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Efficacy of Shufeng Jiedu Capsules in the treatment of sepsis: A prospective, randomized, placebo-controlled trial

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Abstract

Introduction: Sepsis is a potentially life-threatening complication after infection and the second-leading cause of death in non-coronary intensive care unit. The aim of this trial was to evaluate the efficacy and safety of Shufeng Jiedu Capsules (SFJDC) in the treatment of sepsis. This drug was used in this trial as a complementary medicine.

Methods: Hospital inpatients diagnosed with sepsis and who met the trial inclusion/exclusion criteria were randomly allocated into one of two groups; a combination group (antibiotics and SFJDC) and a routine care group (antibiotics and placebo group). The primary outcome was severity assessed by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score. Secondary outcomes included the SOFA score, the traditional Chinese medicine (TCM) symptom score, and 28-day mortality. Additional outcomes included indices of infection (such as the level of procalcitonin (PCT), C reactive protein (CRP), and the white blood cell (WBC) count).
Results: Of 150 patients admitted between July 2016-2017, 129 patients met the inclusion criteria were randomly assigned to either the combination group (n=66) or an single antibiotics group (n=63). The APACHE II score, the TCM symptom score, the level of CRP, the neutrophil-lymphocyte ratio (NLR) and the healing rate differed significantly between the two groups on the 7th day of hospitalization (p=0.046, p=0.020, p=0.009, p=0.001, and p<0.01, respectively). Mortality at 28 days was 3.03% in the combination group and 7.93% in the single antibiotics group according to Per-protocol analysis (p=0.400). However, the healing rate differed significantly between the two groups (p<0.01). The incidence of adverse events did not differ significantly between the 2 groups.

Conclusion: A combination of antibiotics and SFJDC in the treatment of sepsis is superior to routine antibiotic treatment since combination therapy reduces the inflammatory response and improves prognosis for septic patients.

Key Words: Shufeng Jiedu Capsules, sepsis, Randomized controlled trial, “heat-toxin syndrome”, APACHE II score, SOFA score, efficacy

1. Background

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (1,2), considered to be the leading cause of death in patients in intensive care units. According to 2015 estimates, there were more than 230,000 cases of septic shock, with more than 40,000 deaths annually in the United States (3,4). Severe sepsis can readily lead to septic shock, which has a mortality as high as 80% (1). Therefore, sepsis needs to be treated through early intervention.

Sepsis and septic shock can result from an infection, such as pneumonia, influenza, or a urinary tract infection, anywhere in the body. Worldwide, one-third of people who develop sepsis die (5). Many who do survive are left with life-changing aftereffects, such as post-traumatic stress disorder (PTSD), chronic pain and fatigue,
and organ dysfunction and/or amputations\textsuperscript{(6-8)}. In almost every case of sepsis, patients need to be hospitalized, intravenously administered appropriate antibiotics (usually broad-spectrum antibiotics), and given therapy to alleviate any organ dysfunction\textsuperscript{(9)}. Antibiotic-resistant bacteria have emerged with the widespread use of antibiotics\textsuperscript{(10)}. The race for new antibiotics continues, but there is a real concern that bacteria will mutate that medicine does not yet have a treatment for. Moreover, all antibiotics cause adverse reactions. When used appropriately, antibiotics are relatively safe and typically cause few adverse reactions. However, some antibiotics are known to cause adverse reactions that are particularly distressing\textsuperscript{(11)}. Thus, CAM could be a new way to combat bacterial infections.

As a CAM, SFJDC has been widely used in clinical settings to treat infection. Shufeng Jiedu Capsule is a compound Chinese medicine preparation consisting of 8 traditional Chinese medicines including \textit{Huzhang} (\textit{Polygonum cuspidatum}), \textit{Lianqiao} (\textit{Forsythia}), \textit{Banlangeng} (\textit{Radix}), \textit{Caihu} (\textit{Bupleurum}), \textit{Baijiangcao} (\textit{Sabina}), \textit{Mabiancao} (\textit{Verbena}), \textit{Lugeng} (\textit{Reed Root}) and \textit{Gancao} (\textit{Licorice}). \textit{Polygonum cuspidatum} is slightly cold and sputum, with the effect of phlegm and dampness and attacking swollen poison. The resveratrol of its main component can mediate the increasement of sirtuin (SIRT)-1 expression, decrease Phosphotyrosine phosphatase (PTP) -1B, inhibits NF-κB, reduce monocyte tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and inhibit the proinflammatory enzyme JNK -1 and IKK β activity, thus having anti-inflammatory effects\textsuperscript{(12)}. \textit{Forsythia} has the effect of clearing away heat and detoxifying. It also can penetrate the muscle solution, clear the heat and hurricane. The main component of forsythiaside has the ability to inhibit elastase activity, scavenging reactive oxygen, and has obvious anti-inflammatory\textsuperscript{(13)}. \textit{Radix} has the effect of antibacterial, antiviral, anti-inflammatory, anti-endotoxin and immune enhancement\textsuperscript{(14)}.

Over the past few years, complementary and alternative medicine (CAM) has gradually become well-known around the world. CAM is the term for medical products and practices that are not part of standard medical care. As a part of CAM,
complementary medicine is treatments that are used along with standard medical treatments but that are not considered to be standard treatments\(^\text{15,16}\). One form of complementary medicine is traditional Chinese medicine (TCM), which is becoming increasingly popular and accepted worldwide\(^\text{17-19}\). Professor Jinda Wang, a famous Chinese scientist, classified sepsis into heat-toxin syndrome, siltation syndrome and deficiency syndrome according to patient symptoms\(^\text{20}\). A previous study in China found that Shufeng Jiedu Capsules (SFJDC) enhance immunity and have antibacterial action in clinical settings\(^\text{21}\). Conventional medicine and SFJDC were superior to conventional medicine alone when treating children with an acute upper respiratory tract infection and cancer\(^\text{22,23}\). No study has examined a combination therapy of antibiotics and complementary medicine for treatment of sepsis. Therefore, the aim of this trial was to assess the synergistic effect of antibiotics and SFJDC in the treatment of sepsis by intervening in the early stage of sepsis-induced syndromes.

2. Methods

Design. This trial was a prospective, randomized, controlled, double-blind clinical trial. Potential subjects were inpatients at Xinhua Hospital affiliated with Shanghai Jiao Tong University from July 2016 to July 2017. Patients who met the inclusion criteria were randomly allocated into a combination group and an single antibiotics group. All patients were diagnosed by the same physician finally. If the patient was unable to give informed consent at the time of hospitalization due to the severity of their sepsis, informed consent from their next of kin and an independent physician was obtained. This trial was approved by the Institutional Ethics Committee of Xinhua Hospital affiliated with Shanghai Jiao Tong University (XHEC-C-2016-010-2), and this trial adhered to the Declaration of Helsinki and was registered in the Clinical Trial Registry of China (ChiCTR-IPR-16008639).

Inclusion Criteria. All patients provided written consent for participation in this
Inclusion Criteria. The inclusion criteria were as follows: 1) ≥15 years and ≤80 years of age, 2) diagnosed with sepsis, 3) diagnosed with “heat-toxin syndrome”, and 4) within 24 hours of new-onset sepsis.

Exclusion Criteria. Exclusion criteria included 1) an immunocompromised state, 2) burns, small cell lung cancer, C cell carcinoma of the thyroid gland, rheumatoid disease, or the first day of hospitalization after trauma, 3) inability to determine whether dysfunction occurred after infection in patients with chronic hepatic insufficiency, renal insufficiency, or acirculatory system disease, 4) a “qi deficiency syndrome,” 5) psychosis or women who are pregnant, 6) chronic cardiac shock or prolonged organ perfusion abnormalities, 7) gastrointestinal bleeding or shock, and 8) patients taking other traditional Chinese medicines such as Xuebijing injections or ulinastatin. Patients who had serious adverse reactions (such as allergies), incomplete information, or other characteristics that might affect the assessment of efficacy or safety were excluded from this trial.

Randomization and Concealment. A randomization sequence was generated with SPSS 20.0 and password protected. Patients randomized in a stratified manner at a ratio of 1:1 to either the combination group or the single antibiotics group. An independent statistician was responsible for generating a randomization list using the procedure PROCPLAN in the software SAS and then arranging numbers in sequential order (1–150). The number sequence was kept in sealed opaque envelopes and distributed to assessors. Patients, physicians, and nurses were blinded to the treatment allocation.

Sample size considerations. This study was designed to show the superiority of the
SFJDC group compared to placebo treatment. Our primary hypothesis was that adjunct SFJDC in patients with sepsis will result in reduced APACHE II score compared to the placebo. We assumed a APACHE score decline rate of 30% in the placebo group and 60% in the SFJDC group over 7 days based on the previous trials. Thus, a sample size of 150 patients was needed to achieve a statistical power of 80% (a non-inferiority margin of 10%, a two-sided p-value of < 0.05).

Treatment. SFJDC were purchased from Jiren Pharmaceutical (Anhui, China). The content of each SFJDC is 0.52g. The combination group received routine antibiotic treatment and took 4 capsules of SFJDC 3 times a day 30 min after a meal. The single antibiotics group received routine antibiotics and took a placebo in place of SFJDC. All patients were followed for 28 days.

Data Collection. On the first day of hospitalization, the patient’s name, gender, age, and underlying condition were recorded. On the first and seventh day of hospitalization, the patient’s vital signs, routine blood chemistry, clotting, glucose levels, liver function, renal function, electrolytes, myocardial markers, blood gas analysis, the level of procalcitonin (PCT), the level of C-reactive protein (CRP), and the APACHE II, SOFA, and TCM symptom scores were recorded.

Outcome Measures. The primary outcome was the APACHE II score on seventh day of hospitalization. Secondary outcomes included the SOFA score, the TCM symptom score, and 28-day mortality. Additional outcomes included the WBC count, the level of CRP, the level of PCT, and the neutrophil-lymphocyte ratio (NLR).

TCM syndrome scores are scores obtained by TCM based on the quantitative assessment of the symptoms of each sepsis patient's system. The key points of the score include the patient's pulse, color, cough, anorexia, urination, etc. The total score
is 60 points and the lowest is 0 points. The higher its value, the more serious the disease. The TCM diagnosis were performed by the same physician. When the (TCM symptom score(D7) - TCM symptom score(D0))/ TCM symptom score(D0)*100% is greater or equal to 70%, we judge the patient as the Cure. And so on, the Effective is 50% and less than 70%. The Better is less than or equal to 50% and greater than 0. The Invalid is less than 0. We defined the healing rate is (cured cases + effective cases) / total cases × 100%.

Statistical Analyses. Statistical analysis was performed using the software SPSS 20.0. Descriptive statistics were used to summarize the study population. Continuous variables are presented as means (SD) or medians (first quartile, third quartile) depending on the normality of the data. Categorical data are presented as counts with frequencies and were compared between groups using Fisher’s exact test. Depending on the distribution of data, a t-test or Wilcoxon rank sum test was used to compare continuous data between the 2 groups. All hypothesis tests were two-sided, with a significance level of p < 0.05. Analysis of all endpoints will be performed according to the intention-to-treat principle, on which data non-inferiority is based. For the primary outcome, the difference between the SFJDC and placebo (p < 0.05) was calculated with a two-sided Z-score for proportions. Secondary outcomes was analysed using the following tests: two-tailed Z-score for proportions (p < 0.05), t-test and chi-square when appropriate. There was no missing data in the 129 patients we analyzed, so we used per-protocol analysis.

3. Results

Of 215 potential subjects, a total of 150 patients between July 2016 and July 2017. Patients were randomly assigned to a combination group (n=75) or an single antibiotics group (n=75). One hundred and twenty-nine patients (86%) completed the protocol at the 28-day, including 66 (88%) in the combination group and 63 (84%) in the single antibiotics group. One patient, a 78-year-old female who had been assigned
to the single antibiotics group, died 3 days after enrollment due to multiple organ dysfunction syndrome without meeting the recovery criteria. Two other patients withdrew from the trial (Fig. 1).

Baseline characteristics did not differ significantly between the 2 groups, as shown in Table 1. Antibiotic use in the 2 groups did not differ significantly \( (p=0.943) \) (Table 2). In our trial, Carbapenems include Meropenem \( (1\, \text{g ivgtt. q8h}) \) and Imipenem cilastatin \( (0.5\, \text{g ivgtt q8h}) \). Cephalosporins contain Cefmetazole \( (2\, \text{g ivgtt. bid}) \) and Cefepime \( (2\, \text{g ivgtt. bid}) \). Respiratory quinolones composed of Ofloxacin \( (0.5\, \text{g ivgtt. qd}) \) and moxifloxacin \( (0.4\, \text{g ivgtt. qd}) \). Sulperazone \( (3.0\, \text{g ivgtt. bid}) \) and Tazocin \( (4.5\, \text{g ivgtt. q8h}) \) are Enzyme inhibitors. All antibiotics are adjusted according to age, liver and kidney function, etc. and are applied for 7 days.

The source of the infection was also analyzed (Table 3). In the combination group, 54 patients had a pulmonary infection, 5 had an intestinal infection, 5 had a urinary tract infection, 1 had a liver abscess, and 1 had a skin infection. In the single antibiotics group, 49 patients had a pulmonary infection, 3 had an intestinal infection, 9 had a urinary tract infection, 1 had a liver abscess, and 1 had a skin infection. The source of infection did not differ significantly between the 2 groups.

The primary outcome (the APACHE II score) did not differ between the 2 groups on the first day of hospitalization \( (12.18\pm5.11 \text{ vs } 12.67\pm6.18) \), as shown in Table 4. On the seventh day of hospitalization, the combination group had a markedly lower APACHE II score compared to the single antibiotics group \( (5.58\pm4.38 \text{ vs } 7.02\pm3.73, P=0.046) \).

As shown in Table 3, secondary outcomes (the SOFA score and the TCM symptom score) on the first day of hospitalization did not differ between the 2 groups \( (3.09\pm1.72 \text{ vs } 2.92\pm1.46, 13.73\pm5.73 \text{ vs } 14.56\pm6.18, \text{ all } P > 0.05) \). On the seventh day of hospitalization, the placebo group had a SOFA score of 1.29\pm1.21 and the SFJDC group had a score of 1.55\pm1.74. The SOFA score did not differ significantly between the 2 groups \( (p = 0.33) \). On the seventh day of hospitalization, the SFJDC group had a
TCM symptom score of 5.38±3.90 and the placebo group had a score of 7.02±4.00. The TCM symptom score differed slightly between the 2 groups (p = 0.020).

On the first day of hospitalization, the WBC count, the NLR, the level of CRP, and the level of PCT differed significantly between the 2 groups (10.01(7.57,14.85) vs 8.57(7.50,10.62), 7.46(4.59,14.20) vs 7.18(3.82,10.96), 106.5(28.5,160.0) vs 83.0(25.0,138), 0.31(0.07,8.27) vs 0.41(0.09,5.19, all p>0.05). On the seventh day of hospitalization, the level of CRP and the NLR differed significantly between the 2 groups (p=0.009 and p=0.001).

As shown in Table 5, mortality at 28 days was 3.03% (2/66) in the combination group and 7.93%(6/63) in the single antibiotics group. Mortality at 28 days did not differ significantly between the 2 groups (p=0.40) according to Per-protocol analysis. The healing rate ((cured patients + responders) / total patients × 100%) differed significantly between the 2 groups (75.7% vs 41.2%, p<0.01) (Table 6).

The adverse events were also analyzed. In the single antibiotics group, 2 patients had diarrhea. There is no adverse events occur in the combination group.

4. Discussion

TCM has been used for thousands of years in China for treating pneumonia, and it is widely used in many countries. Evidence from both clinicians and patients suggests that TCM may improve sepsis survival rates. However, the available evidence has been derived from only a few small randomized controlled trials.

Some studies have shown that TCM may have a beneficial effect on patients with CAP, including those with severe pneumonia (26). In these patients, reviews show that TCM may reduce either length of hospital stay or mortality without causing complications(27). However, insufficient data on sepsis are available, and the treatment in some studies was not according to syndrome differentiation. In view of these findings, a large prospective and adequately powered trial should conclusively
determine the risks and benefits of adding TCM according to syndrome differentiation to the treatment of patients with sepsis.

Results of *in vitro* antibacterial testing indicated that SFJDC is a broad-spectrum antibacterial (28). In addition, a study indicated that SFJDC can effectively reduce mortality due to *Staphylococcus aureus* and beta-hemolytic streptococcal infections in mice, increase average survival time, and improve outcomes in experiments *in vivo* (29). A recent study further verified that various components of SFJDC alleviate extracellular signal-regulated protein kinases (ERKs) and p21-activated kinase (PAK) induced in an upper respiratory tract infection via multiple targets (30). Phosphorylation might be a key event regulated specifically by verbenalin, phillyrin, and emodin.

In the current trial, improvement in the APACHE II score served as the primary outcome. The APACHE II score is the most widely used and authoritative system with which to assess critical illness. In general, this risk rating precisely reflects the severity of illness, which means a higher score corresponds to more severe disease and a higher risk of death. According to a previous study, the APACHE II score had better calibration and discrimination than several other scoring systems when determining the prognosis for critically ill patients (31). The secondary outcomes in the current trial included several severity-of-illness scoring systems, such as the SOFA score, the TCM symptom score, and 28-day mortality. These systems reflect patient status from different perspectives and are predictive of patient mortality. Consequently, the current trial used indices to reflect patient status and to determine the significance of therapy. In this trial, the combination group had a significantly lower APACHE II score, a significantly lower healing rate, a significantly lower level of serum CRP, and a significantly lower NLR. This indicates that combination therapy may improve prognosis for septic patients.

**Strengths** This is the first randomized controlled trial of a combination of antibiotics and SFJDC to treat sepsis and was designed with reference to previous studies. Patient interests were protected by obtaining ethical approval and written informed consent and by monitoring AEs. Several scoring systems served as primary
and secondary outcomes with which to evaluate efficacy in the combination group. Throughout the trial, safety outcomes were closely monitored to avoid AEs.

*Limitations* Inflammatory factors and Immune parameters contributing to sepsis need to be analyzed at different times to ascertain the possible mechanism by which SFJDC alleviates sepsis. The results of this trial may be valid only for the specific type, dose, and duration of TCM studied. This study is powered for APACHE II score, but not for related mechanism of action. More in vitro experiments will be needed to study related pathways.

5. Conclusion

A combination of antibiotics and SFJDC in the treatment of sepsis is superior to routine antibiotic treatment since combination therapy reduces the inflammatory response and improves prognosis for septic patients. If the primary outcome was SOFA, this study cannot be said to be successful.

Ethics approval and consent to participate

This trial was approved by the Ethics Board of Xinhua Hospital and all patients provided written, informed consent (XHEC-C-2016-010-2).

Author’s contributions

YQL and AHF conceived, designed, and wrote the paper. YY and HD conducted clinical data collect. All authors read and approved the final manuscript.

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Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to the laboratory policies but are available from the corresponding author on reasonable request.

References


[2]. Ishii K, Hamamoto H and Sekimizu K,Studies of host-pathogen interactions and


[10]. Tang Q, Song PP, Li JJ, Kong FL, Sun L and Xu LZ, Control of antibiotic


Figure 1 Study flow chart

Assessed for eligibility (n=215)

Excluded (n=65)
- Does not meet inclusion criteria (n=40)
- Meets exclusion criteria (n=25)

Randomized (n=150)

SSIDC group (n=75)
- Withdraw from the trial because of the patient’s refusal (n=1)
- Analyzed (n=66)

Placebo group (n=75)
- Died at 3rd day (n=4)
- Withdraw from the trial because of the patient’s refusal (n=1)
- Analyzed (n=63)
<table>
<thead>
<tr>
<th>Demographics</th>
<th>The SFJDC group (n=66)</th>
<th>The placebo group (n=63)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – mean years (SD)</td>
<td>66.23±16.63</td>
<td>67.98±13.88</td>
<td>0.310</td>
</tr>
<tr>
<td>Sex –male /female</td>
<td>34/32</td>
<td>38/25</td>
<td>0.314</td>
</tr>
<tr>
<td>Co-morbidities – No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>30.3%</td>
<td>30.2%</td>
<td>0.986</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45.5%</td>
<td>50.8%</td>
<td>0.544</td>
</tr>
<tr>
<td>Diabetes</td>
<td>22.7%</td>
<td>30.2%</td>
<td>0.338</td>
</tr>
<tr>
<td>Laboratory values at enrollment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood count (x10^9)</td>
<td>12.02±10.56</td>
<td>9.81±5.02</td>
<td>0.134</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>116.89±18.07</td>
<td>118.78±19.08</td>
<td>0.566</td>
</tr>
<tr>
<td>Platelet (x10^12)</td>
<td>159.00(113.00,196.25)</td>
<td>165.00(126.00,208.00)</td>
<td>0.523</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>91.47±83.34</td>
<td>90.98±73.03</td>
<td>0.972</td>
</tr>
<tr>
<td></td>
<td>32.0(13.0,49.5)</td>
<td>22.0(14.0,43.0)</td>
<td>0.272</td>
</tr>
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</table>
TABLE 2. Comparison of antibiotic use between SFJDC and placebo groups

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>B+C</th>
<th>C+D</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>SFJDC</td>
<td>14</td>
<td>12</td>
<td>21</td>
<td>8</td>
<td>7</td>
<td>4</td>
<td>0.943</td>
</tr>
<tr>
<td>Placebo</td>
<td>12</td>
<td>8</td>
<td>24</td>
<td>7</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

A: Carbapenems       B: Cephalosporins
C: Respiratory quinolones  D: Enzyme inhibitors

The number indicate the number of patients using a certain antibiotics.
<table>
<thead>
<tr>
<th>Groups</th>
<th>Source of infection</th>
<th>SUM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intestinal tract</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinary tract</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liver abscess</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>SFJDC</td>
<td></td>
<td>129</td>
<td>0.611</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>63</td>
<td></td>
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<tr>
<td>SUM</td>
<td></td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>D0</td>
<td>P0</td>
<td>D7</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-------------</td>
<td>------------</td>
<td>-------------</td>
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<tr>
<td><strong>The primary outcome</strong> (mean±sd)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE II</td>
<td>SFJDC</td>
<td>12.18±5.11</td>
<td>0.627</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>12.67±6.18</td>
<td>7.02±3.73</td>
</tr>
<tr>
<td><strong>The secondary outcomes</strong> (mean±sd)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFA</td>
<td>SFJDC</td>
<td>3.09±1.72</td>
<td>0.546</td>
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<td>Placebo</td>
<td>2.92±1.46</td>
<td>1.29±1.21</td>
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<tr>
<td>TCM symptom score</td>
<td>SFJDC</td>
<td>13.73±5.73</td>
<td>0.431</td>
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<tr>
<td></td>
<td>Placebo</td>
<td>14.56±6.18</td>
<td>7.02±4.00</td>
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<tr>
<td><strong>The additional outcomes</strong> P50(P25,P75)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PCT(ng/ml)</td>
<td>SFJDC</td>
<td>0.31(0.07,8.27)</td>
<td>0.761</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>0.41(0.09,5.19)</td>
<td>0.12(0.05,0.41)</td>
</tr>
<tr>
<td>CRP(mg/l)</td>
<td>SFJDC</td>
<td>106.5(28.5,160.0)</td>
<td>0.208</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>83.0(25.0,138)</td>
<td>21.0(13.0,43.0)</td>
</tr>
<tr>
<td>WBC(10^9/l)</td>
<td>SFJDC</td>
<td>10.01(7.57,14.85)</td>
<td>0.091</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>8.57(7.50,10.62)</td>
<td>7.00(5.70,10.20)</td>
</tr>
<tr>
<td>NLR</td>
<td>SFJDC</td>
<td>7.46(4.59,14.20)</td>
<td>0.471</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>7.18(3.82,10.96)</td>
<td>2.51(1.77,4.44)</td>
</tr>
</tbody>
</table>
TABLE 5. Comparison of SFJDC and placebo - 28-day mortality

<table>
<thead>
<tr>
<th>Groups</th>
<th>Numbers (n)</th>
<th>Survival (n)</th>
<th>Death (n)</th>
<th>28-day mortality (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFJDC</td>
<td>66</td>
<td>64</td>
<td>2</td>
<td>3.03</td>
<td>0.400</td>
</tr>
<tr>
<td>Placebo</td>
<td>63</td>
<td>58</td>
<td>5</td>
<td>7.93</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 6. Comparison of SFJDC and placebo healing rates

<table>
<thead>
<tr>
<th>Groups</th>
<th>Cure (n)</th>
<th>Effective (n)</th>
<th>Better (n)</th>
<th>Invalid (n)</th>
<th>SUM (n)</th>
<th>Healing rate (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFJDC</td>
<td>20</td>
<td>30</td>
<td>11</td>
<td>5</td>
<td>66</td>
<td>75.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Placebo</td>
<td>6</td>
<td>20</td>
<td>28</td>
<td>9</td>
<td>63</td>
<td>41.2</td>
<td></td>
</tr>
</tbody>
</table>

Cure: \((\text{TCM symptom score(D7)} - \text{TCM symptom score(D0)}) / \text{TCM symptom score(D0)} \times 100\% \geq 70\%

Effective: \(\geq 50\% \text{ and } < 70\%\)  
Better: \(> 0 \text{ and } < 50\%\)  
Invalid: \(< 0\)

healing rate = \((\text{cured cases + effective cases}) / \text{total cases} \times 100\%\)