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Original Article

The curative effect of Shenfu-injection in the treatment of burn sepsis and its effect on the patient's immune function, HMGB, and vWF

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Abstract: Objective: To investigate and analyze the immune regulatory effect of Shenfu-Injection (SFI) on patients with burn-injured sepsis by monitoring the serum level of high mobility group box 1 (HMGB1) and von Willebrand factor (vWF). Methods: In this retrospective study, the Acute Physiology and Chronic Health Evaluation (APACHE II) score, Marshall score, peripheral blood T lymphocyte count, and NK cell concentration, levels of cytokines such as HMGB-1, and vWF in peripheral blood before and after treatment in patients from the control group (convention treatments, n=51) and the observation group (convention treatments plus SFI treatment, n=57) were analyzed. The prognosis of the two groups of patients at 28 days was analyzed and compared. Results: After treatment, APACHE II score, Marshall score, IL-6, CPR, HMGB-1, and vWF in patients from the two groups decreased greatly when compared with those before the treatment ($P<0.05$). The APACHE II score, Marshall score, IL-6, CPR, HMGB-1, and vWF in the group for observation were significantly lower ($P<0.05$) than those in the control group. Concentrations of $CD3^+$, $CD4^+$, and NK cells in these two groups after 7 days of treatment were greatly higher than those before the treatment ($P<0.05$). Concentrations of $CD3^+$, $CD4^+$, and NK cells in the observation group were higher than those in the control group after treatment ($P<0.05$). There was no significant difference in terms of mortality between these two groups after 28 days ($P<0.05$). The average survival time of the non-survivors in the observation group was significantly longer than that in the control group ($P<0.05$). Conclusion: SFI can effectively improve the immunity of patients with burn-injured sepsis, reduce the expression of cytokines such as HMGB and vWF, and is of great help for the improvement of clinical prognosis.

Keywords: Shenfu-injection, burn-injured sepsis, clinical efficacy, immunity, cytokines

Introduction

Burn-injured patients face high risk of infection including sepsis, which can lead to multiple organ dysfunction syndrome (MODs) and even death [1]. During past decades, the burn care had been greatly improved, but the therapeutic outcomes in the severe burn injury patients with sepsis were not satisfied [2]. The severe burn is usually defined as the total burned surface area (tBSA) >10% by the guidelines developed by American Burn Association (ABA) in 2007 [3]. The risk of all types of infections including pneumonia, bacteremia, and genitourinary infections increases in the severe burn-injured patients, leading to high mortality rate (~50%) in patients with septic shock [4]. It is urgent to find a new approach to improve the treatment outcomes for burn-injured sepsis.

Sepsis results in a systemic inflammatory response syndrome. Recent studies have shown that the immune system is playing critical roles in initiating and developing the sepsis. More importantly, the immune system will affect the prognosis of sepsis [5]. The uncontrolled immune response during sepsis includes two concurrent phases, i.e., an activated immune response in the beginning and a chronic immunosuppressive period. This abnormality of

immune response leads to the immune cell death and leaves patients in the immune-comprised status, increasing the secondary infection risks [6]. Recovering the patients' immune system, e.g., inhibition of immunosuppression, has become a hot spot in clinical treatment.

The concept of Yin and Yang, a traditional Chinese medical philosophy, has been adopted to understand the co-inhibitory receptors in immunosuppression (e.g., T-cell exhaustion) in cancer treatment [7]. The essence of Yin and Yang theory is to find the hemostasis for immune response. To date, some of the natural medicines have shown the potentials in immune modulation [8]. For example, Shenfu-Injection (SFI) which contains ginsenoside (0.8 mg/mL) and aconitine (0.1 mg/mL), has been used in clinical treatments to improve the immune functions. Both ginsenoside and aconitine have been reported as a daily supplementary for immune enhancement [9]. Clinical studies indicated the additional application of SFI served as the immune booster to overcome the tumor-related immunosuppression. Whether the SFI can boost the immune function in burn-injured patients remains unknown.

High mobility group box 1 (HMGB1) is a damage-associated molecular pattern (DAMP) protein, which participates in many inflammatory cascades. Recent studies showed that decreased level of HMGB1 was found in the survivors of severe sepsis patients when compared to the non-survivors. von Willebrand factor (vWF) is a glycoprotein mainly produced by megakaryocytes. Both HMGB-1 and vWF expression levels are closely associated with MODs and the immune response in sepsis patients. We evaluated the function of SFI on immune modulation by accessing the serum level of HMGB-1 and vWF and found the SFI can improve the immune response in severe burn-injured patients.

Methods and clinical data

Clinical data

This was a retrospective study. There were 108 patients who were diagnosed with burn sepsis treated in Binzhou Medical University Hospital from September 2018 to December 2020 who were chosen as the study objects in this research. Based on the treatment scheme, patients were classified into the group for observation and the control group, with 57 and 51 individuals, respectively. This study was approved by the ethic committee of Binzhou Medical University Hospital (No. 2018080102).

Standard for inclusion and exclusion

Inclusion standard: ① Patients with sepsis who were confirmed by relevant diagnostic standard; ② Patients with total burn area (TBSA) >30%; ③ Patients with an age ≥18 years old; ④ Patients burned by a flame or hot object; ⑤ Patients who were admitted into the hospital within 24 hours after burn injury; ⑥ Patients with no obvious organ injury, serious cardiovascular, or cerebrovascular diseases before being burned.

Exclusion criteria: ① Patients with burned by electricity or chemical material; ② Patients with mental disorders; ③ Patients in pregnant or lactating period; ④ Patients who received glucocorticoid drugs or drugs that have an impact on immune function within 24 weeks before the experiment; ⑤ Patients with congenital or secondary immunodeficiency diseases; ⑥ Patients with combined with malignant tumor, chronic liver or kidney damage, and blood system diseases.

Method

Conventional treatment was provided for all patients with severe burn sepsis, including anti infection treatment, fluid resuscitation treatment, nutrition support treatment, and escharectomy and skin grafting. During the treatment, the vital signs of patients were closely monitored with a focus on the changes of body temperature and respiration. Severe patients were provided with 24-hour ECG monitoring and low flow oxygen inhalation. The hygiene of wards, beds, proper ventilation, and warmth preservation were ensured.

The observation group was administered 100 ml Shenfu-Injection (Huarun Sanjiu (Ya'an) Pharmaceutical Co., Ltd., z200243117) and 250 ml 5% glucose intravenously, once a day for 7 days.

Indicators for the observation

The APACHE II score and Marshall score, including acute physiological score, age score, and

Table 1. Comparison of clinical data between these two groups

Clinical material	Observation group (n=57)	Control group (n=51)	t/χ^2	*P*
Gender				
Male	31	30	0.216	0.642
Female	26	21		
Age (years old, $\bar{x}\pm s$)	58.77±8.79	56.44±7.19	1.489	0.140
tBSA (%, $\bar{x}\pm s$)	54.37±14.63	55.34±17.93	0.306	0.760
APACHE II score (points, $\bar{x}\pm s$)	18.11±5.38	18.67±5.95	0.506	0.614
Marshall score (points, $\bar{x}\pm s$)	10.90±2.57	11.18±3.04	0.528	0.598

Note: tBSA: total burned surface area. APACHE II: Acute Physiology and Chronic Health Evaluation.

the score for chronic health, in the two groups before and 7 days after the treatment were compared. The score ranges from 0~71 points. The lower the score, the lower the possibility of mortality in the hospital.

In the Marshall score system, especially the Marshall multiple organ dysfunction score system, corresponding indicators are assessed to evaluate the organs of six systems: lung, kidney, liver, heart, blood, and brain. The functional state score of each organ ranges from 0 to 4 points with a total score of 24 points. The higher the score, the more serious the patient's situation.

The serum IL-6 level, CPR, HMGB-1, and vWF cytokines were compared between these two groups before the treatment and 7 days after the treatment. The peripheral venous blood of the two groups was collected, and the serum was centrifuged. Serum IL-6 level, CPR, HMGB-1, and vWF levels were determined with ELISA, and the detection was carried out strictly based on the instructions of the kit (American Invitrogen Corporation).

The peripheral blood T lymphocyte count and NK cell concentration between the two groups before the treatment and 7 days after the treatment were compared. The peripheral venous blood of the two groups was collected. The count of $CD3^+$, $CD4^+$, $CD8^+$, and NK cells was detected through flow cytometry. The mortality rate after 28 days and the average survival time of the two groups was compared. Antibodies used in flow cytometry were APC-labeled mouse anti-human CD8, PE-Cy7-labeled mouse anti-human CD56, PE-labeled mouse anti-human CD4 antibody (American BD Company, 746471, 347747, 340962), and FITC-labeled mouse anti-human CD3 antibody (American BD Company, 349201).

Statistical analysis

SPSS 26.0 was adopted for processing and analysis of the data. The measured data were expressed as $\bar{x}\pm s$, and were analyzed through the t-test. The counting data were expressed by percentage (%) and were analyzed through χ^2 test. $P<0.05$ indicated statistically significant difference.

Results

Clinical data

As shown in **Table 1**, 26 females and 31 males were assigned in the observation group, and 21 females and 30 males were assigned in the control group. The average age, TBSA, APACHE II score, and Marshall score of patients in the observation group were (58.77±8.79) years old, (54.37%±14.63)%, (18.11±5.38) points, and (10.90±2.57) points, respectively. The average age, TBSA, APACHE II score, and Marshall score of patients in the control group were (56.44±7.19) years old, (55.34%±5.95)%, (18.67±5.95) points, and (11.18±3.04) points, respectively. No significant difference was found among the genders, age, TBSA, APACHE II score, and Marshall score between the control group and the observation group before the treatment.

Changes of the score of APACHE II and Marshall in these two groups before and after treatment

No obvious difference was found in terms of the APACHE II score and Marshall score between the two groups before the treatment (P=0.614, P=0.598). After the treatment, the score of APACHE II and Marshal in the observation and the control group significantly decreased by 46.00%, 34.07%, 39.65%, and 22.18%, respectively when compared to the before treatment. Marshall score of the two groups were greatly lower than those before

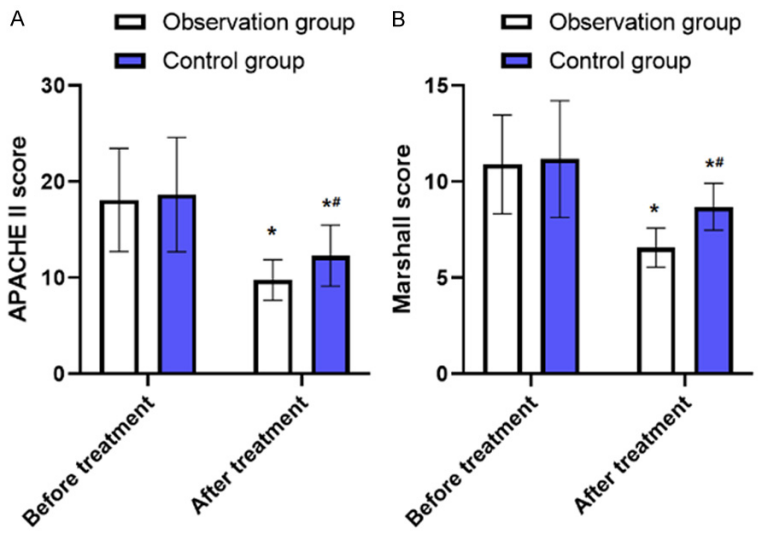

Figure 1. Changes of APACHE II score and Marshall score in the two groups before and after treatment. Note: APACHE II, Acute Physiology, and Chronic Health Evaluation. Compare with before treatment, paired samples t-test, *P<0.05; compare with Observation group, independent samples t-test, #P<0.05.

treatment (P<0.05). The score of APACHE II and Marshall of the observation group were significantly lower than those observed in the control group (P<0.05, **Figure 1**).

Changes of cytokine levels before and after the treatment in the two groups

As seen in **Table 2**, before treatment, there were no significant differences between the two groups regarding the serum IL-6 level, CPR level, HMGB-1 level, and vWF level (P=0.553, P=0.476, P=0.222, and P=0.410). After treatment, the levels of serum IL-6, CPR, HMGB-1, and vWF were greatly lower than those before the treatment (All P<0.001). The serum IL-6 level, CPR concentration, HMGB-1 concentration, and vWF concentration in the observation group were significantly lower when compared to those in the control group (All P<0.001).

Changes of peripheral blood T lymphocyte count and NK cells before and after the treatment in these two groups

As summarized in **Table 3** and **Figure 2**, no obvious difference was found regarding the peripheral blood T lymphocyte subsets and NK cells among these two groups before the treatment (P=0.636, P=0.458, P=0.920, and P=0.837). After treatment, concentrations of $CD3^+$, $CD4^+$, and NK cells in the two groups were greatly increased. Concentrations of $CD3^+$, $CD4^+$, and NK cells in the observation group were greatly higher than those in the control group after treatments (All P<0.001).

Mortality rate and average survival time of non-survived patients after 28 days of treatment

No obvious difference was found in the mortality rate between the two groups after treatment for 28 days (P> 0.05, **Table 4**). In average, patients in the observation group survived much longer than those in the control group (P<0.05, **Table 5**).

Discussion

The clinical treatments for patients with burn-induced sepsis mainly include anti-infection, fluid resuscitation, nutritional support, and maintaining electrolyte balance. The clinical treatment (conventional treatment) efficacy is not ideal enough [10]. APACHE II (Acute physiology and chronic health evaluation II) scoring system was used in the ICU to describe the severity of the patients. Marshall scoring system is the representative of MODS scoring system [11, 12]. After treatment, APACHE II and Marshall score were decreased in the two groups regardless of patients receiving the conventional treatment (control group) or the conventional treatment plus SFI treatment (observation group). This indicated that both treatments had significant therapeutic effects.

Not much is known about the mechanism of post-sepsis immunosuppression and inflammation. Recent studies indicated that the immune activations and the inflammation are necessary for fighting post-sepsis infection [13]. The failures in the clinical trials suggested that the inhibition of inflammation would not show benefits to the sepsis treatment [14, 15]. Higher immune activities were observed in the survivors of severe patients when compared to those in the non-survivors. As demonstrated by

Table 2. Changes of cytokines in two groups before and after treatment ($\bar{x}\pm s$)

Group	Time	IL-6 (pg/ml)	CPR (mg/L)	HMGB1 (μg/L)	vWF
Observation group (n=57)	Before treatment	88.29±15.49	129.42±27.60	137.38±23.04	9.38±1.25
	After treatment	50.32±12.31*	80.32±19.02*	108.29±16.72*	4.65±0.97*
	t	14.489	11.059	7.715	22.570
	P	0.000	0.000	0.000	0.000
Control group (n=51)	Before treatment	90.12±16.42	133.42±30.54	132.19±20.54	9.17±1.39
	After treatment	71.35±19.21	109.58±17.85	119.87±17.60	6.43±1.02
	t	5.304	4.813	3.253	11.349
	P	0.000	0.000	0.002	0.000

Note: Compared with the control group at the same time, independent samples t-test, *P<0.05. HMGB1: high mobility group box 1. vWF: von Willebrand factor.

Table 3. Changes of peripheral blood T lymphocyte count and NK cells in the two groups (%, $\bar{x}\pm s$)

Group	Time	$CD3^+$	$CD4^+$	$CD8^+$	NK
Observation group (n=57)	Before treatment	37.42±6.59	30.84±4.32	21.04±3.21	23.94±4.15
	After treatment	56.83±9.22*	45.23±5.01*	20.74±2.93	36.25±5.11*
	t	12.931	16.423	0.521	14.118
	P	0.000	0.000	0.603	0.000
Control group (n=51)	Before treatment	38.05±7.21	30.19±4.75	20.98±2.97	24.10±3.91
	After treatment	50.17±7.03	39.42±4.39	21.15±3.01	31.23±4.95
	t	8.595	10.191	0.229	8.072
	P	0.000	0.000	0.819	0.000

Note: Compared with the control group at the same time, independent samples t-test, *P<0.05.

Yu et al., the $CD3^+$, $CD4^+$, and $CD8^+$ T cell numbers were highly associated with the prognosis of severe sepsis [16]. CD3 plays an important role in T cell activation and consequently enhances the immune response [17]. The counts of $CD3^+$, $CD4^+$, and $CD8^+$ T cells directly reflect the immune activation. In this study, the counts of activated T cells including $CD3^+$, $CD4^+$, and $CD8^+$ T cells in the observation groups were significantly higher than those in the control group, indicating the SFI treatment can help immune recovery in sepsis patients. The increased amount of pro-inflammatory cells including NK cells, $CD3^+$, $CD4^+$, and $CD8^+$ T cells also indicated the treatment of SFI can maintain the inflammatory status in sepsis patients.

During sepsis, the IL-6 mediates a systematic immune response including the fever and expression of C-reactive protein (CRP) [18, 19]. The increased concentration of IL-6 is positively associated with the overall morality and MODs in sepsis patients [20]. In this study, the expression amount of IL-6 and CRP were decreased regardless of patients receiving the conventional treatment (control group) or the conventional treatment plus SFI treatment (observation group). This indicated that both treatments showed significant therapeutic effects. The combination treatment of SFI shows even better effects in IL-6 suppression.

By dynamically monitoring the plasma HMGB1 concentration during sepsis care, it was found that the decreased concentration of HMGB1 in plasma was highly correlated with therapeutic outcomes [21]. High level of HMGB1 shows negative impacts in immune activation through the inhibition of several different kinds of immune cells. For example, NADPH oxidase activities in neutrophils was inhibited by HMGB1, causing the dysfunction of neutrophils in killing bacteria in an animal study [22]. Our data suggested that SFI restores immune activities by suppressing the HMGB1 in severe sepsis patients.

Endothelial cells are damaged in sepsis, leading to abnormal endothelial cell function such

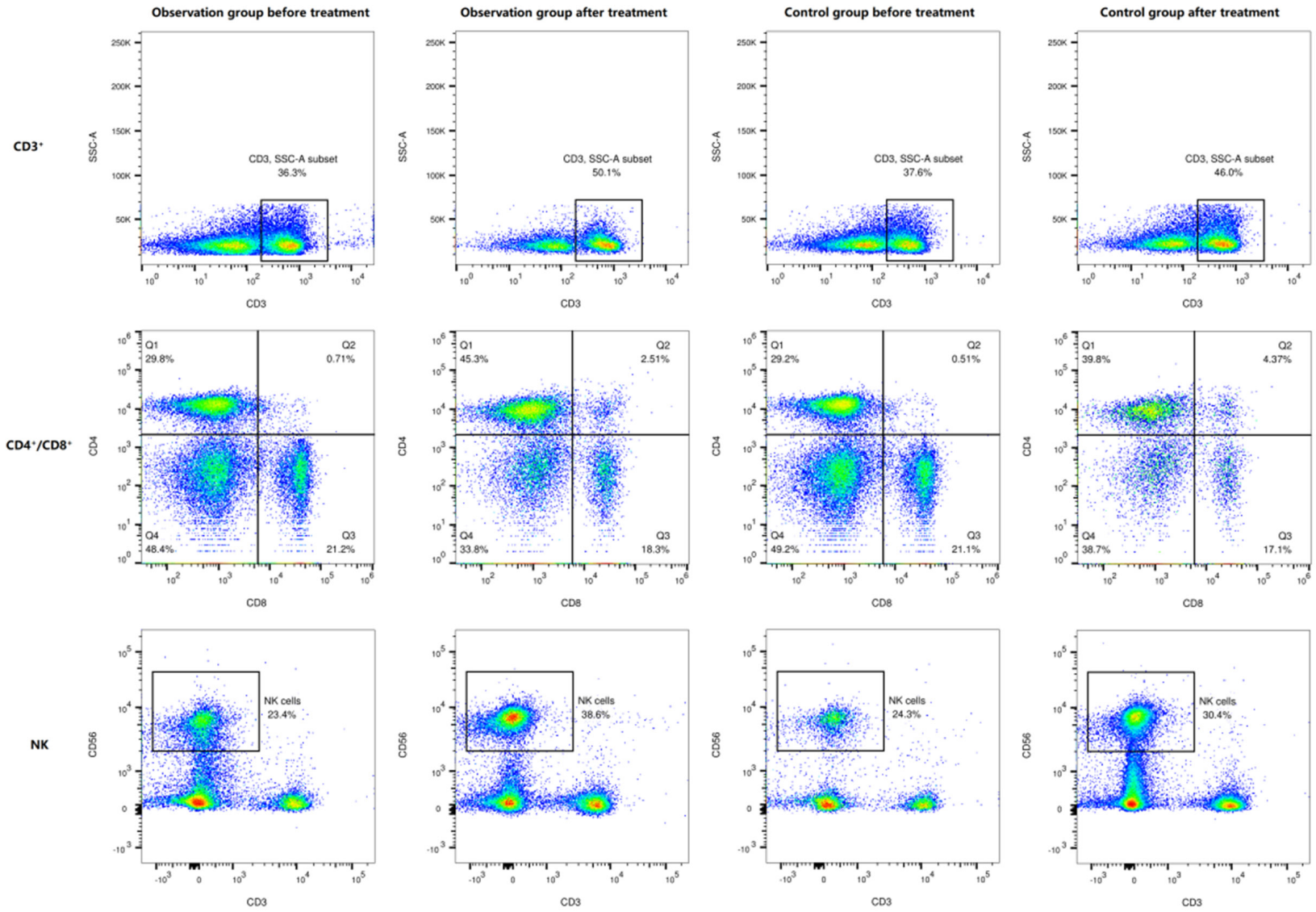

Figure 2. Changes of peripheral blood T lymphocyte count and NK cells in the two groups.

Table 4. Comparison of the mortality rate between the two groups after 28 days

Group	cases	28 d Death cases	28 d Mortality rate (%)	χ^2	P
Observation group	57	14	24.56	0.324	0.570
Control group	51	15	29.41		

Table 5. Comparison of average living time of patients who died after 28 days of treatment between these two groups (d)

Group	28 d death cases	Average living cases	t	P
Observation group	14	25.30±3.28	7.809	0.000
Control group	15	17.02±2.39		

as overproduction of plasminogen activator inhibitor-1 (PAI-1) and the activation of thrombin-activatable fibrinolysis inhibitor (TAFI) [23]. The excess PAI-1 and uncontrolled TAFI will lead to organ dysfunction due to the thrombosis induced damages on tissues [24]. The expression of endothelial injury related markers can reflect the severity of the disease [25]. Among endothelial markers, vWF is a well-studied marker for endothelial dysfunction which is also involved in thrombosis [26]. It has been reported that [27] the increase of vWF in peripheral blood in patients with sepsis is proportional to the degree of the sepsis [28]. The SFI treatment suppressed the expression vWF in severe burn-injured patients, indicating the SFI can contribute to a better therapeutic outcome for patients. Due to limited cases, deviation may exist in the results of the study. The specific mechanism of Shenfu injection in the body has not been elucidated. There may be multiple mechanisms which need more animal studies in future study to illustrate the mechanism of SFI in immune modulation in sepsis patients.

This study evaluated the treatment efficacy of conventional treatment combined with SFI in severe burn injury patients with sepsis. In this study, the additional SFI treatment did not decrease the morality rate when compared to that of patients who received conventional treatment only. The additional SFI treatment extended the average survival time in the non-survivors. The application of SFI can improve the immunity in severe burn injury patients with sepsis, which is of great significance for improving patients' clinical prognosis.

Disclosure of conflict of interest

None.

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