Postprint: Clinical Manifestations and Syndrome Type Distribution in Hashimoto' s Thyroiditis Complicated by Thyrotoxicosis

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Abstract

Background Traditional Chinese Medicine (TCM) has developed a systematic understanding of the occurrence, progression, diagnosis, and treatment of Hashimoto' s thyroiditis complicated with thyrotoxicosis. However, current research on the distribution of clinical symptoms and syndrome patterns in TCM for this patient population is scarce, and national industry standards also lack descriptions regarding syndrome pattern distribution and diagnostic criteria for this condition. Objective To investigate the distribution patterns of clinical symptoms and syndrome patterns in patients with Hashimoto' s thyroiditis complicated with thyrotoxicosis using factor analysis combined with cluster analysis, thereby providing a basis for clinical syndrome differentiation and promoting standardized research on syndrome patterns of Hashimoto' s thyroiditis complicated with thyrotoxicosis. Methods A total of 171 patients with Hashimoto' s thyroiditis complicated with thyrotoxicosis who met the diagnostic criteria were collected from the thyroid disease outpatient clinics of Dongcheng Campus and Tongzhou Campus of Dongzhimen Hospital, Beijing University of Chinese Medicine, and Sun Simiao Hospital of Beijing University of Chinese Medicine between December 2020 and December 2021. The "Information Collection Form for Four TCM Diagnostic Methods in Hashimoto' s Thyroiditis Complicated with Thyrotoxicosis" was used to collect information on symptoms/signs, tongue manifestations, pulse characteristics, and other four diagnostic data. Factor analysis and cluster analysis were employed to investigate the distribution patterns of symptoms and syndrome patterns in Hashimoto' s thyroiditis complicated with thyrotoxicosis. Results Among the 171 patients with Hashimoto' s thyroiditis complicated with thyrotoxicosis, there were 17 males and 154 females, with a mean age of (39.98$±$13.30) years, and patients aged 20-60 years accounted for 87.72%. Regarding symptom distribution, frequently observed symptoms included fatigue, palpitations,

irritability or quick temper; signs included anterior neck enlargement and finger tremor; common tongue manifestations included red tongue, thin tongue, and teeth-marked tongue; pulse manifestations were wiry pulse and rapid pulse. Factor analysis was performed on 82 four-diagnosis items collected from the questionnaire, extracting 25 common factors with a cumulative variance contribution rate of 70.562%, and screening out 62 meaningful symptoms. Using the 25 common factors obtained from factor analysis as variables, R-type hierarchical cluster analysis was conducted, resulting in five syndrome pattern classifications: Liver Depression and Phlegm Coagulation Pattern, Yin Deficiency with Fire Effulgence Pattern, Spleen-Kidney Yang Deficiency Pattern, Liver Depression and Qi Stagnation Pattern, and Qi-Yin Deficiency Pattern. Conclusion The basic TCM syndrome patterns of Hashimoto' s thyroiditis complicated with thyrotoxicosis can be classified into Liver Depression and Phlegm Coagulation Pattern, Yin Deficiency with Fire Effulgence Pattern, Spleen-Kidney Yang Deficiency Pattern, Liver Depression and Qi Stagnation Pattern, and Qi-Yin Deficiency Pattern.

Full Text

Study on the Distribution of Clinical Symptoms and Syndromes in Hashimoto' s Thyroiditis Complicated with Thyrotoxicosis

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Abstract

Background: Traditional Chinese Medicine (TCM) has developed a systematic understanding of the occurrence, development, diagnosis, and treatment of Hashimoto' s thyroiditis complicated with thyrotoxicosis. However, current research on the clinical symptoms and syndrome distribution of this condition in TCM is scarce, and national industry standards lack standardized descriptions of syndrome patterns and diagnostic criteria for this disease.

Objective: This study employed factor analysis combined with cluster analysis to investigate the distribution of clinical symptoms and syndrome patterns in

Hashimoto' s thyroiditis complicated with thyrotoxicosis, providing a basis for clinical syndrome differentiation and promoting standardized research on TCM syndrome classification for this condition.

Methods: From December 2020 to December 2021, we collected data from 171 patients with Hashimoto' s thyroiditis complicated with thyrotoxicosis who met diagnostic criteria at the thyroid disease outpatient clinics of Dongzhimen Hospital (Dongcheng and Tongzhou campuses) and Sunsimiao Hospital of Beijing University of Chinese Medicine. We used the "Four Diagnostic Information Collection Form for Hashimoto' s Thyroiditis Complicated with Thyrotoxicosis" to gather information on symptoms/signs, tongue characteristics, and pulse patterns. Factor analysis and cluster analysis were applied to study the symptom and syndrome distribution patterns.

Results: Among the 171 patients, 17 were male and 154 were female, with a mean age of (39.98$±$13.30) years; 87.72% were aged 20-60 years. High-frequency symptoms included fatigue and lassitude, palpitations, irritability or irascibility, and anxiety. Common signs were anterior neck swelling and finger tremor. Frequent tongue presentations were red tongue, thin tongue body, and teeth-marked tongue, while the predominant pulse patterns were wiry pulse and rapid pulse. Factor analysis of 82 four-diagnostic items extracted 25 common factors with a cumulative variance contribution rate of 70.562%, screening 62 meaningful symptoms. Using these 25 common factors as variables for R-type hierarchical cluster analysis yielded five syndrome pattern classifications: Liver Depression with Phlegm Congealing Pattern, Yin Deficiency with Effulgent Fire Pattern, Spleen-Kidney Yang Deficiency Pattern, Liver Depression and Qi Stagnation Pattern, and Dual Deficiency of Qi and Yin Pattern.

Conclusion: The basic TCM syndromes of Hashimoto's thyroiditis complicated with thyrotoxicosis can be classified into five patterns: Liver Depression with Phlegm Congealing, Yin Deficiency with Effulgent Fire, Spleen-Kidney Yang Deficiency, Liver Depression and Qi Stagnation, and Dual Deficiency of Qi and Yin.

Keywords: Hashimoto disease; Hashimoto thyroiditides; Hashimoto thyroiditis complicated with thyrotoxicosis; Traditional Chinese medicine syndrome; Regularity of distribution; Factor analysis; Cluster analysis

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1. Materials and Methods

1.1 Study Population and Data Collection

We selected patients who visited the thyroid disease outpatient clinics of Dongzhimen Hospital (Dongcheng and Tongzhou campuses) and Sunsimiao Hospital of Beijing University of Chinese Medicine between December 2020 and December 2021. A total of 171 patients meeting the diagnostic criteria were enrolled based on inclusion and exclusion criteria. This study was

approved by the Medical Ethics Committee of Sunsimiao Hospital (Approval No.: SSMYY-KYPJ-2021-003).

1.2 Diagnostic Criteria

The diagnosis of Hashimoto' s thyroiditis and hyperthyroidism followed the "Chinese Guidelines for the Diagnosis and Treatment of Thyroid Diseases" issued by the Endocrinology Branch of the Chinese Medical Association in 2008, which includes: (1) elevated anti-thyroid peroxidase antibody (TPOAb) and anti-thyroid globulin antibody (TGAb) titers; (2) decreased serum thyroid stimulating hormone (TSH) and/or elevated thyroid hormones; and (3) ultrasound showing diffuse thyroid enlargement, typically with marked isthmus thickening and heterogeneous hypoechoic "reticular" appearance.

1.3 Inclusion and Exclusion Criteria

Inclusion criteria: (1) Diagnosis of Hashimoto' s thyroiditis; (2) Diagnosis of hyperthyroidism/thyrotoxicosis; (3) No severe chronic medical conditions.

Exclusion criteria: (1) Post-total or subtotal thyroidectomy; (2) Malignant tumor comorbidity; (3) Severe primary diseases of kidney, brain, liver, or heart; (4) Any missing data items in the questionnaire.

1.4 Data Collection Instrument Development

Literature review: We systematically searched CNKI, VIP, and CBM databases using subject terms and free words: ("Hashimoto' s thyroiditis + hyperthyroidism + thyrotoxicosis") AND ("syndrome + syndrome pattern + pattern differentiation"). Literature published until June 30, 2021, was retrieved. Additional manual searches and modern works on TCM pattern differentiation for "Hashimoto' s hyperthyroidism" were obtained through the Superstar Mobile Library.

Expert consultation: Based on the Beijing Association of Integrative Medicine Thyroid Disease Professional Committee, we consulted 30 experts (associate senior title or above) engaged in thyroid disease clinical and research work. Using a self-administered semi-closed questionnaire, experts rated the relevance and importance of each item on a 5-point scale (very important=5, important=4, general=3, not important=2, very unimportant=1) and evaluated their "judgment basis" and "familiarity degree." We received 28 valid questionnaires (93.3% validity rate) with an average authority coefficient of 0.725, indicating high expert authority and reliable results. Items with full-score percentages <50.0% were deleted.

Formulation of collection form: Following clinical epidemiological survey methods, we conducted a cross-sectional study. The final collection form included 82 four-diagnostic items covering symptoms/signs, tongue, and pulse characteristics, with binary scoring (1=present, 0=absent).

1.5 Data Quality Control

Survey personnel consisted of clinical physicians, master' s students, and doctoral students from the thyroid disease department. Before the survey, all investigators received training on clinical research procedures and quality control standards to ensure consistent symptom identification. Two associate senior-level thyroid specialists reviewed all medical records, discussing and confirming each patient' s four-diagnostic information. Participant privacy was respected, and manual verification ensured data completeness and accuracy. Discrepancies were reasonably explained or corrected by data collectors. Data entry used independent double-entry into WPS Excel, with registration and timely reporting of any issues. Post-entry quality checks were performed through sampling, followed by double-entry verification to establish the final database.

1.6 Statistical Analysis

We used WPS Excel for data entry of general information and four-diagnostic data. After consistency checks, logical error detection, and outlier analysis, the final analytical database was established. SPSS 21.0 software was used for statistical description and analysis. Exploratory factor analysis employed principal component analysis (common factor number determined by cumulative contribution rate >70% or eigenvalue >1) to obtain major TCM syndrome classifications for Hashimoto' s thyroiditis complicated with thyrotoxicosis. Factor rotation (selecting variables with loading coefficients >0.4) optimized interpretation, and the main common factors were subjected to cluster analysis. Cluster analysis used R-type hierarchical clustering on the 25 common factors.

1.7 TCM Syndrome Classification

A panel of three TCM physicians (associate senior title or above) referenced the "Diagnostics of Chinese Medicine," "Differential Diagnostics of TCM Symptoms," and "Syndrome Element Differentiation" to classify each cluster into a TCM syndrome pattern based on clinical reality.

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2. Results

2.1 Patient Characteristics

We enrolled 171 patients with Hashimoto' s thyroiditis complicated with thyrotoxicosis, including 17 males and 154 females (ratio 1:9). Ages ranged from 12 to 77 years, with a mean age of (39.98$±$13.30) years; 87.72% were aged 20-60 years.

2.2 Distribution of Four-Diagnostic Information

Symptoms and signs: Among 59 collected symptoms and signs, high-frequency manifestations included fatigue and lassitude, palpitations, irritability or irascibility, and anxiety. Common signs were anterior neck swelling and finger tremor. Symptoms with frequency $ $10% are shown in .

Tongue characteristics: Analysis of 23 tongue items revealed the most frequent tongue color was red tongue; the most common tongue shapes were thin tongue body and teeth-marked tongue . The most frequent coating color was white coating, and the most common coating texture was thin coating .

Pulse patterns: The most frequent pulse patterns were wiry pulse and rapid pulse .

2.3 Factor Analysis

Factor analysis was performed on four-diagnostic items with frequency >10% using principal component analysis with varimax rotation (maximum convergence iterations=27). The Kaiser-Meyer-Olkin (KMO) value was 0.564 (>0.50) and Bartlett' s test of sphericity was significant (p<0.01), confirming suitability for factor analysis. Based on variance results, 25 common factors (denoted as "F") were extracted according to cumulative contribution rate >70% or eigenvalue >1, with a cumulative variance contribution rate of 70.562% . The scree plot is shown in [Figure 1: see original paper].

After 29 iterations, the rotation converged. Selecting factor loading coefficients >0.4 as the threshold, we analyzed correlations between original variables and common factors to interpret their meanings. The 25 common factors were saved as variables for further cluster analysis, with detailed relationships and loadings shown in .

2.4 Cluster Analysis

Using the 25 common factors as variables, R-type hierarchical cluster analysis was performed [Figure 2: see original paper]. The dendrogram showed that at a Euclidean distance of 15, the model could be divided into five categories. Based on factor and cluster analysis results, combined with "Syndrome Element Differentiation," professional knowledge, and expert consensus, three associate senior-level thyroid specialists identified five syndrome patterns: Liver Depression with Phlegm Congealing Pattern, Yin Deficiency with Effulgent Fire Pattern, Spleen-Kidney Yang Deficiency Pattern, Liver Depression and Qi Stagnation Pattern, and Dual Deficiency of Qi and Yin Pattern .

3. Discussion

3.1 Distribution of Four-Diagnostic Information in Patients

Statistical analysis of four-diagnostic information frequencies revealed that symptoms occurring in >50% of patients could be categorized into four groups: physical and mental status (fatigue and lassitude, chest oppression, shortness of breath, irritability, dream-disturbed sleep, palpitations, tidal fever, heat intolerance), emotional symptoms (irritability or irascibility, anxiety, emotional depression, frequent sighing), local symptoms (anterior neck swelling, foreign body sensation in throat, finger tremor, dry mouth and throat, heavy lower limbs), and sleep disturbances (light sleep with easy awakening, difficulty falling asleep). Tongue and pulse presentations predominantly showed red tongue, thin coating, white coating, wiry pulse, and rapid pulse.

Patients often experienced major life changes or had pre-existing temperamental tendencies toward irritability. Improper expression of long-standing worry, anger, or emotional stagnation easily led to liver qi stagnation patterns, manifesting as irritability, anxiety, and other emotional symptoms. Qi stagnation commonly persists throughout the disease course. When qi movement is obstructed, fluid distribution becomes impaired, leading to phlegm formation. Phlegm and qi stagnation obstructing the neck cause local symptoms like anterior neck swelling and foreign body sensation in the throat. Phlegm stagnation further obstructs qi movement, aggravating qi stagnation. Prolonged stagnation easily transforms into liver fire, and phlegm stagnation over time can also transform into fire, stirring liver wind and causing dizziness and tremors. Fire disturbing the heart spirit and preventing yang from entering yin results in sleep disturbances. Long-standing liver fire consumes liver yin, leading to yin deficiency with effulgent fire or dual deficiency of qi and yin patterns, explaining the coexistence of heat intolerance, sweating, and fatigue.

3.2 Syndrome Pattern Regularities in Hashimoto' s Thyroiditis Complicated with Thyrotoxicosis

Factor loading represents the covariance between variables and their common factors, equivalent to variable weight within the factor. Larger absolute loading values indicate stronger correlations with the common factor. Based on factor and cluster analysis results, combined with "Syndrome Element Differentiation," professional knowledge, and expert consensus, five syndrome patterns were identified:

First category (Liver Depression with Phlegm Congealing Pattern): High loadings for insomnia (0.81), light sleep (0.771), difficulty falling asleep (0.771), easy awakening (0.744), dream-disturbed sleep (0.602), neck distention (0.793), neck compression sensation (0.752), sticky unsmooth stools (0.759), tension/anxiety (0.683), and emotional depression (0.681) indicate this pattern. Emotional disharmony causing liver qi stagnation manifests as irritability, anxiety, or depression. Massive production of TPOAb and TGAb attacking thyroid

tissue corresponds to "formless substances are called qi" and "excess qi becomes fire," disturbing heart spirit and causing sleep disturbances. Qi stagnation and phlegm congealing obstruct the neck, causing swelling and foreign body sensations.

Second category (Yin Deficiency with Effulgent Fire Pattern): High loadings for thirst with preference for cold drinks (0.86), dry mouth and throat (0.85), alternating dry and loose stools (0.673), abdominal distention (0.559), weight loss (0.826), increased appetite with easy hunger (0.779), emaciation (0.649), scanty coating (0.737), and fatigue (0.79) indicate this pattern, often coexisting with spleen qi deficiency.

Third category (Spleen-Kidney Yang Deficiency Pattern): High loadings for frequent stools (0.646), loose stools (0.643), skin itching (0.777), lumbar and knee coldness (0.554), lower limb edema (0.849), eyelid edema (0.832), and cold intolerance (-0.443) indicate this pattern. Prolonged disease damages spleen qi, which further impairs yang. Impaired spleen-kidney yang qi leads to fluid metabolism dysfunction, causing diarrhea, cold limbs, and edema.

Fourth category (Liver Depression and Qi Stagnation Pattern): High loadings for eye distention (0.699), frequent sighing (0.503), slippery pulse (0.684), dark purple tongue (0.518), chest and hypochondriac distention (0.699), and hypochondriac pain (0.509) indicate this pattern.

Fifth category (Dual Deficiency of Qi and Yin Pattern): High loadings for chest oppression (0.735), shortness of breath (0.718), irritability (0.652), palpitations (0.632), hot palms and soles (0.796), heat intolerance (0.691), tidal fever (0.637), sweating (0.608), scanty or absent menstruation (0.746), pale tongue (0.816), enlarged tongue (0.803), teeth-marked tongue (0.734), wiry pulse (0.769), and rapid pulse (0.679) indicate this pattern. Prolonged liver depression transforming into heat consumes yin, while chronic disease and essence-blood deficiency cause qi deficiency symptoms.

Clinical presentations are complex, often involving two or more combined patterns. The disease typically begins with excess patterns dominated by liver qi stagnation, gradually transforming into deficiency patterns (qi and yin deficiency) over time, resulting in mixed deficiency-excess patterns. Patients with Liver Depression with Phlegm Congealing Pattern often show emotional symptoms from liver qi stagnation and local symptoms from phlegm-qi obstruction. Spleen deficiency leads to phlegm formation and blood deficiency, while liver-spleen disharmony causes qi stagnation and blood stasis. Liver-kidney interaction leads to patterns of liver depression with kidney deficiency. Long-standing liver fire consuming yin produces prominent yin deficiency with effulgent fire patterns, while yin damage affecting yang can produce concurrent spleen-kidney qi/yang deficiency.

3.3 Limitations and Future Directions

This study has several limitations: (1) The sample was primarily from Beijing with few from Shaanxi, creating geographic limitations and failing to fully reflect regional, dietary, lifestyle, and constitutional influences on syndrome manifestations. (2) As a retrospective study, randomization was not possible, making it susceptible to bias and confounding factors. (3) The study lacked objective quantitative scoring indicators. (4) The relatively small sample size may introduce bias. Future research should employ prospective designs with multi-center, large-sample data collection to provide more comprehensive and accurate theoretical foundations for TCM syndrome classification.

In conclusion, using factor analysis and cluster analysis, this study identified five major syndrome patterns in Hashimoto' s thyroiditis complicated with thyrotoxicosis: Liver Depression with Phlegm Congealing, Yin Deficiency with Effulgent Fire, Spleen-Kidney Yang Deficiency, Liver Depression and Qi Stagnation, and Dual Deficiency of Qi and Yin. These findings provide an evidence-based foundation for standardized TCM syndrome differentiation and treatment of this condition.

Author Contributions: GE Yaxue was responsible for study conception and design, result analysis and interpretation, statistical processing, and manuscript writing; CHEN Xiaoheng conducted study implementation and feasibility analysis; QI Shuo and LI Huilong performed manuscript revision; DING Zhiguo and HU Rui were responsible for quality control and review, overall supervision, and management.

Conflict of Interest: The authors declare no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.