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Chinese Medicine for Inflammatory Coagulation in Sepsis

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Abstract: With the improvement of medical technology and level, more and more research on sepsis malefactors, the diagnosis and treatment of the disease are now more accurate and perfect with the gradual deepening of people's understanding of the disease, Western medicine has its own standards and norms of treatment, but also has its limitations and shortcomings, therefore, the search for new treatment methods is imperative, Chinese medicine as the traditional medicine of the motherland, in the process of inheritance of continuous innovation As a traditional medicine of the motherland, TCM is constantly innovating in the process of transmission, giving TCM an understanding of new diseases and proposing treatment options. The main objective of this paper is to analyse research related to the treatment of inflammatory coagulation caused by sepsis in Chinese medicine. It is found that the early stage of sepsis is characterised by more evidence of solid heat, which should be treated from the perspective of clearing heat and detoxifying the blood, cooling the blood and nourishing the yin, so as to interrupt the disease in a timely manner and avoid the emergence of severe symptoms of sepsis such as deficiency and decompensation. The study of TCM theory has provided new ideas and methods to be tried for the clinical adjunctive treatment of sepsis in TCM. From time to time, clinicians, especially TCM clinicians, use herbs, herbal injections or TCM external treatments as adjuncts in the treatment of sepsis. With the gradual development of basic and clinical applications of TCM in the treatment of sepsis, TCM has become more and more effective in improving coagulation disorders and coping with inflammatory reactions.

1. Introduction

Sepsis is a critical condition with high morbidity, mortality and disability, and is one of the leading causes of death in the ICU. Modern medical research into the mechanisms of sepsis has progressed from inflammation and coagulation to immunity and metabolism, and treatment measures have been improved and advanced. Western medical treatment of sepsis is currently at a relative bottleneck, and the widespread use of antibiotics has led to widespread drug resistance, making the treatment of sepsis increasingly difficult. Chinese medicine has made many useful discoveries in this area and has shown good promise, such as enhancing antibacterial efficacy and reducing drug resistance, enhancing immunity and regulating immune disorders [1-2].

In a related study, Priti et al. mentioned that sepsis is considered the most determinant condition for infant mortality, but has never been considered for mortality prediction [3]. Therefore, a state-of-the-art deep neural model was deployed and a comparative analysis of machine learning models was performed to predict infant mortality based on the most important features, including sepsis. In addition, interpretable artificial intelligence models such as Dalex and Lime were deployed in order to assess the predictive reliability of the black-box deep neural model. This will help non-technical people such as doctors and practitioners to understand and make decisions accordingly.Redwan et al. designed non-invasive, deep learning classification models for accurate and effective prediction of early sepsis in neonates in neonatal intensive care units [4]. By being non-invasive, this means that no external instruments or foreign objects are introduced when collecting data for the classifier. Furthermore, the data collected for predicting and classifying patients with neonatal sepsis is structured data in tabular form. The proposed deep learning classification model is designed to process time series, sequence or image data.

The incidence and mortality of sepsis continues to increase year by year, drawing the attention of many medical practitioners. In recent years, there have been many clinical and experimental studies related to sepsis, but the complete pathogenesis and pathological evolution of sepsis has not been explored so far [5-6]. In this paper, we analyse the distribution characteristics of TCM evidence patterns in ICU patients with sepsis, explore the relationship between different TCM evidence patterns in sepsis and general clinical data, physiological and biochemical indicators and prognosis, further evaluate the efficacy of specific indicators on the diagnosis and prognosis of TCM evidence patterns, and provide theoretical basis and objective guidance for TCM identification and treatment of sepsis, with a view to improving the prognosis of sepsis.

2. Design Research

2.1 Study Population

(1) Source of cases

In this study, 98 cases were included in the Chinese medicine clinical pathway for sepsis in ICU ward of Hospital A for six months. 94 cases were finally included according to the inclusion and exclusion criteria.

(2) Diagnostic criteria

The diagnostic criteria for the TCM evidence of sepsis[7-8] are shown in Table 1.

(3) Inclusion criteria

1) Meeting the Chinese and Western medical diagnostic criteria for sepsis.

2) Age >18 years.

(4) Exclusion criteria

1) End-stage malignancy.

2) autoimmune diseases or long-term use of immunosuppressive drugs.

3) pregnant or lactating women.

(5) Exclusion criteria

1) Death within 24 hours.

2) Those with incomplete clinical data.

Table 1. Diagnostic criteria for Chinese medical evidence of sepsis

	Main symptoms	Secondary symptoms
Toxic-Heat Evidence	Persistent high fever, irritability, red or reddish-red tongue, counted pulse	Dizziness, redness of the face and eyes, dryness of the mouth and desire to drink, yellowish phlegm, nausea and vomiting, constipation, short and red urine
Blood Stasis	High fever, stabbing pains, blood away from the menstruum, subcutaneous petechiae, blood stasis in the veins, symptoms of stagnation, purple and dull tongue or petechiae, astringent or no pulse	dizziness or seizure or amnesia, skin and nail disorders, numbness or hemiparesis of the limbs, abnormal local sensation, history of trauma, surgery, abortion
Internal Qi blockage	abdominal distention and fullness, abdominal pain, yellowish coating on the tongue, stringent pulse	No bowel movements, diminished or absent bowel sounds, vomiting or feeling relieved after getting gas
Acute deficiency	confusion, cold sweat or sweating like oil, cold extremities or fever, pale face or flushed face, pale tongue with moist coating or red tongue without fluid, weak pulse or thin and rapid pulse	Eyes closed, mouth open, hand urination, short voice, sunken orbits, skin folds, little or no urination
Note: The diagnosis is made when 2 main symptoms or 1 main symptom + 2 secondary symptoms are met.		

2.2 Analysis of Chinese Medicine Evidence Patterns

In this study, we found that blood stasis evidence and acute deficiency evidence were more common in 94 sepsis patients in the ICU ward, with blood stasis evidence > acute deficiency evidence > internal qi obstruction evidence > toxic heat evidence [9-10]. When analysing the differences in the findings, the source of the cases was considered to be the main reason for the differences in the distribution of the evidence patterns. Most of the sepsis cases in the emergency department were characterised by high fever, but at this time the positive energy was still present and the condition was not critical, despite the intense struggle between evil and positive, so toxic-heat evidence was the main type of evidence and acute deficiency evidence was rare. In contrast, sepsis cases in the ICU are generally more severe, and in addition to high fever, they usually show signs of dizziness, delirium or even deficiency, and heat often enters the Ying-Blood component, which explains why most of the cases in the ICU are characterized by the Ying-Blood component or blood stasis. In addition to the departmental influence and the natural progression of the disease as described above, the distribution of evidence in this study may also be related to the fact that more of the cases included had an underlying history of cerebrovascular disease, which led to the prevalence of blood stasis. However, when all the above studies are combined, the consistent conclusion is that sepsis is more often associated with the Ying-Blood subtype.

Therefore, rigorous inclusion of larger samples and standardization of evidence patterns are needed to provide more reliable evidence-based evidence regarding the distribution pattern of TCM evidence patterns in sepsis [11-12].

2.3 Pathogenesis of Sepsis

Modern medical research has advanced the understanding of sepsis from the cellular, molecular and metabolic levels, but the mechanisms are complex and still unclear, mainly involving key aspects such as inflammatory imbalance, immune dysregulation and coagulation disorders, which in turn interact with each other in a cascade response that subsequently leads to a series of organ dysfunctions [13-14].

(1) Inflammatory imbalance

Infection is an important pathophysiological basis for sepsis. The early inflammatory response is a protective immune response, immediately followed by the activation of a compensatory anti-inflammatory response, where the release of anti-inflammatory cytokines (e.g. IL-10) will suppress IL-6 and interferon gamma and stimulate the production of TNF and IL-1 antagonists to neutralise TNF-α and IL-1.

When the anti-inflammatory response is excessive, inflammatory mediators such as neutrophils activate the oxidative stress response and a large number of ROS (e.g. hydroxyl radicals, NO, etc.) are released, damaging cellular proteins, lipids and DNA, and impairing mitochondrial function, which leads to cellular energy failure and apoptosis. At the same time, the damaged cells release endogenous molecules (e.g. ATP, mitochondrial DNA, HMGB1), which stimulate immune cells to release IL-1β and IL-18 through damage-associated molecular patterns (DAMP), leading to a stronger inflammatory response and programmed cell death.

(2) Immune dysregulation

Sepsis is a death race between the pathogen and the host immune response in search of their respective strengths. Early death is mainly due to an excessive inflammatory response, a 'cytokine storm', while later death is mainly due to ongoing immunosuppression and opportunistic infections. Apoptosis-induced depletion of immune cells is one of the main mechanisms of immune dysregulation in sepsis. However, there is no consensus on exactly how apoptosis occurs. Some theoretical studies suggest that cytokines are the driving factors, with pro-inflammatory cytokines such as TNF-α and HMGB1 regulating apoptosis by directly regulating the signalling activity of the protease caspase-8 to induce cell death, and the release of anti-inflammatory cytokines such as IL-10 and TGF-β accelerating apoptosis. The process of apoptosis results in massive loss of immune cells, a decline in cell numbers and function, and ultimately a severely impaired innate and adaptive immune response.

(3) Coagulation disorders

It has been clinically found that nearly half of sepsis patients with combined coagulation disorders develop DIC. coagulation disorders in sepsis are mainly manifested by: 1) procoagulant activation: in response to inflammatory stimuli, large amounts of tissue factor are released and exogenous coagulation pathways are initiated. In addition the formation of neutrophil extracellular networks (NETs) stimulated by inflammation not only accelerates thrombus formation but also promotes platelet activation, adhesion, aggregation and formation of platelet thrombi. 2) Impaired anticoagulation: the activated procoagulant response causes massive depletion of anticoagulant factors and a decrease in antithrombin levels. 3) Fibrinolysis inhibition: massive release of thrombin inhibits fibrinolysis, fibrinolytic inhibitors are activated, and a decrease in fibrinogen (3) Fibrinolysis inhibition: massive release of thrombin inhibits fibrinolysis, fibrin inhibitors are activated, and reduced fibrinogen levels also lead to reduced fibrinolytic activity.

(4) Endothelial damage and microcirculatory disorders

The endothelium is the primary target of endotoxin attack. On the one hand, damaged endothelial cells activate inflammatory coagulation pathways, triggering coagulation dysfunction and the formation of microthrombi, resulting in microcirculatory disorders and local tissue ischemia and hypoxia; on the other hand, inflammatory storms cause disruption of intercellular junctions in the vascular endothelium, degradation of the glycocalyx, destruction of endothelial barrier function and increased permeability, resulting in capillary leakage and inadequate tissue perfusion, exacerbating organ dysfunction.

3. Experimental Study

3.1 Study Protocol

With the aid of the electronic medical record system and the case room of Hospital A, a retrospective study was conducted to collect 98 cases from the ICU ward of Hospital A that were included in the TCM clinical pathway for sepsis in six months. 94 cases were finally included according to the inclusion and exclusion criteria. The TCM clinical pathway form for sepsis was administered by 2 TCM physicians with the title of attending or above in the ICU, who registered and completed detailed and standardised information records of the four TCM consultations and evidence-based diagnosis on the day of patient admission. General clinical data, physiological and biochemical indicators (based on the worst value within 24 hours of sepsis diagnosis), prognosis (based on survival at 28 days) and SOFA and APACHEII scores were collected accordingly and all data collected were recorded on the case data collection form. Finally, the distribution of TCM evidence types in sepsis and the relationship between different TCM evidence types and general clinical data, physiological and biochemical indicators and prognosis were analysed with the help of SPSS software, and the diagnostic efficacy of the evidence types and prognostic efficacy of the special indicators were assessed.

The general clinical data included age, gender, previous medical history and site of infection, while the physiological and biochemical indicators included inflammatory indicators (WBC, N, PCT), coagulation indicators (PLT, D-D, FIB, APTT, PT) and blood gas indicators (PH, Lac, K, Na). The blood gas indicators were obtained from the fully automated blood gas analyser in the ICU unit, while the others were obtained from the laboratory department of Hospital A.

The technical roadmap is shown in Figure 1.

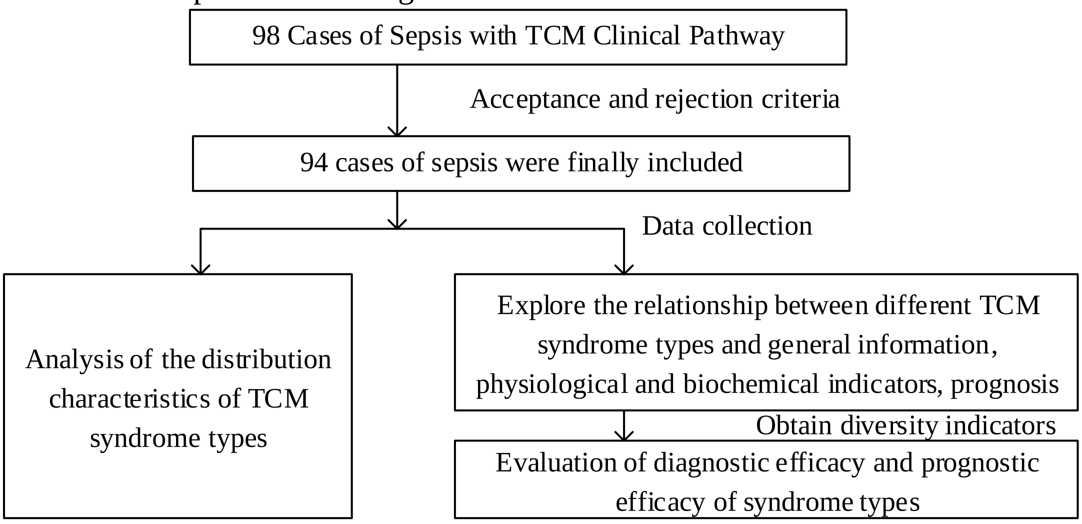

Figure 1. Technical roadmap

3.2 Logistic Regression

Given a data set $\{x_i,y_i|y_i\in\{0,1\},i=1,\ldots,n\}$, there are $X\beta = \sum_{i=1}^{n} x_i^T\beta$, where $x_i\in R^s$,β belongs to

R^s.

First construct the hypothesis function $h_\beta(x)$.

$$P(y=1|x;\beta)=h_\beta(x)=\frac{1}{1+\exp(-x_i^T\beta)}=p \quad (2)$$

Which $g(z)=\frac{1}{1+\exp(-z)}$ is called a logistic function (or a sigmoid function).

The graph of the function g(z) in two dimensions looks like an uppercase letter "S". As z increases, the function g(z) increases slowly, then rapidly, then begins to decelerate gradually, and finally expands again, but not beyond 1. Note that g(z) tends to 1 as z → +∞ and to 0 as z → -∞. Thus, the exponential function g(z) and the exponential function hβ(x) take values between 0 and 1.

Given the data set $\{x_i,y_i|y_i\in\{0,1\},i=1,\ldots,n\}$, let $h_\beta(x)$ denote the conditional probability p when y =1 , then we have

$$P(y=1|x;\beta)=h_\beta(x)=\frac{1}{1+\exp(-x_i^T\beta)}=p \quad (2)$$

Correspondingly, there are

$$P(y=0|x;\beta)=1-h_\beta(x)=1-p \quad (3)$$

In summary, $X \in R^{n\times p}$ and the class label Y ∈ Rn (yi ∈ {0,1}) obeys the Bernoulli distribution, i.e., Y ~ B(1,p).

Combining equations (2) and (3), a logistic regression model can be obtained as follows.

$$P(y|x;\beta)=p^y(1-p)^{(1-y)} \quad (4)$$

where P(y|x;β) denotes the conditional probability that for a given sample x belongs to class y. β denotes the parameter vector of the variable.

4. Experiment Analysis

4.1 Multi-Factor Regression Analysis

Statistically significant data from the univariate analysis were included in a logistic regression model for multi-factor analysis, the results of which are shown in Table 2 below.

Table 2. Risk factors of sepsis associated thrombocytopenia by multivariate logistic regression analysis

Independent variables	Regression coefficient	Standard Error	Wals	OR value	P
Lactate	0.125	0.082	2.292	1.133	0.13
APACHE II score	0.106	0.048	4.778	1.111	0.029
Albumin minimum	-0.251	0.076	10.932	0.778	0.001
Age > 65 years	1.362	0.594	5.258	3.905	0.022

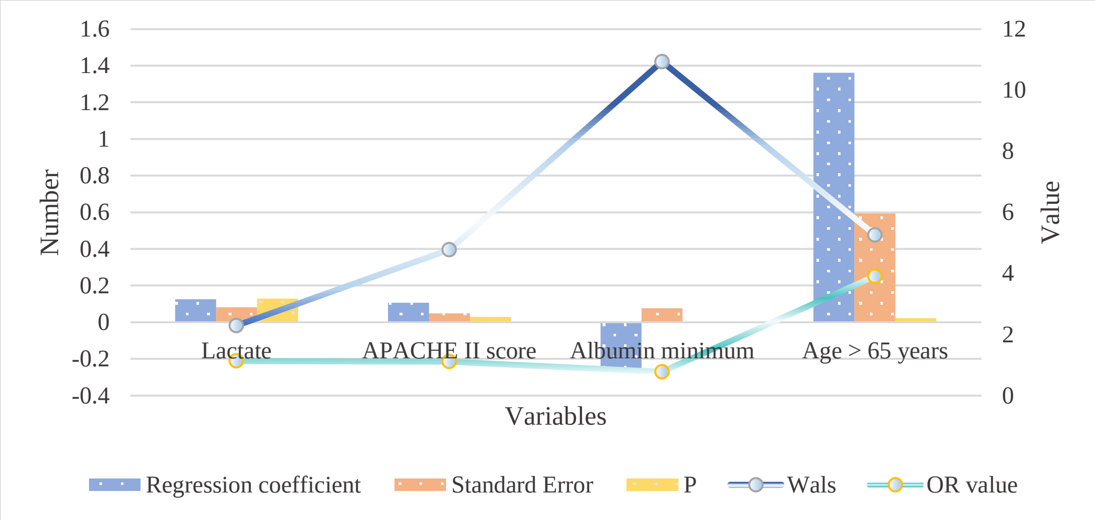

Figure 2. Risk factors analysis of sepsis associated thrombocytopenia by multifactor logistic regression analysis

As can be seen from Figure 2, elevated APACHE II scores, reduced serum albumin concentrations and age >65 years are independent risk factors for the development of thrombocytopenia in patients with sepsis.

4.2 Relationship between Evidence Type and Inflammatory Indicators

See Table 3 for details.

Table 3. Comparison of different TCM syndrome types and inflammation indexes (X ±S)

Chinese Medicine Evidence	WBC(g/L)	N(g/L)	PCT(ng/ml)
Toxic-Heat Evidence	14.75±4.97	13.18±5.00	11.56±13.33*
Internal Qi blockage	19.60±7.96	18.37±7.67	34.20±30.83
Acute deficiency	16.46±12.00	14.94±11.55	9.06±18.61*
Blood stasis	16.06±8.20	13.39±7.39	10.93±17.69*
F-value	0.543	0.849	3.496
P-value	0.656	0.475	0.023

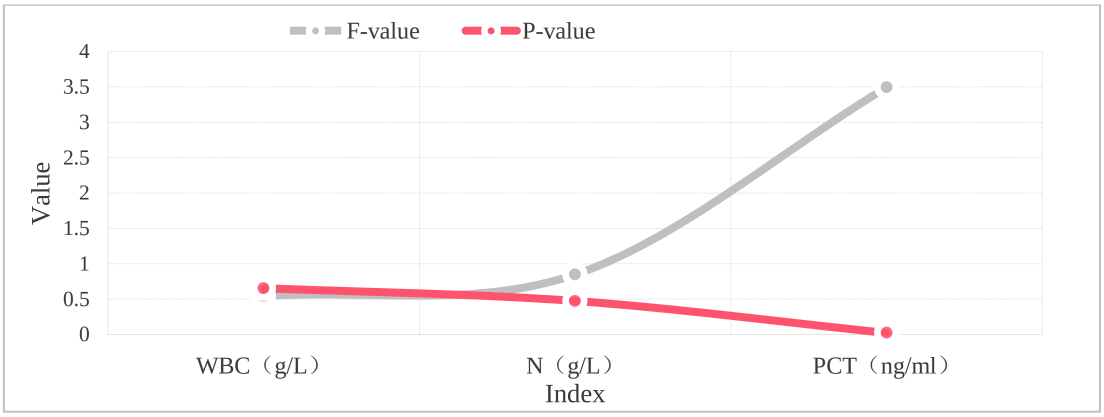

Figure 3. Comparison and analysis of different TCM syndrome types and inflammation indexes

The comparison of TCM evidence types and inflammatory markers in Figure 3 shows that the group with evidence of internal Qi blockage had higher WBC, N and PCT values. One-way ANOVA showed no statistical difference between the type of Chinese medicine indication and WBC and N (P>0.05) and a statistically significant difference with PCT (P<0.05).

4.3 Relationship between Evidence Type and Coagulation Index

The comparison of coagulation indicators among the four groups of TCM evidence types is shown in Table 4 below.

Table 4. Comparison of different TCM syndrome types and coagulation indexes (X ±S)

	PLT(g/L)	D-D(mg/L)	FIB(g/L)	APTT(s)	PT(s)
Toxic-Heat Evidence	202.10±87.45	2.81±1.22*	3.96±0.83	32.69±6.00	15.13±4.25
Internal Qi blockage	166.80±104.41	4.24±2.85*	3.73±1.08	31.19±5.65	14.77±2.56
Acute deficiency	153.00±70.44	5.90±4.78*	3.80±1.31	34.81±11.46	17.02±5.26
Blood stasis	171.43±69.65	8.93±4.20	4.02±1.58	37.56±7.15	18.14±15.51
F-value	0.694	6.086	0.128	1.294	0.350
P-value	0.561	0.020	0.943	0.289	0.789

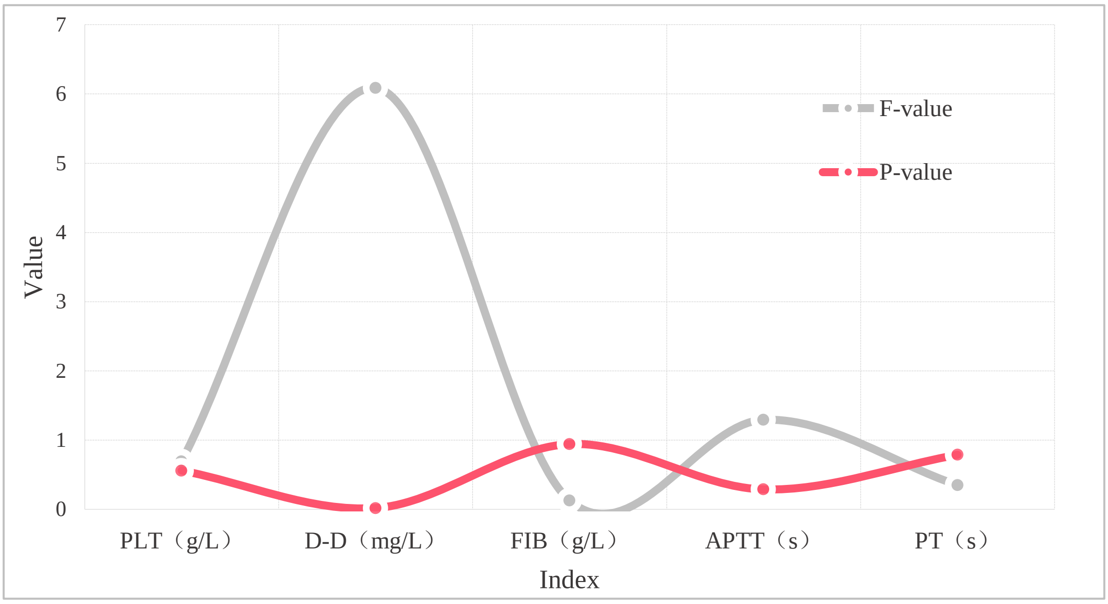

Figure 4. Comparison and analysis of different TCM syndrome types and coagulation indexes

According to the comparison in Figure 4, the distribution of PLT is still in the normal range (100-350g/L), and there is no statistically significant difference between syndrome types (P>0.05). D-D, FIB, APTT and PT were all highest in blood stasis. The differences in FIB, APTT and PT were not statistically significant (P>0.05). There was a significant difference between Blood Stasis, Toxic-Heat, Internal Qi and Acute Deficiency (P < 0.05), while the differences between the other evidence types were not statistically significant.

5. Conclusion

The core of Chinese medicine is the identification and treatment of evidence, and clinicians are plagued by the problem of how to accurately identify evidence in the special environment of the

ICU, and how to correctly guide the theory and prescription of medicine in cases where the evidence is complex and intertwined. In ICU wards, patients are often sedated, intubated, or intravenous, and a series of resuscitation measures may overshadow or interfere with the accurate acquisition of information from the four diagnoses, resulting in inaccurate identification of evidence and thus affecting the effectiveness of TCM treatment. However, in the ICU, timely and comprehensive monitoring and care is superior to that in the general ward, assisting clinicians to quickly obtain physical and chemical indicators to clarify diagnosis and guide treatment. Therefore, how to make clinical physicochemical data assist in TCM diagnosis and make TCM diagnosis of sepsis more objective, accurate and effective. Based on the above summary and considerations, this study analyses the distribution of TCM evidence patterns in ICU patients with sepsis in the context of TCM evidence, and investigates the relationship between TCM evidence patterns and clinical data, physicochemical indicators and prognosis by using general clinical data and physiological and biochemical indicators that can be quickly obtained, and then evaluates the effectiveness of specific indicators for the diagnosis of TCM evidence patterns and prognosis, with a view to providing objective TCM evidence patterns for sepsis. The aim is to provide a reference for the objectivity of TCM diagnosis of sepsis, so as to guide accurate and effective TCM treatment.

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Data Availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Conflict of Interest

The author states that this article has no conflict of interest.

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