping

The sample size was estimated according to the formula: $n = 2(ms_e/D^2) \times (Q + \mu\beta)^2$, where n is the number of samples required by each group, mse is the mean square of error, and D is the intergroup difference. Commonly, α = 0.05, β = 0.05, Q = 3.4, and $\mu\beta$ = 1.645 were considered. Meanwhile, the pre-experiment showed ms_e = 40 and D = 6. As a result, n was obtained as $\approx$ 57. In other words, we included $\geq$ 57 cases in each group. The patients were divided into a survival group or a death group according to the 28-day prognosis. Of the 154 included patients, 70 survived and 84 died after 28 days (Figure 1).

3.4. Observation Indices

The observation indices were selected by combining the previous literature reporting the severity and risk factors of patients with septic shock with the factors reflecting the status of these patients.

The clinical data of all patients were collected, including age, gender, BMI, infection site, history of previous diseases, and complications. We also recorded body temperature (T), respiratory rate (RR), heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) at admission, SI at admission (SI1), and SI at 3 h after fluid recovery (SI2). This study excluded patients with atrial fibrillation; so, SI = HR/SBP, where SI < 0.5 means no shock, SI = 1.0 - 1.5 means complication with shock, and SI > 2.0 means complication with severe shock. A higher SI suggests a more severe shock. We measured PVPI at admission (PVPI1) and PVPI at 3 h after fluid resuscitation (PVPI2), as follows. In the supine position, a deep venous catheter was placed through the subclavian vein and a PiCCO catheter was placed through the femoral artery. The catheter electrode was connected to a PiCCO monitor and the deep venous catheter end was connected to a PiCCO temperature sensor. Thus, PVPI was detected by arterial thermodilution. At admission, we detected white blood cell (WBC) count, platelet (PLT) count, and levels of hemoglobin (Hb), blood urea nitrogen (BUN), serum creatinine (SCr), alanine aminotransferase (ALT), albumin (Alb), aspartate aminotransferase (AST), procalcitonin (PCT), C-reactive protein (CRP), and blood lactate (Lac). The lactate clearance rate (LCR) was tested 3 hours after liquid resuscitation. The severity of septic shock was evaluated using the acute physiology and chronic health evaluation II (APACHE-II) score and sequential organ failure assessment (SOFA) score (10).

All equipment in this study was calibrated, quality-controlled, and performance-tested to decrease errors. All

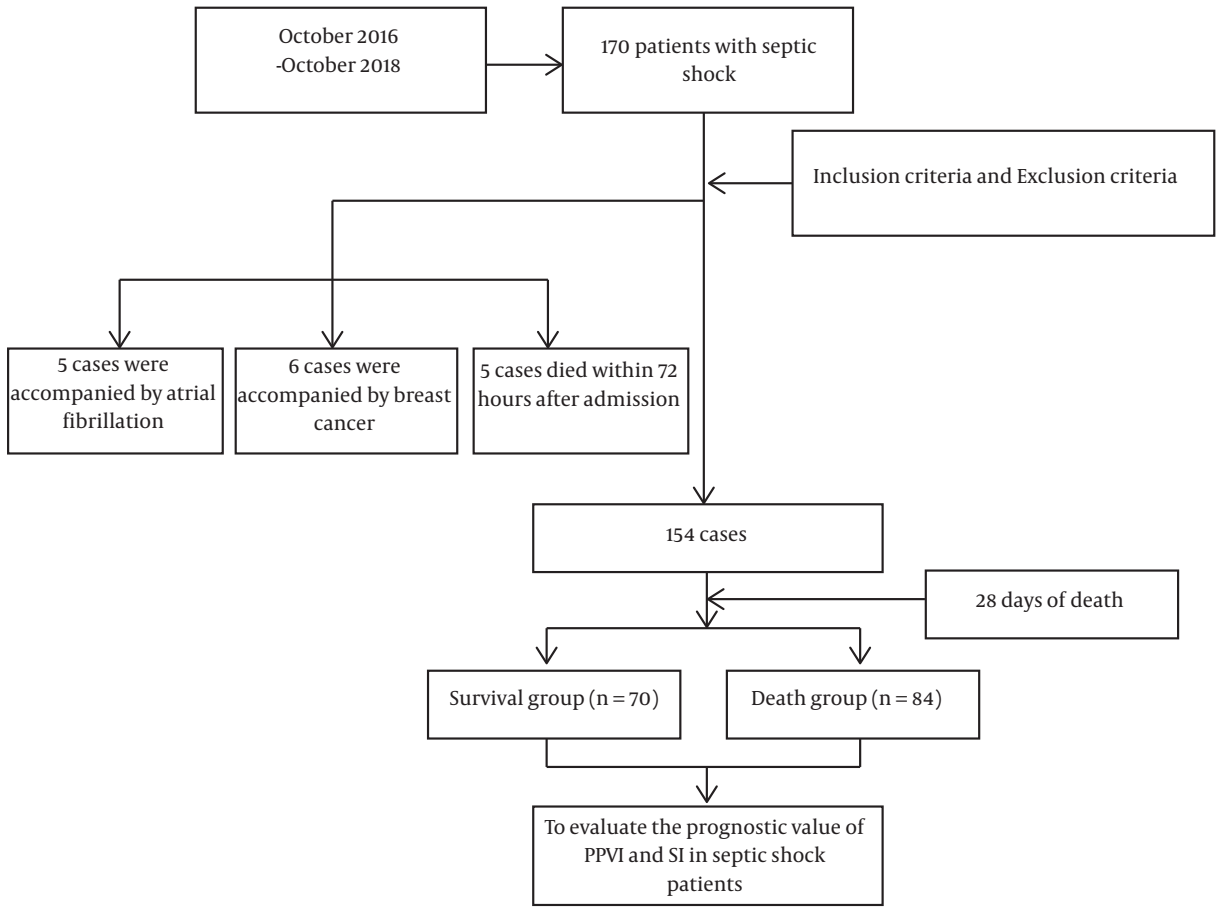

Figure 1. Flow chart of case inclusion and grouping

indices were measured three times independently and averaged. Three observers were set and the Kappa index was 0.718, suggesting good consistency.

3.5. Statistical Analysis

All data were analyzed by SPSS16.0 software. The normally distributed categorical data were expressed as mean ± standard deviation, and intergroup comparisons were made by the independent *t*-test. The non-normally distributed categorical data were represented as median (quartile) [M (Q_L, Q_U)], and intergroup comparisons were made with the rank-sum test. The numerical data were expressed as percentages, and intergroup comparisons were made by the χ^2 test. Correlations were assessed by Pearson or Spearman correlation analysis. By using the parametric method of the binormal model, receiver operating characteristic (ROC) curves were plotted for the diagnostic values of PVPI and SI and the areas under the curve (AUCs) were calculated. The optimal cutoff value and corresponding sensitivity, specificity, Youden index, predictive value, and likelihood ratio were found. We considered $P < 0.05$ as statistically significant.

4. Results

4.1. Clinical Data of Patients with Different Prognoses

Among 154 cases, 70 survived after 28 days and 84 died. We found that SI1, SI2, PVPI1, PVPI2, APACHE-II score, and SOFA score were significantly lower in the survival group than in the death group, and LCR was significantly higher ($P < 0.05$) (Table 1).

4.2. Correlations of SI With LCR, APACHE-II, and SOFA Scores of Patients with Septic Shock

In this study, SI1 and SI2 were positively correlated with APSCHEII and SOFA scores of patients with septic shock, but negatively correlated with LCR ($P < 0.05$) (Figure 2).

Table 1. Clinical Data of Patients with Different Prognoses[a]

	Survival Group (N = 70)	Death Group (N = 84)	χ^2/t	P
Gender (case, male/female)	43/37	52/32	1.118	0.290
Age, y	62.79 ± 4.45	63.01 ± 4.52	0.303	0.762
BMI, kg/m^2	22.34 ± 1.89	22.46 ± 1.91	0.390	0.697
Infection site [case, %]			0.081	0.994
Lung	47	56		
Abdominal cavity	11	13		
Urinary system	7	8		
Other	5	7		
Complication [case, %]				
Hypertension	29	36	0.032	0.858
Diabetes	21	25	0.001	0.974
Hyperlipidemia	24	28	0.016	0.901
COPD	15	17	0.033	0.856
Previous history [case, %]				
Smoking	27	34	0.058	0.810
Alcohol drinking	25	28	0.171	0.679
ALI [case, %]	38	44	0.391	0.532
T, °C	37.76 ± 1.24	37.81 ± 1.21	0.252	0.801
RR, bpm	24.32 ± 2.29	25.01 ± 2.23	1.889	0.061
HR, bpm	124.51 ± 10.29	125.13 ± 9.95	0.379	0.705
SBP, mmHg	82.32 ± 5.47	81.19 ± 5.62	1.258	0.210
DBP, mmHg	55.38 ± 4.38	56.45 ± 4.32	1.521	0.130
SI1	1.36 ± 0.31	1.63 ± 0.29	5.575	< 0.001
SI2	0.92 ± 0.14	1.37 ± 0.13	20.653	< 0.001
PVPI1	3.56 ± 0.54	4.76 ± 0.52	14.012	< 0.001
PVPI2	2.38 ± 0.38	3.97 ± 0.37	26.229	< 0.001
WBC, × 10^9/L	14.52 ± 2.29	13.89 ± 2.31	1.692	0.093
Hb, g/L	104.98 ± 10.29	105.24 ± 9.96	0.159	0.874
PLT, × 10^9/L	96.58 ± 9.08	97.28 ± 9.23	0.472	0.638
BUN, μmol/L	12.57 ± 2.14	12.43 ± 2.09	0.409	0.683
SCr, μmol/L	106.72 ± 10.23	107.14 ± 10.12	0.255	0.799
ALT, U/L	46.79 ± 3.29	47.02 ± 3.31	0.431	0.667
AST, U/L	39.62 ± 2.12	40.21 ± 2.09	1.733	0.085
Alb, g/L	35.48 ± 3.19	35.67 ± 3.22	0.366	0.715
CRP, mg/L	124.89 ± 11.24	125.43 ± 10.98	0.301	0.764
PCT, ng/L	0.85 ± 0.12	0.84 ± 0.11	0.539	0.591
Lac, mmol/L	6.23 ± 0.79	6.31 ± 0.81	0.617	0.538
LCR, %	28.59 ± 3.29	14.38 ± 2.19	31.993	< 0.001
APACHE-II score, point	13.58 ± 2.98	17.68 ± 3.02	8.439	< 0.001
SOFA score, point	6.29 ± 0.45	9.46 ± 0.51	40.497	< 0.001

Abbreviations: Alb, albumin; ALI, acute lung injury; ALT, alanine aminotransferase; APACHE-II: acute physiology and chronic health evaluation II; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DBP, diastolic blood pressure; Hb, hemoglobin; HR, heart rate; Lac, lactate; LCR, lactate clearance rate at 3 h after fluid resuscitation; PCT, procalcitonin; PLT, platelet; PVPI1, PVPI2, PVPI at admission and 3 h after fluid resuscitation; RR, respiratory rate; SBP, systolic blood pressure; SCr, serum creatinine; SI1, SI2, SI at admission and 3 h after fluid resuscitation; SOFA, sequential organ failure assessment; T, body temperature; WBC, white blood cell.
[a]Values are expressed as mean ± SD.

4.3. Correlations of PVPI with LCR, APACHE-II, and SOFA Scores of Patients with Septic Shock

We observed that PVPI1 and PVPI2 were positively correlated with APSCHE-II and SOFA scores of patients with septic shock, but negatively correlated with LCR ($P < 0.05$) (Figure 3).

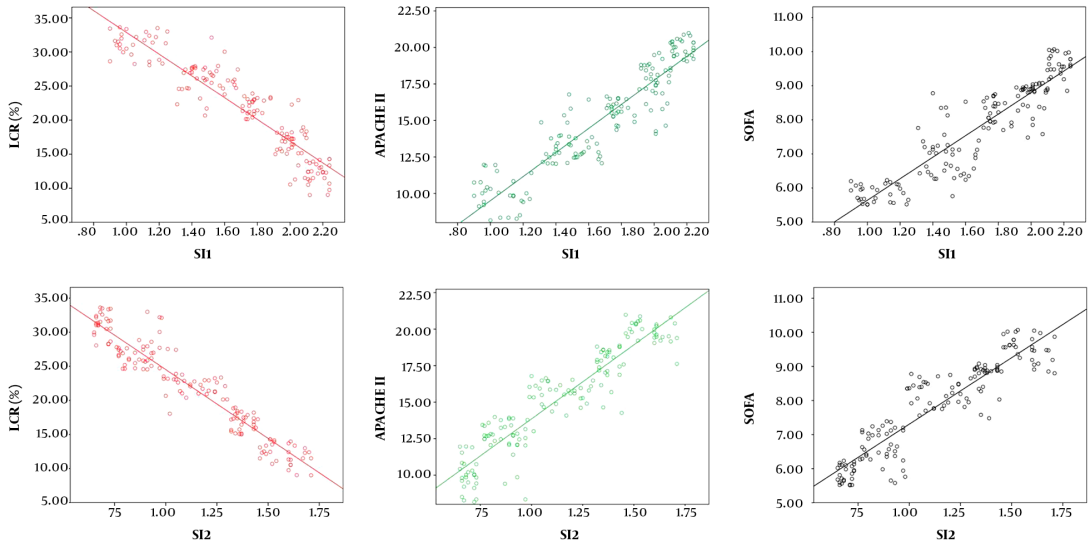

Figure 2. Correlations of SI with LCR, APACHE-II, and SOFA scores of patients with septic shock

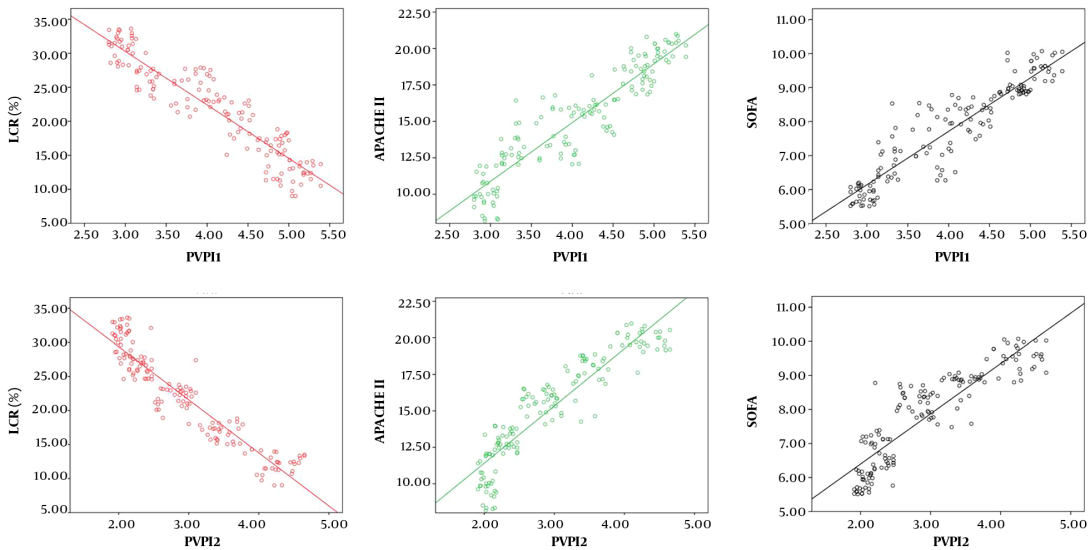

Figure 3. Correlations of PVPI with LCR, APACHE-II, and SOFA scores of patients with septic shock

4.4. Predictive Values of SI and PVPI for Prognosis of Septic Shock

We found that SI2 could predict the prognosis of patients with septic shock significantly better than SI1, PVPI1, and PVPI2 did. When SI2 was 1.22, the Youden index was 0.822, the sensitivity was 91.23%, the specificity was 89.47%, the positive predictive value was 0.912 and the negative predictive value was 0.924. The positive and negative likelihood ratios were 0.897 and 0.375, respectively (Table 2 and Figure 4).

5. Discussion

Sepsis shock, the most serious stage of sepsis, can cause the dysregulated proportion of anti-inflammatory factors and pro-inflammatory factors due to a massive release of TNF-α, IL-8, and IL-6, which leads to the systemic inflammatory response syndrome, eventually inducing multiple organ failure and even death (11, 12). Because of the large number of capillaries in the lungs, alveolar edema and pul-

Table 2. Predictive Values of SI and PVPI for Prognosis of Septic Shock

	AUC	95% CI	Optimal Cutoff Value	Sensitivity, %	Specificity, %	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio	Negative Likelihood Ratio	Youden Index	P
SI1	0.897	0.674 - 0.931	1.72	91.23	89.47	0.912	0.924	0.897	0.375	0.822	< 0.05
SI2	0.913	0.718 - 0.974	1.22	90.11	85.78	0.895	0.911	0.884	0.463	0.695	< 0.05
PVPI1	0.856	0.603 - 0.886	4.14	88.65	82.19	0.874	0.903	0.865	0.548	0.562	< 0.05
PVPI2	0.851	0.713 - 0.894	3.87	87.94	80.67	0.853	0.896	0.851	0.534	0.549	< 0.05

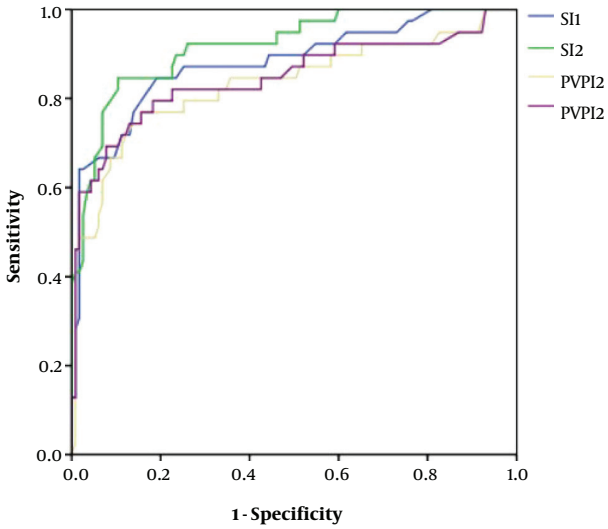

Figure 4. Predictive values of SI and PVPI for the prognosis of septic shock

monary interstitial disease are often caused by inflammatory factors and free radical attacks, resulting in a series of physiological changes such as reduced lung capacity, decreased compliance, and increased intrapulmonary bypass (13). The PiCCO monitor can provide a range of detection indicators, including PVPI. Extravascular lung water is less affected by ventilation tidal volume, oxygenation index, and positive end-expiratory pressure, thus visually reflecting the severity of pulmonary edema (14). Indeed, PVPI is the ratio of extravascular lung water to intrapulmonary blood volume, which offsets the effect of increased pulmonary blood volume on lung water; so, it can accurately reflect the permeability of pulmonary capillaries.

The diagnosis and treatment techniques for sepsis have been greatly improved since the introduction of the "surviving sepsis campaign" in 2002. Song et al. verified the application of sepsis standard for evaluating the diagnosis and prognosis of septic patients in ICUs (15), suggesting that SOFA is more suitable for the diagnosis and prognosis assessment of such patients than quick SOFA. At present, the initial treatment of septic shock is still controversial, but most ICU doctors follow the EGDT principle for clustering treatment. Fluid resuscitation is an effective method for treating severe sepsis and septic shock caused by trauma. It can markedly improve patients' myocardial function, systemic oxygen metabolism, tissue perfusion, and then prognosis, thus being of high clinical value (16). Patients with good fluid reactivity have elevated blood pressure and central vein, but HR and Lac levels decline, often accompanied by increased tissue perfusion, while SI can reflect hemodynamic changes, which is simple and easily available (17). The correlations between SI and PVPI changes before and after fluid resuscitation and the severity of septic shock and the prognosis have rarely been reported.

The APACHE-II and SOFA scores not only can assess the patients' condition, but also predict the mortality rate, which is the authoritative assessment scale for ICU applications worldwide. Studies have shown that the higher the APACHE-II and SOFA scores, the more serious the condition of sepsis patients (18). There is a significant positive correlation between the two and the severity of multiple organ failure. In this study, among 154 patients with septic shock, 84 died within 28 days, with a mortality rate of 54.54%. The clinical data of the survival group and the death group underwent univariate analysis. The results showed that no statistically significant difference was found between the two groups in age, gender, BMI, past history, and laboratory indicators. However, SI1, SI2, PVPI1, PVPI2, APACHE-II, and SOFA of the survival group were significantly lower than those of the death group, and LCR was significantly higher than that of the death group, with statistically significant differences ($P < 0.05$). It suggested that patients who eventually died were accompanied by more severe multiple organ dysfunction at admission and had poor fluid reactivity after EGDT. Therefore, for patients with higher scores, more attention needs to be paid to the treatment so as to reduce the mortality rate as much as possible. The results of the correlation analysis showed that SI1 and SI2 were positively correlated with APACHE-II and SOFA, but negatively correlated with LCR, suggesting that SI can reflect the patients' reactivity to initial fluid resuscitation to a certain extent. The lower the SI after initial treatment, the better the correction of the patients' shock. Moreover, it also indi-

rectly reflects that these patients have obtained better tissue perfusion, which is conducive to organ function recovery. There was a significant positive correlation between PVPI1 and PVPI2 and APACHE-II and SOFA in patients with septic shock, but a significant negative correlation with LCR (both $P < 0.05$). This may be because the pathogens in the patients were effectively removed as the condition improved, the inflammatory response was controlled, pro-inflammatory factor levels were reduced, capillary leakage of lung tissue was reduced, oxygenation was improved, and tissue hypoxia was corrected, ultimately improving the condition. The results of the ROC curve showed that SI1, SI2, PVPI1, and PVPI2 could predict the prognosis outcome of patients with septic shock. The SI predictive value was the highest after fluid resuscitation. When SI2 was 1.22, the Youden index was 0.822, sensitivity was 91.23%, specificity was 89.47%, positive predictive value was 0.912, negative predictive value was 0.924, positive likelihood ratio was 0.897, and negative likelihood ratio was 0.375.

As a non-invasive hemodynamic indicator, SI is often used in emergency areas. In recent years, SI has unique advantages in identifying critically ill patients (19, 20). Rady et al. (21) found that there was a good linear relationship between SI and invasive hemodynamic parameters, such as stroke volume and cardiac index. In patients with sepsis, SI and the inflammatory factors IL-1β and TNF-α were significantly positively correlated, and the higher the SI, the more serious the target organ damage (22). Kobayashi et al. (23) reported that raised SI was associated with higher in-hospital mortality of patients with non-ST-segment elevation myocardial infarction. Besides, Yussof et al. (24) found that SI after 2 h of fluid resuscitation in the emergency department was a feasibly reliable predictor for the death of patients with severe sepsis and septic shock.

In this study, SI perfectly reflected the responsiveness of septic shock patients after fluid resuscitation, and SI at this time also minimized the influence of the factors at the original admission of the patients, such as heart disease and body temperature. Therefore, SI can more accurately reflect the organ function and hemodynamic status, showing important values in the prognosis of patients.

5.1. Conclusions

In summary, compared to SI, PVPI, and PVPI after fluid resuscitation, SI is more valuable in the prognosis of patients with septic shock after fluid resuscitation. However, this study only compared the outcome of 28-day septic shock patients. The long-term outcome prediction of SI and PVPI in patients with septic shock also requires large-scale and long-term multicenter studies.

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Footnotes

Authors' Contribution: All authors reviewed and approved the submitted manuscript for publication. Jinfeng Xiao was the project administrator and contributed to the design, data curation, literature review, and critical revision of the study. Hongyuan Zhou contributed to the conceptualization, literature review, and data curation of the study. Yuanyuan Guo contributed to the conceptualization, software, and literature review of the study. The author agrees to be accountable for all the aspects of work ensuring integrity and accuracy.

Conflict of Interests: The authors report no conflict of interest associated with this work.

Ethical Approval: This study was approved by the Ethics Committee of Weifang Traditional Chinese Hospital (no.: WTCH201610-02).

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Informed Consent: Written consent was obtained from all patients.

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