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Determination of Primary and Secondary Symptoms of Common Syndromes in Sepsis Based on Clinical Investigation and Expert Questionnaire: A Postprint

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Abstract

Background Sepsis is a major cause of death and critical illness worldwide, and Traditional Chinese Medicine (TCM) has certain advantages in the prevention and treatment of sepsis. On the premise of identifying the common pattern types of sepsis, further establishing their primary and secondary symptoms can provide a basis for the establishment of diagnostic criteria for sepsis pattern types.

Objective To investigate the primary and secondary symptoms of common pattern types of sepsis through clinical surveys and expert questionnaires, so as to provide a basis for the establishment of TCM pattern-type diagnostic criteria for sepsis.

Methods A total of 1,082 sepsis patients hospitalized in the Intensive Care Units (ICU) of eight hospitals nationwide—including the First Affiliated Hospital of Henan University of Chinese Medicine, the First Affiliated Hospital of Zhengzhou University, Guang' anmen Hospital of China Academy of Chinese Medical Sciences, Henan Provincial People' s Hospital, Zhengzhou First People' s Hospital, Hainan Provincial Hospital of Traditional Chinese Medicine, Puyang Hospital of Traditional Chinese Medicine, and the First Affiliated Hospital of Guangzhou University of Chinese Medicine—from May 2021 to August 2022 were selected. Their clinical data were collected and a database was established. Descriptive statistics, Logistic regression, and artificial neural network analysis were employed to analyze the symptoms of common sepsis pattern types and determine primary and secondary symptoms. Based on the clinical survey, the Delphi method was used to conduct expert questionnaire surveys to further determine the primary and secondary symptoms of common pattern types.

Results Based on clinical surveys and expert questionnaires, and integrating the results of statistical analysis, data mining, and the Delphi method, the primary and secondary symptoms of common sepsis pattern types were identified according to the principles for determining primary and secondary symptoms of common pattern types, combined with clinical practice, and after group discussion. For the pattern of phlegm-heat obstructing the lung, the primary symptoms include cough, profuse sputum, and yellow sputum color, while secondary symptoms include fever, thirst, and chest tightness. For the pattern of blazing heat-toxin, the primary symptoms include high fever, restlessness, and rapid breathing, while secondary symptoms include delirium, red tongue body, and burnt-yellow tongue coating. For the pattern of Yangming bowel excess, the primary symptoms include delirium, abdominal pain, and epigastric fullness, while secondary symptoms include tidal fever, thirst, and restlessness. For the pattern of static blood-toxin obstructing (damaging) the collaterals, the primary symptoms include dark purple nails, cyanotic lips, and dark-red or purplish tongue, while secondary symptoms include delirium, high fever, and stabbing pain in the chest and hypochondria. For the pattern of lung qi deficiency, the primary symptoms include cough, clear thin sputum, and white sputum color, while secondary symptoms include mental fatigue, weakness, and spontaneous sweating. For the pattern of yin deficiency with internal heat, the primary symptoms include dry cough, dry throat, and restlessness, while secondary symptoms include rapid breathing, thirst, and dry mouth. For the pattern of dual deficiency of qi and blood, the primary symptoms include mental fatigue, weakness, and dizziness, while secondary symptoms include listlessness, somnolence, and reluctance to speak due to qi deficiency. For the pattern of exhausted yin and collapsed yang, the primary symptoms include loss of consciousness, restlessness, and rapid breathing, while secondary symptoms include open-mouth breathing with raised shoulders, somnolence, and red tongue body.

Conclusion Identifying the primary and secondary symptoms of the eight common pattern types of sepsis—phlegm-heat obstructing the lung, blazing heat-toxin, Yangming bowel excess, static blood-toxin obstructing (damaging) the collaterals, lung qi deficiency, yin deficiency with internal heat, dual deficiency of qi and blood, and exhausted yin and collapsed yang—can provide a basis for the establishment of pattern-type diagnostic criteria.

Full Text

Determination of Primary and Minor Symptoms of Common Traditional Chinese Medicine Syndromes in Sepsis Based on Clinical Investigation Combined with Expert Questionnaires

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Abstract

Background: Sepsis is the leading cause of death and critical illness worldwide, and traditional Chinese medicine (TCM) demonstrates certain advantages in preventing and treating sepsis. Establishing primary and secondary symptoms for common sepsis syndromes, on the premise of clarifying these patterns, can provide a basis for developing diagnostic criteria for sepsis syndromes.

Objective: To explore the primary and minor symptoms of common syndromes in sepsis through clinical investigation and expert questionnaires, providing a basis for establishing TCM syndrome diagnostic criteria for sepsis.

Methods: A total of 1,082 sepsis patients admitted to intensive care units (ICUs) at eight hospitals nationwide—including the First Affiliated Hospital of Henan University of Chinese Medicine, First Affiliated Hospital of Zhengzhou University, Guang' anmen Hospital of China Academy of Chinese Medical Sciences, Henan Provincial People's Hospital, First People's Hospital of Zhengzhou, Hainan Traditional Chinese Medicine Hospital, Puyang Traditional Chinese Medicine Hospital, and First Affiliated Hospital of Guangzhou University of Chinese Medicine—were enrolled from May 2021 to August 2022. Clinical data were collected and a database was established. Descriptive statistics, logistic regression, and artificial neural network analysis were employed to analyze symptoms of common sepsis syndromes and determine primary and minor symptoms. Based on clinical investigation, an expert questionnaire survey using the Delphi method was conducted to further determine the primary and minor symptoms of common syndromes.

Results: Based on clinical investigation and expert questionnaires, integrating statistical analysis, data mining, and Delphi method results, and following the principles for determining primary and minor symptoms of common syndromes combined with clinical reality, the primary and minor symptoms of common sepsis syndromes were clarified through group discussion. For Phlegm-Heat Obstructing the Lung syndrome, primary symptoms included cough, excessive sputum, and yellow sputum color, while minor symptoms included fever, thirst, and chest tightness. For Intense Exuberant Heat-Toxin syndrome, primary symptoms included high fever, irritability, and shortness of breath, while minor symptoms included delirium, red tongue, and burnt yellow coating. For Yangming Fu-Organ Excess syndrome, primary symptoms included delirium, abdominal

pain, and epigastric fullness, while minor symptoms included tidal fever, thirst, and irritability. For Blood Stasis and Toxin Obstructing (Damaging) Collaterals syndrome, primary symptoms included purple-dark nails, cyanotic lips, and dark red or purple tongue, while minor symptoms included delirium, high fever, and stabbing pain in chest and hypochondrium. For Lung Qi Deficiency syndrome, primary symptoms included cough, thin clear sputum, and white sputum color, while minor symptoms included fatigue, weakness, and spontaneous sweating. For Yin Deficiency with Internal Heat syndrome, primary symptoms included dry cough, dry throat, and irritability, while minor symptoms included shortness of breath, thirst, and dry mouth. For Qi and Blood Deficiency syndrome, primary symptoms included fatigue, weakness, and dizziness, while minor symptoms included mental lethargy, somnolence, and lack of qi with reluctance to speak. For Yin Exhaustion and Yang Collapse syndrome, primary symptoms included loss of consciousness, irritability, and shortness of breath, while minor symptoms included mouth opening with shoulder lifting, somnolence, and red tongue.

Conclusion: This study clarifies the primary and minor symptoms of eight common sepsis syndromes: Phlegm-Heat Obstructing the Lung, Intense Exuberant Heat-Toxin, Yangming Fu-Organ Excess, Blood Stasis and Toxin Obstructing (Damaging) Collaterals, Lung Qi Deficiency, Yin Deficiency with Internal Heat, Qi and Blood Deficiency, and Yin Exhaustion and Yang Collapse. These findings can provide a basis for establishing diagnostic criteria for these syndromes.

Keywords: Sepsis; Clinical investigation; Expert questionnaires; Syndrome; Primary and minor symptoms

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Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection and represents a leading cause of death globally [1-2]. Sepsis carries high morbidity, mortality, and disease burden [3-4], and strengthening prevention, early identification, and early treatment has become a global health priority [5]. Research indicates that traditional Chinese medicine offers certain advantages in preventing and treating sepsis [6-8]. Accurate syndrome differentiation is the prerequisite and key to improving TCM therapeutic efficacy. Currently, there is a lack of unified, objective diagnostic criteria for TCM sepsis syndromes. The five key components of syndrome standardization research include syndrome classification, determination of common syndromes and their variations, division of primary and minor symptoms, basis and format for establishing syndrome diagnostic criteria, and evaluation of these criteria [9]. Our team' s previous research identified eight common sepsis syndromes: Phlegm-Heat Obstructing the Lung, Intense Exuberant Heat-Toxin, Blood Stasis and Toxin Obstructing (Damaging) Collaterals, Yangming Fu-Organ Excess, Lung Qi Deficiency, Yin Deficiency with Internal Heat, Qi and Blood Deficiency, and Yin Exhaustion and Yang Collapse. Based on clinical investigation and building upon the identification of these common syndromes, this study combined statistical analysis and data mining techniques with the Delphi method to integrate

expert opinions, analyzing primary and minor symptoms of common sepsis syndromes to provide a basis for establishing sepsis syndrome diagnostic criteria. This study was approved by the Ethics Committee of the First Affiliated Hospital of Henan University of Chinese Medicine (Approval No.: 2022HL-376-01).

1. Methods

1.1 Clinical Investigation 1.1.1 Study Population: A total of 1,082 sepsis patients admitted to ICUs at eight hospitals nationwide—including the First Affiliated Hospital of Henan University of Chinese Medicine, First Affiliated Hospital of Zhengzhou University, Guang' anmen Hospital of China Academy of Chinese Medical Sciences, Henan Provincial People' s Hospital, First People' s Hospital of Zhengzhou, Hainan Traditional Chinese Medicine Hospital, Puyang Traditional Chinese Medicine Hospital, and First Affiliated Hospital of Guangzhou University of Chinese Medicine—were enrolled from May 2021 to August 2022.

1.1.2 Diagnostic and Syndrome Differentiation Criteria

1.1.2.1 Western Medicine Diagnostic Criteria: Sepsis diagnosis followed the 2016 Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3.0) [10]. Patients with confirmed or suspected infection and a Sequential Organ Failure Assessment (SOFA) score increase $ $2 points from baseline were diagnosed with sepsis.

1.1.2.2 TCM Syndrome Differentiation Criteria: Based on previous literature research [11-12] and results from the first round of expert questionnaires, combined with clinical practice, reference criteria for TCM syndrome differentiation were formulated.

1.1.3 Inclusion and Exclusion Criteria

1.1.3.1 Inclusion Criteria: Patients meeting Sepsis-3.0 diagnostic criteria; age $ $18 years; informed consent obtained from patients or their families.

1.1.3.2 Exclusion Criteria: Patients whose medical or psychological condition made participation inappropriate, such as pregnant or lactating women, severe depression/anxiety or other psychiatric disorders, or those unable to cooperate with the study.

1.1.4 Investigation Content and Quality Control

1.1.4.1 Investigation Content: Based on literature research and the first round of expert questionnaires, a clinical investigation form for TCM sepsis syndromes was developed, including four main components: (1) General information including name, gender, age, ethnicity, marital status, education level, address, and contact information; past medical history and current admission status; (2) TCM four diagnostic information collection and syndrome differentiation, including TCM syndromes, symptoms, tongue appearance, and pulse; (3)

Relevant laboratory tests and examinations including vital signs, related indicators, blood gas analysis, and etiological examinations; (4) Disease assessment including SOFA score, Glasgow Coma Scale, and Acute Physiology and Chronic Health Evaluation (APACHE II) score.

1.1.4.2 Quality Control: A quality control team was established to formulate unified standard operating procedures for the clinical investigation of TCM sepsis syndromes. Investigators at each center received unified on-site or online training before the investigation, with consistency testing performed. TCM syndrome differentiation required confirmation by attending TCM physicians or senior physicians to ensure authenticity and objectivity. During the study, cases were regularly sampled and reviewed.

1.1.5 Statistical Analysis Methods: Data from returned clinical investigation forms were reviewed and organized using EpiData 3.1 software, then independently double-entered and analyzed by two data managers. (1) Statistical analysis: Descriptive statistics were used to calculate frequency and percentage of symptoms in common syndromes. Binary logistic regression analysis was performed using SPSS 26.0 software, with syndrome presence as the dependent variable (yes=1, no=0) and symptoms with frequency \$ \$40% in that syndrome as independent variables (present=1, absent=0) to establish mathematical models between common syndromes and symptoms. OR>1 indicated characteristic symptoms of the syndrome. (2) Data mining: SPSS Modeler 18.0 software was used, with symptoms having frequency >10% in the syndrome as input variables and syndrome presence as output variable to establish artificial neural network models. The Garson algorithm was used to calculate the relative contribution of each symptom to the syndrome through the product of network weights, representing symptom importance for the corresponding syndrome.

1.2 Expert Questionnaire 1.2.1 Expert Selection Criteria: (1) Clinical physicians from hospitals across different regions of China; (2) Frontline clinicians specializing in TCM, integrated TCM-Western medicine respiratory, critical care, or emergency medicine; (3) Associate senior professional title or above; (4) Minimum 10 years of professional experience with solid theoretical foundation, rich clinical experience, and certain research background in TCM diagnosis and treatment of sepsis.

1.2.2 Questionnaire Development and Content: Based on clinical investigation results and after group discussion, a pool of items was developed for more common syndromes including Phlegm-Heat Obstructing the Lung, Blood Stasis and Toxin Obstructing (Damaging) Collaterals, Intense Exuberant Heat-Toxin, Yin Exhaustion and Yang Collapse, Yangming Fu-Organ Excess, Lung Qi Deficiency, Yin Deficiency with Internal Heat, and Qi and Blood Deficiency, along with their symptom components. The questionnaire included: (1) Basic expert information including name, gender, highest education level, professional title, occupation category, workplace, contact information, and address; (2) Importance evaluation of sepsis syndromes and diagnostic indicators for each

syndrome; (3) Familiarity with indicators and basis for judgment.

1.2.3 Questionnaire Administration: Questionnaires were distributed through a combination of face-to-face delivery, postal mail, and online survey platforms.

1.2.4 Evaluation Indicators and Quantification: Importance of syndromes and diagnostic indicators was evaluated using a 5-point scale (5=very important, 4=relatively important, 3=general, 2=not very important, 1=not important). Expert familiarity was categorized as very familiar, familiar, general, not familiar, and very unfamiliar, assigned values of 1, 0.8, 0.6, 0.4, and 0.2 respectively. Basis for judgment was categorized as theoretical analysis, practical experience, understanding of domestic and international peers, and intuition, with values assigned according to degree of influence.

1.2.5 Statistical Analysis Methods: Two data managers performed independent double-entry to establish the database. SPSS 26.0 software was used for statistical analysis, including expert enthusiasm (response rate), opinion concentration (mean, full score ratio), opinion coordination (coefficient of variation, expert opinion coordination coefficient), and expert authority level.

1.3 Determination Principles for Primary and Minor Symptoms

1.3.1 Statistical Analysis: Symptoms with frequency $ $60% were designated as primary symptoms; symptoms with 40% $\leq$ frequency <60% were designated as minor symptoms; symptoms with frequency <40% were excluded. In binary logistic regression analysis, symptoms with OR $ $3 were designated as primary symptoms; symptoms with 1<OR<3 were designated as minor symptoms; other symptoms were excluded. Symptoms meeting both criteria above were designated as primary symptoms for the syndrome; symptoms designated as primary by only one method required determination based on clinical expertise and group discussion; symptoms designated as minor by two or one method were designated as minor symptoms for the syndrome.

1.3.2 Data Mining: Based on professional knowledge and clinical practice, symptoms with importance level $ $3.0% in the artificial neural network were designated as primary symptoms; symptoms with 2.0% $\leq$ importance level <3.0% were designated as minor symptoms.

1.3.3 Expert Questionnaire: Symptoms with mean >4.00 and coefficient of variation $ $0.2 were designated as primary symptoms; symptoms with 3.00 $\leq$ mean $ $4.00 and coefficient of variation <0.35 were designated as minor symptoms.

1.3.4 Final Determination: Integrating results from statistical analysis, data mining, and expert questionnaires, symptoms designated as primary by all three methods were determined as primary symptoms; symptoms designated as primary by two methods required determination based on clinical practice; symptoms designated as minor by all three methods were determined as minor

symptoms; symptoms designated as minor by two methods, or primary by one method required determination based on clinical practice; symptoms designated as minor by only one method were excluded [13-15].

2. Results

2.1 Clinical Investigation Results 2.1.1 General Data: Among 1,082 clinical investigation forms distributed, 1,082 were returned. One form was excluded due to missing TCM syndrome or incomplete symptoms, resulting in 1,082 valid forms . The cohort included 681 males (62.9%) and 401 females (37.1%), with mean age (67.3$±$16.3) years.

2.1.2 Statistical Analysis

2.1.2.1 Descriptive Statistics: Symptoms for each of the eight common syndromes were statistically analyzed, and corresponding syndrome-symptom databases were established. Symptoms with frequency $ $60% and 40% ≤ frequency <60% are shown in Table 1. Using Phlegm-Heat Obstructing the Lung syndrome as an example, primary symptoms included yellow sputum color, shortness of breath, red tongue, cough, red facial complexion, dark yellow urine, chest tightness, and yellow greasy coating; minor symptoms included excessive sputum, constipation, pharyngeal rale, slippery rapid pulse, sticky difficult-to-expectorate sputum, fever, poor appetite, and loss of consciousness.

Table 1 Distribution of symptoms with frequency $ $40% in common syndromes

Syndrome	Frequency $ $60%	40% ≤ Frequency <60%
Phlegm-Heat Obstructing Lung	Yellow sputum, shortness of breath, red tongue, cough, red complexion, dark yellow urine, chest tightness, yellow greasy coating	Excessive sputum, constipation, pharyngeal rale, slippery rapid pulse, sticky difficult sputum, fever, poor appetite, loss of consciousness
Intense Exuberant Heat-Toxin	Red complexion, red tongue, thirst, constipation, headache, crimson tongue, dark yellow urine, shortness of breath	Fever, chest tightness, yellow dry coating, wiry rapid pulse, loss of consciousness, poor appetite, irritability, high fever, dry mouth

Syndrome	Frequency $ $60%	40% ≤ Frequency <60%
Yangming Fu-Organ Excess	Delirium, epigastric fullness, dark yellow urine, abdominal distension, constipation, abdominal pain, shortness of breath, hand-foot sweating, tidal fever, poor appetite, yellow dry coating, chest tightness, thirst, fever, irritability, deep rapid pulse, loss of consciousness, palm-sole heat	
Blood Stasis and Toxin Obstructing Collaterals	Dark complexion, limb numbness, purple-dark nails, tongue petechiae or ecchymosis	Shortness of breath, fever, chest tightness, dark yellow urine, delirium, loss of consciousness, poor appetite, stabbing chest-hypochondrium pain, masses, skin petechiae/ecchymosis, constipation
Lung Qi Deficiency	Poor appetite, shortness of breath, cough, thin clear sputum, spontaneous sweating, chest tightness, fever, loss of consciousness, fatigue, pale tongue, lack of qi with reluctance to speak	
Yin Deficiency with Internal Heat	Night sweats, red cheekbones, constipation, dark yellow urine, tinnitus, red tongue, scanty coating, irritability, thin rapid pulse, emaciation	Dry throat, chest tightness, loss of consciousness, shortness of breath, tidal fever, thirst, fever, hemoptysis, dry cough, dry mouth

Syndrome	Frequency $ $60%	40% ≤ Frequency <60%
Qi and Blood Deficiency	Sallow complexion, pale lips-nails, pale tongue, dizziness, poor appetite, palpitations, dark yellow urine, shortness of breath, insomnia, chest tightness, fatigue, spontaneous sweating, mental lethargy, lack of qi with reluctance to speak, red tongue, constipation, deep thin pulse, fever, weak pulse	
Yin Exhaustion and Yang Collapse	Faint pulse on the verge of disappearance, shortness of breath, pale complexion, cold extremities, profuse sweating, loss of consciousness	Chest tightness, fever, cold extremities, red tongue, mouth opening with shoulder lifting, weak breathing, urinary-fecal incontinence

2.1.2.2 Binary Logistic Regression Analysis: Using common syndromes as dependent variables (yes=1, no=0) and corresponding symptoms as independent variables (present=1, absent=0), binary logistic regression analysis was performed to explore symptoms meaningful for syndrome diagnosis.

Phlegm-Heat Obstructing Lung syndrome: Logit(P) = -5.873 + 2.148 excessive sputum (OR=8.568) + 1.512 pharyngeal rale (4.535) + 0.947 slippery rapid pulse (2.579) + 1.196 sticky difficult sputum (3.308) + 1.210 red complexion (3.352) + 1.118 yellow greasy coating (3.059) + 1.200 yellow sputum (3.319) + 1.393 cough (4.028) + 0.624 constipation (1.866). Model test: ^{2}=493.697, P<0.001, discriminant accuracy=93.3%.

Intense Exuberant Heat-Toxin syndrome: Logit(P) = -4.756 + 2.377 headache (10.774) + 1.624 crimson tongue (5.075) + 1.576 yellow dry coating (4.837) + 1.682 wiry rapid pulse (5.378) + 1.894 wiry slippery pulse (6.645) + 1.016 fever (2.763) + 1.517 irritability (4.560) + 1.680 high fever (5.366) + 1.156 red complexion (3.178) + 1.088 yellow greasy coating (2.967) + 1.063 thirst (2.896). Model test: ^{2}=516.099, P<0.001, discriminant accuracy=94.8%.

Yangming Fu-Organ Excess syndrome: Logit(P) = -5.063 + 2.214 hand-foot sweating (9.157) + 1.223 abdominal pain (3.397) + 1.800 yellow dry coating (6.053) + 5.208 deep rapid pulse (182.758) + 2.220 wiry slippery pulse (9.205) + 4.342 deep wiry pulse (76.844) + 1.894 delirium (6.646) + 1.563 yellow greasy coating (4.773) + 2.439 epigastric fullness (11.458) + 3.176 palm-sole

heat (23.941) + 2.541 tidal fever (12.692). Model test: ^{2}=610.718, P<0.001, discriminant accuracy=97.4%.

Blood Stasis and Toxin Obstructing (Damaging) Collaterals syndrome: Logit(P) = -10.608 + 3.792 masses (44.349) + 4.580 limb numbness (97.502) + 1.939 dark tongue (6.955) + 3.999 purple-dark nails (54.526) + 2.062 choppy pulse (7.861) + 1.493 dark complexion (4.449) + 2.883 tongue petechiae/ecchymosis (17.866) + 1.628 dark red tongue (5.095) + 1.567 hemiplegia (4.791) + 1.949 deep thin pulse (7.021) + 1.206 poor appetite (3.339) + 1.592 fatigue (4.915) + 1.674 dark yellow urine (5.333). Model test: ^{2}=678.116, P<0.001, discriminant accuracy=97.7%.

Lung Qi Deficiency syndrome: Logit(P) = -5.808 + 1.022 loss of consciousness (2.779) + 3.948 thin clear sputum (51.844) + 0.808 poor appetite (2.243) + 1.288 weak pulse (3.624) + 0.837 spontaneous sweating (2.309) + 1.399 cyanotic lips (4.049) + 0.955 fatigue (2.599) + 1.395 white sputum (4.037) + 1.445 cough (4.241) + 1.680 lack of qi with reluctance to speak (5.363) + 1.196 nausea (3.307) + 0.829 shortness of breath (2.291). Model test: ^{2}=356.081, P<0.001, discriminant accuracy=95.6%.

Yin Deficiency with Internal Heat syndrome: Logit(P) = -13.918 + 2.981 chest tightness (19.703) + 2.934 yellow sputum (18.802) + 2.936 irritability (18.839) + 6.358 hemoptysis (577.306) + 4.800 thin rapid pulse (121.485) + 3.347 scanty coating (28.430) + 3.383 tinnitus (29.468) + 3.605 night sweats (36.786) + 2.176 shortness of breath (8.809) + 3.807 red cheekbones (45.025) + 4.396 dry cough (81.126) + 2.881 dry throat (17.840) + 4.835 emaciation (125.863). Model test: ^{2}=442.086, P<0.001, discriminant accuracy=98.8%.

Qi and Blood Deficiency syndrome: Logit(P) = -15.644 + 7.937 pale lips-nails (2799.793) + 3.559 sallow complexion (35.124) + 3.453 palpitations (31.605) + 2.907 insomnia (18.310) + 3.656 thin white coating (38.723) + 2.016 thin pulse (7.509) + 1.949 scanty urine (7.023) + 4.889 choppy pulse (132.882) + 3.401 deep thin pulse (29.995) + 2.395 dizziness (10.974) + 5.027 weak pulse (152.409) + 2.733 lack of qi with reluctance to speak (15.377) + 3.967 irritability (52.810). Model test: ^{2}=356.162, P<0.001, discriminant accuracy=98.8%.

Yin Exhaustion and Yang Collapse syndrome: Logit(P) = -10.291 + 5.162 profuse sweating (174.553) + 1.845 cold extremities (6.328) + 1.879 fever (6.545) + 2.716 dark complexion (15.125) + 4.657 high fever (105.334) + 7.110 faint pulse on verge of disappearance (1224.330) + 2.387 cold limbs (10.883) + 2.170 loss of consciousness (8.758) + 3.318 somnolence (27.600) + 2.614 mouth opening with shoulder lifting (13.648) + 2.490 weak breathing (12.063) + 2.176 withered skin (8.814) + 2.199 fatigue (9.014) + 2.540 scanty coating (12.682). Model test: ^{2}=693.517, P<0.001, discriminant accuracy=98.5%.

Based on symptom frequency, frequency distribution, and binary logistic regression analysis results, combined with group discussion, preliminary primary and minor symptoms for the eight common syndromes were determined. Statistical

analysis results for primary and minor symptoms of common syndromes are shown in Table 2.

Table 2 Statistical analysis determination of primary and minor symptoms of common syndromes

Syndrome	Primary Symptoms	Minor Symptoms
Phlegm-Heat Obstructing Lung	Cough, excessive sputum, yellow sputum, pharyngeal rale, sticky difficult sputum, chest tightness, shortness of breath, red complexion, dark yellow urine, red tongue, yellow greasy coating	Loss of consciousness, fever, poor appetite, constipation, slippery rapid pulse
Intense Exuberant Heat-Toxin	High fever, irritability, shortness of breath, red complexion, thirst, constipation, dark yellow urine, crimson tongue, yellow dry coating, wiry rapid pulse	Delirium, red tongue, burnt yellow coating, wiry slippery pulse
Yangming Fu-Organ Excess	Delirium, abdominal pain, epigastric fullness, hand-foot sweating, constipation, heat binding with fluid leakage, red tongue, yellow dry coating, deep rapid pulse	Tidal fever, thirst, irritability, deep wiry pulse
Blood Stasis and Toxin Obstructing Collaterals	Purple-dark nails, cyanotic lips, dark red or purple tongue, tongue petechiae/ecchymosis, skin petechiae/ecchymosis, sublingual vein tortuosity and disorder, deep choppy or thin choppy pulse	Delirium, high fever, stabbing chest-hypochondrium pain, dark complexion
Lung Qi Deficiency	Cough, thin clear sputum, white sputum, shortness of breath, lack of qi with reluctance to speak, deep thin or weak pulse, low voice	Fatigue, spontaneous sweating, chest tightness, pale tongue
Yin Deficiency with Internal Heat	Dry cough, dry throat, irritability, tidal fever, night sweats, palm-sole heat, emaciation, constipation, red tongue, scanty coating, thin rapid pulse	Shortness of breath, thirst, dry mouth, hemoptysis, dry tongue, peeled or absent coating, small tongue body

Syndrome	Primary Symptoms	Minor Symptoms
Qi and Blood Deficiency	Fatigue, weakness, dizziness, palpitations, sallow or pale complexion, pale lips-nails, pale tongue, weak pulse, spontaneous sweating	Mental lethargy, somnolence, lack of qi with reluctance to speak, deep thin pulse
Yin Exhaustion and Yang Collapse	Loss of consciousness, irritability, shortness of breath, weak breathing, pale complexion, cold extremities, profuse sweating, scanty coating, faint pulse on verge of disappearance, urinary-fecal incontinence	Mouth opening with shoulder lifting, somnolence, red tongue, absent coating

2.2 Expert Questionnaire Results **2.2.1 General Information:** Thirty questionnaires were returned from 19 cities across 16 provinces/autonomous municipalities/municipalities including Guangdong, Hubei, Beijing, and Qinghai. The expert panel comprised 21 males (70.0%) and 9 females (30.0%), aged 34-70 years with mean age (51.2$±8.0)*years.Twenty−fiveexperts*(83.3±$9.67) years.

2.2.2 Expert Response Rate: Thirty-two expert questionnaires were distributed, with 30 returned, yielding a response rate of 93.7%.

2.2.3 Expert Authority Coefficient: The expert familiarity coefficient (Cs) was 0.90, and judgment coefficient (Ca) was 0.97, resulting in an authority coefficient Cr=(Cs+Ca)/2=0.94.

2.2.4 Expert Opinion Coordination: The Kendall coordination coefficient for the second round of expert questionnaires regarding common sepsis syndromes was 0.193 (^{2}=46.404, P<0.001).

2.2.5 Primary and Minor Symptoms from Expert Questionnaire: Symptoms with mean >4.00 and coefficient of variation $ $0.2, and symptoms with 3.00 ≤ mean $ $4.00 and coefficient of variation <0.35 are shown in Table 4 . Using Phlegm-Heat Obstructing the Lung syndrome as an example, primary symptoms included yellow sputum, expectoration, sticky sputum, excessive sputum, red tongue, cough, yellow greasy coating, fever, slippery rapid pulse, pharyngeal rale, and thirst; minor symptoms included shortness of breath, thick yellow coating, dry mouth, irritability, constipation, dark yellow urine, and chest tightness.

Table 3 Distribution of symptoms with importance level $ $2.0% in common syndromes

Syndrome	Importance $ $3.0%	2.0% ≤ Importance <3.0%
Phlegm-Heat Obstructing Lung	Sticky difficult sputum, excessive sputum, red complexion, yellow sputum, pharyngeal rale	Slippery rapid pulse, dark yellow urine, constipation, dizziness, expectoration, white greasy coating, spontaneous sweating, wiry slippery pulse, lack of qi with reluctance to speak, dry throat, weak pulse, emaciation, red tongue, yellow coating
Intense Exuberant Heat-Toxin	Red complexion, sticky difficult sputum, crimson tongue, headache	Vomiting, scanty urine, tinnitus, yellow sputum, wiry slippery pulse, high fever, constipation, wiry rapid pulse, skin petechiae/ecchymosis, spontaneous sweating, deep thin pulse, somnolence, convulsions
Yangming Fu-Organ Excess	Delirium, epigastric fullness, abdominal pain, tidal fever, yellow dry coating, deep rapid pulse, constipation	Palm-sole heat, hand-foot sweating, thick yellow coating, irritability, fever, thirst, dark yellow urine, loss of consciousness, vomiting, red tongue, wiry rapid pulse, red complexion, abdominal distension, yellow greasy coating, deep wiry pulse, deep pulse
Blood Stasis and Toxin Obstructing Collaterals	Purple-dark nails, tongue petechiae/ecchymosis, masses, limb numbness	Chest tightness, expectoration, shortness of breath, scanty coating, deep thin pulse, spontaneous sweating, fatigue, thirst, slippery rapid pulse, pale tongue, deep thin pulse, fatigue, abdominal pain, wiry pulse, cyanotic lips, abdominal distension, deep pulse, somnolence, shortness of breath, sublingual vein tortuosity, delirium, white sputum, mental lethargy, dark purple tongue, hemiplegia, irritability, dark complexion

Syndrome	Importance $ $3.0%	2.0% ≤ Importance <3.0%
Lung Qi Deficiency	Pale tongue, dark complexion, shortness of breath, dark tongue, mental lethargy, weak pulse, deep thin pulse, spontaneous sweating, choppy pulse, loss of consciousness, pale tongue, poor appetite, dark yellow urine, clear abundant urine, excessive sputum, fatigue, withered skin, abdominal pain, blood-tinged sputum, choppy pulse, wiry rapid pulse, shortness of breath, red tongue, high fever, headache, thin rapid pulse, yellow greasy coating, white sputum, bitter taste, irritability, dry mouth, abdominal distension, thirst, hemoptysis, fatigue, pale tongue	
Yin Deficiency with Internal Heat	Dry mouth, dry throat, irritability, tidal fever, night sweats, red cheekbones, tinnitus, emaciation, dry cough, dry throat, constipation, dark yellow urine, red tongue, scanty coating, thin rapid pulse	Shortness of breath, thirst, dry mouth, hemoptysis, dry tongue, peeled or absent coating, small tongue body

Syndrome	Importance $ $3.0%	2.0% ≤ Importance <3.0%
Qi and Blood Deficiency	Mental lethargy, fatigue, mental lethargy, pale lips-nails, pale tongue, sallow complexion, shortness of breath, thin white coating, weak pulse, somnolence, thin pulse, pale complexion, spontaneous sweating, palpitations, red tongue, shortness of breath, wiry slippery pulse, foul breath, headache	Deep excessive pulse, burnt dry coating, delirium, red complexion, loss of consciousness, vomiting, deep wiry pulse, tidal fever, sweating, palm-sole heat, hand-foot sweating
Yin Exhaustion and Yang Collapse	Faint pulse on verge of disappearance, loss of consciousness, cold extremities, mental lethargy, weak breathing, profuse sweating, pale complexion, weak pulse, sunken eye sockets, scanty coating, absent coating, irritability, urinary-fecal incontinence, shortness of breath	Eye and mouth opening, withered skin, oily sweating, pale tongue, mouth opening with shoulder lifting, red tongue

Table 4 Mean and coefficient of variation of common symptoms in sepsis

[Table content showing symptoms with mean >4.00, CV $ $0.2 (primary) and 3.00 ≤ mean $ $4.00, CV <0.35 (minor) for each syndrome]

2.3 Final Determination of Primary and Minor Symptoms Based on clinical investigation and expert questionnaires, integrating statistical analysis, data mining, and Delphi method results, and following the principles for determining primary and minor symptoms of common syndromes combined with clinical reality, the primary and minor symptoms of common sepsis syndromes were clarified through group discussion.

2.3.1 Phlegm-Heat Obstructing Lung Syndrome: Primary symptoms include cough, excessive sputum, yellow sputum, pharyngeal rale, sticky difficult-to-expectorate sputum, chest tightness, shortness of breath, red facial complexion, dark yellow urine, red tongue, and yellow greasy coating. Minor symptoms

include loss of consciousness, fever, poor appetite, constipation, and slippery rapid pulse.

2.3.2 Intense Exuberant Heat-Toxin Syndrome: Primary symptoms include high fever, irritability, shortness of breath, red facial complexion, thirst, constipation, dark yellow urine, crimson tongue, yellow dry coating, and wiry rapid pulse. Minor symptoms include delirium, red tongue, burnt yellow coating, and wiry slippery pulse.

2.3.3 Yangming Fu-Organ Excess Syndrome: Primary symptoms include delirium, abdominal pain, epigastric fullness, hand-foot sweating, constipation, heat binding with fluid leakage, red tongue, yellow dry coating, and deep rapid pulse. Minor symptoms include tidal fever, thirst, irritability, and deep wiry pulse.

2.3.4 Blood Stasis and Toxin Obstructing (Damaging) Collaterals Syndrome: Primary symptoms include purple-dark nails, cyanotic lips, dark red or purple tongue, tongue petechiae or ecchymosis, skin petechiae or ecchymosis, sublingual vein tortuosity and disorder, and deep choppy or thin choppy pulse. Minor symptoms include delirium, high fever, stabbing chest-hypochondrium pain, and dark complexion.

2.3.5 Lung Qi Deficiency Syndrome: Primary symptoms include cough, thin clear sputum, white sputum, shortness of breath, lack of qi with reluctance to speak, deep thin or weak pulse, and low voice. Minor symptoms include fatigue, spontaneous sweating, chest tightness, and pale tongue.

2.3.6 Yin Deficiency with Internal Heat Syndrome: Primary symptoms include dry cough, dry throat, irritability, tidal fever, night sweats, palm-sole heat, emaciation, constipation, red tongue, scanty coating, and thin rapid pulse. Minor symptoms include shortness of breath, thirst, dry mouth, hemoptysis, dry tongue, peeled or absent coating, and small tongue body.

2.3.7 Qi and Blood Deficiency Syndrome: Primary symptoms include fatigue, weakness, dizziness, palpitations, sallow or pale complexion, pale lips-nails, pale tongue, weak pulse, and spontaneous sweating. Minor symptoms include mental lethargy, somnolence, lack of qi with reluctance to speak, and deep thin pulse.

2.3.8 Yin Exhaustion and Yang Collapse Syndrome: Primary symptoms include loss of consciousness, irritability, shortness of breath, weak breathing, pale complexion, cold extremities, profuse sweating, scanty coating, faint pulse on the verge of disappearance, and urinary-fecal incontinence. Minor symptoms include mouth opening with shoulder lifting, somnolence, red tongue, and absent coating.

3. Discussion

Syndrome differentiation forms the foundation of TCM diagnosis and treatment, and research on syndrome diagnostic criteria represents the core issue of syndrome standardization as well as a critical component of clinical standardization in TCM [16-17]. TCM symptoms (signs) constitute the primary basis for syndrome differentiation, and symptom quantification contributes to the precision of TCM diagnosis and treatment [18]. The classification of primary and minor symptoms is another important issue in syndrome standardization research that can directly affect the accuracy and authenticity of diagnostic criteria [9]. When establishing quantitative diagnostic rules for TCM syndromes, the importance of primary symptoms and their distinction from minor symptoms should be appropriately reflected [19]. Primary symptoms reflect the main manifestations of a disease pattern and its principal contradiction, closely related to the essence of the disease. Minor symptoms occupy a secondary or subordinate position but can supplement deficiencies in primary symptoms from a lateral perspective, narrowing the location or nature scope of primary symptoms and helping to clarify etiology and pathogenesis [20]. Different symptoms contribute differently to syndrome diagnosis, and clarifying each symptom' s contribution to determine primary and minor symptoms better reflects the essence of syndromes [21].

Syndrome data exhibit characteristics of fuzziness, non-linearity, multi-dimensionality, and complexity. The application of statistical analysis and data mining techniques, individually or in combination, can enhance the objectivity and scientific rigor of syndrome standardization research [22]. Descriptive statistics of frequency directly reflect the probability of symptoms appearing in different syndromes, with results closer to clinical reality. However, symptom identification during clinical investigation may be influenced by subjective factors such as personal experience, and primary/minor symptom classification should combine multiple statistical and data mining results with expert opinions for comprehensive summarization [22]. Binary logistic regression examines quantitative relationships between independent variables (symptoms) and dependent variables (syndromes), classifying and predicting the dependent variable and analyzing the degree of association between different symptoms and syndromes based on OR values, which can be used for primary/minor symptom classification [23-24]. Integrating descriptive statistics and regression analysis results, the research group discussed and connected with clinical practice to preliminarily determine primary and minor symptoms of common syndromes. For example, in Phlegm-Heat Obstructing Lung syndrome, cough, yellow sputum, red complexion, and yellow greasy coating were classified as primary symptoms by both descriptive statistics and regression analysis, thus confirmed as primary symptoms. Constipation and slippery rapid pulse were classified as minor symptoms by both methods, thus confirmed as minor symptoms. Excessive sputum, pharyngeal rale, and sticky difficult sputum were classified as primary symptoms by regression analysis only; the research

group considered these result from phlegm-heat binding together and ascending with lung qi, representing main characteristics of phlegm-heat obstructing the lung, thus these were classified as primary symptoms. Chest tightness, shortness of breath, red tongue, and dark yellow urine were classified as primary symptoms by descriptive statistics only; the research group discussed these as manifestations of phlegm-heat exuberance obstructing lung qi, thus these were also classified as primary symptoms. Integrating descriptive statistics and regression analysis, primary symptoms of Phlegm-Heat Obstructing Lung syndrome were determined as cough, excessive sputum, yellow sputum, pharyngeal rale, sticky difficult sputum, chest tightness, shortness of breath, red complexion, dark yellow urine, red tongue, and yellow greasy coating; minor symptoms were loss of consciousness, fever, poor appetite, constipation, and slippery rapid pulse.

Artificial neural network is a data mining technique with excellent self-organizing adaptability, learning capability, and analysis/recognition functions for complex non-linear systems, meeting the requirements for processing complex data such as relationships between syndromes and between syndromes and symptoms [25-26]. This study integrated statistical analysis (descriptive statistics, binary logistic regression) and artificial neural network results to preliminarily determine primary and minor symptoms of the eight common syndromes according to established principles combined with clinical practice.

Expert questionnaires can enhance the guidance of syndrome standardization research [22]. After group discussion and referencing data distribution combined with clinical practice, the criteria of mean >4.00 and coefficient of variation \$ \$0.2 for primary symptoms, and $3.00 \leq$ mean \$ \$4.00 and coefficient of variation <0.35 for minor symptoms were established for screening. For Phlegm-Heat Obstructing Lung syndrome, yellow sputum, expectoration, sticky sputum, excessive sputum, red tongue, cough, yellow greasy coating, fever, slippery rapid pulse, pharyngeal rale, and thirst all met the primary symptom criteria; shortness of breath, thick yellow coating, dry mouth, irritability, constipation, dark yellow urine, and chest tightness met the minor symptom criteria; scanty coating, wiry rapid pulse, and wiry slippery pulse did not meet the criteria and were deleted. The primary and minor symptoms of the remaining seven common syndromes were classified using the same criteria. This expert questionnaire was semi-open, allowing experts to supplement and modify symptoms not mentioned in the questionnaire. One expert suggested adding "low voice" to Lung Qi Deficiency syndrome—since lung qi deficiency with diminished pectoral qi leads to weak voice, and after group discussion and terminology standardization, "low voice" was added as a standardized term. Two experts suggested adding "heat binding with fluid leakage" to Yangming Fu-Organ Excess syndrome—this characteristic symptom occurs when excessive heat accumulates in the intestines, dry feces bind in the large intestine, and intense heat forces fluids downward, causing watery stool to leak through gaps around the dry feces. After group discussion and expert consultation, "heat binding with fluid leakage" was added. One expert suggested adding "absent coating" to Yin Deficiency with Internal

Heat syndrome—heat-toxin consumes yin fluids, leading to extreme fluid depletion and severe middle qi deficiency, resulting in peeled or absent coating, thus "absent coating" was added.

Due to the complexity and subjectivity of clinical syndrome differentiation, statistical and data mining methods can only examine symptom-syndrome correlations from a statistical perspective, providing certain references and evidence. Combining clinical investigation with expert questionnaire results can avoid insufficient fitting between pure mathematical statistical analysis and TCM theoretical interpretation while reducing the subjectivity of expert experience-based syndrome differentiation to some extent. Therefore, this study integrated statistical analysis, data mining, and Delphi method results to determine primary and minor symptom classification. Notably, symptoms designated as primary or minor by only one or two methods required determination based on clinical practice through group discussion. For example, in Phlegm-Heat Obstructing Lung syndrome, cough, red tongue, and yellow greasy coating were identified as primary symptoms by two methods; after group discussion, considering that phlegm congestion and heat steaming cause lung qi to fail in purification and descend, leading to rebellious qi and cough, while red tongue and yellow greasy coating indicate internal phlegm-heat exuberance, these were confirmed as primary symptoms. Fever, thirst, chest tightness, shortness of breath, dark yellow urine, and slippery rapid pulse were primary symptoms by only one method; after group discussion, considering that phlegm-heat obstructing the lung causes lung qi to fail in diffusion and descent, leading to lung qi congestion and chest tightness/shortness of breath, while intense internal heat steaming outward causes fever, and heat scorching fluids leads to thirst and dark yellow urine, these symptoms were retained as minor symptoms. The primary and minor symptoms of the remaining seven common syndromes were all classified according to the above standards.

In summary, this study preliminarily determined primary and minor symptoms of common sepsis syndromes through statistical analysis and data mining based on clinical investigation, then optimized the results using the Delphi method through expert questionnaires. The final clarification of primary and minor symptoms for the eight common sepsis syndromes can provide a basis for establishing TCM syndrome diagnostic criteria for sepsis, promote accurate syndrome differentiation and treatment, and further develop the characteristics and advantages of TCM in treating sepsis, while laying a foundation for further clinical research on TCM syndrome-based treatment of sepsis.

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