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Study of Traditional Chinese Medicine Syndrome Differentiation in post-COVID patients with Respiratory Symptoms in Thailand

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Abstract

Post-COVID-19 has a significant impact on recovered individuals. Traditional Chinese Medicine (TCM) offers a framework for understanding and treatment, but its utility in post-COVID cases remains under investigation. This study aimed to investigate the TCM syndromes in patients experiencing post-COVID with respiratory symptoms and explore alternative clinically practical assessment tools (spirometry and Fatigue Severity Scale [FSS]) for differentiating TCM patterns. A cross-sectional study was conducted involving 150 subjects with post-COVID respiratory symptoms in Thailand. TCM differentiation was diagnosed by three certified TCM practitioners, and spirometry was conducted by a physical therapist who holds a spirometry certification. Both spirometry and FSS were used for evaluation. Lung and Spleen Qi Deficiency Syndrome (FPQX) was the dominant TCM pattern (72%), followed by Deficiency of Both Qi and Yin Syndrome (QYLX) (28%). Spirometry revealed a statistically significant, but small decrease in lung function (FEV_1/FVC) within the FPQX group compared to the QYLX group. However, both groups remained within the normal range. FSS scores did not differ significantly between the groups. This study suggests that FPQX is prevalent in post-COVID patients in Thailand. It also indicates that spirometry might not be sensitive enough to capture the full extent of lung dysfunction in post-COVID respiratory symptoms. While the FSS confirmed the presence of fatigue in both groups, it may not be the best tool for differentiating between specific TCM syndromes. Future research should explore more sensitive biomarkers for TCM diagnosis and consider potential neurological contributions to post-COVID respiratory symptoms.

Keywords: *TCM syndrome; zheng; fatigue; FSS; neurology; spirometry*

1. Introduction

The COVID-19 pandemic has had a lasting impact on various organs, especially lung function. The National Institute for Health and Care Excellence (NICE) defines "post-COVID syndromes" as symptoms that persist for more than 12 weeks following infection and cannot be attributed to other diagnoses (National Institute for Health and Care Excellence (NICE), 2003). Patients recovering from COVID-19 often exhibit impaired lung function, with diffusion capacity identified as the most affected parameter in respiratory function testing (Torres-Castro et al., 2021). Individuals with post-COVID syndromes frequently present with reduced lung function, fatigue, and dyspnea (Vishnu et al., 2023). Research indicates that fatigue persists in 19–41% of patients for over three months, severely impacting their daily activities (Joli et al., 2022). Despite increasing recognition of these

symptoms, diagnosing post-COVID respiratory issues remains challenging, and treatment strategies are still largely under investigation, often within the context of small and uncontrolled studies.

TCM offers a unique perspective on health, emphasizing the restoration of balance within the body. This philosophy underpins syndrome differentiation, a diagnostic method for identifying specific disharmony patterns. TCM shows potential in treating COVID-19 through antiviral, anti-inflammatory, immunomodulatory, and organ-protective effects (Ren et al., 2021b). This fundamental philosophy underpins syndrome differentiation, a diagnostic method used to identify specific patterns of disharmony, which has a long history of effectively managing infectious diseases (Conroy et al., 2020; Jiang et al., 2012). Studies suggest that the integration of TCM into community healthcare services may alleviate COVID-19 severity and mortality (Li et al., 2021). Notably, China's National Health Commission incorporated TCM into official COVID-19 treatment guidelines (Wei, 2020), covering both the acute and rehabilitation phases. In the rehabilitation phase, the syndrome can be divided into two groups, allowing for a more individualized approach to treatment. These syndromes include the deficiency of both Qi and Yin Syndrome (QYLX) and lung and spleen Qi deficiency syndrome (FPQX). By identifying the underlying disharmony pattern, the TCM practitioners can tailor prescriptions, acupuncture, or other TCM therapies to address the specific needs of patients with post-COVID-19 symptoms.

Current assessment tools, such as the FSS and spirometry, are widely used for evaluating respiratory health (De Azevedo Vieira et al., 2023). Spirometry plays a vital role in assessing lung function and is instrumental in diagnosing lung diseases and monitoring respiratory health (Chung et al., 2014). Notably, in COVID-19 patients, respiratory scores often reflect those of healthy individuals, underscoring spirometry's value for symptomatic evaluation and early intervention (Zhang et al., 2023). A significant study employing TCM syndrome differentiation with 180 stable COPD patients revealed notable differences in FEV_1%Pred and FEV_1/FVC across the four TCM syndrome groups (Kang et al., 2022). Additionally, the FSS effectively quantifies overall fatigue in post-COVID-19 patients, showing a correlation between fatigue levels and improvements in lung function (De Azevedo Vieira et al., 2023).

In Thailand, challenges remain in applying TCM syndrome differentiation to post-COVID respiratory symptoms due to a lack of evidence-based guidelines. While spirometry and the FSS are useful in assessing the respiratory system, they have not been effective in addressing the complexities of these symptoms within the TCM framework. Addressing this need is essential for improving patient care and effectively integrating TCM with modern medicine in managing post-COVID respiratory conditions.

2. Objectives

This study investigates TCM syndromes in patients with post-COVID respiratory symptoms in Thailand. Furthermore, it aims to identify effective assessment tools for integrating TCM diagnostics, thereby paving the way for a comprehensive approach to the diagnosis and treatment of post-COVID respiratory issues.

3. Materials and Methods

3.1 Study Design

This cross-sectional study was conducted from March to December 2023, with participants recruited from Subdistrict Health Promotion Hospitals in Chiang Rai and Phayao provinces, Thailand. Subjects were eligible if they exhibited long-term post-COVID-19 persistent respiratory symptoms consistent with the NICE definition of post-COVID-19 condition (National Institute for Health and Care Excellence (NICE), 2003), including tiredness, weakness, difficulty breathing, or a chronic cough, or had a Modified Medical Research Council (MRC) score of $\geqslant 2$, lasting for at least two months and not explained by an alternative diagnosis. Subjects aged between 20 and 65 years were included in the study. However, individuals with underlying respiratory diseases such as asthma, emphysema, allergies, or tuberculosis, those with spirometry contraindications, or those who were unable to understand the Thai language were excluded.

This study was approved by the Mae Fah Luang University Ethics Committee on Human Research (Protocol No. EC 22215-25, date of approval: February 15, 2023), and all subjects provided written informed consent prior to enrollment.

3.2 Sample Size Calculation

The sample size calculation was based on the mean and standard deviation (SD) forced vital capacity (FVC) between the control group and post-COVID-19 subjects after three months of recovery, as reported by Salem et al., (2021). FVC was chosen as the primary outcome due to its sensitivity in detecting

changes in lung function, which is crucial for identifying the extent of respiratory impairment in post-COVID-19 patients. Measurement of FVC was performed following the American Thoracic Society (ATS) and European Respiratory Society (ERS) guides which indicated that the reduction of FVC<80% predicted was considered a restriction pattern (Graham et al., 2019). Which is related to pathophysiology after receiving the COVID-19 virus. (Vishnu et al., 2023). The sample size was calculated using the G*Power 3.0.10 program. The mean and SD of %FEV_1/FVC of the spirometry control group and post-COVID-19 group were 80.43 ± 5.00 Liters and 82.55± 5.00 Liters, respectively. The power value was set equal to 0.8, the alpha level equal to 0.05, found that the effect size should be at least 140 subjects, 70 QYLX groups, and 70 FPQX groups.

3.3 Research Protocols

The subjects were screened and assessed for eligibility according to the study criteria. The demographics included age and sex. The TCM differentiation of post-COVID syndrome was confirmed by two certified TCM practitioners based on clinical symptoms and signs, and subsequently approved by a third certified TCM practitioner who had not met the patients to avoid bias. The diagnosis followed the "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)" (2020): 1) Lung and Spleen Qi deficiency (FPQX), Main symptoms: fatigue, sallow complexion, and shortness of breath. Secondary symptoms: easy sweating and loose stools. Concurrent symptoms: epigastric distension fullness, bitter mouth, sticky mouth, anxiety, fear; pale and/or purple tongue, thin coating fatty and thready and/or astringent pulse. 2) Deficiency of both Qi and Yin syndrome (QYLX). Main symptoms: shortness of breath, fatigue, and dry mouth. Secondary symptoms: easy sweating and irritability. Concurrent symptoms: bitter mouth, sticky mouth, anxiety; red or dark purple tongue, thin and dry fur, and thready and/or rough pulse. Pulmonary function assessment included the Fatigue Severity Scale (FSS) and spirometry. The Thai version of the FSS (Sawasdee et al., 2014) was employed to measure the severity of fatigue. Initially developed in English by Krupp et al., (1989), this 9-item scale required participants to select a number from 1 (strongly disagree) to 7 (strongly agree) that corresponded to their fatigue level. The categorization into non - fatigue (FSS $\leqslant$4.0), borderline fatigue (4.0 < FSS < 5.0), and fatigue (FSS $\geqslant$5.0) has also been suggested (Krupp et al., 1989). Lung function was evaluated using a portable spirometer (Vyntus Spiro, Vyaire Medical GmbH, Hoechberg, Germany). Spirometry was conducted by a physical therapist certified in spirometry following the guidelines of the American Thoracic Society/European Respiratory Society (ATS/ERS) (Graham et al., 2019). To ensure accurate measurements, subjects received standardized training and practice on proper spirometry techniques before testing. Lung function parameters, FVC, forced expiratory volume in the first second (FEV_1), the ratio of FEV_1/FVC, and forced expiratory flow at 25–75% of FVC (FEF25–75%) were recorded. A maximum of three attempts were allowed, with the best effort (highest FVC) chosen for data analysis. Between attempts, subjects received one-minute rest periods. Normal FEV_1/FVC ratio of >70% and an FVC of >80% are predicted. The Global Lung Function Initiative (GLI) reference equation (Southeast Asian population) (Cooper et al., 2017) was used to predict. All subjects were instructed not to use any bronchodilator on the day before the procedure. For data collection, two individuals were responsible for data input and double-checking, ensuring they were not involved in the assessment process.

3.4 Statistical Analysis

Descriptive statistics were used to analyze the demographic data (age and sex). The results are expressed as the mean ± standard deviation. An independent sample t-test was used to analyze TCM syndromes between the two groups for continuous data. To compare the spirometry and FSS between the groups, the independent t-test was used, with significance set at p = 0.05. All statistical analyses were performed using IBM SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). p-values <0.05 were considered statistically significant.

4. Results

4.1 Demographic Characteristics

A total of 150 subjects (37 males and 113 females) with post-COVID-19 and persistent respiratory symptoms were recruited in Thailand, all of whom completed the study. The mean age was 39.92±17.75 years. The subjects were classified into two TCM syndromes: QYLX syndrome (28%, N = 42) and FPQX syndrome (72%, N = 108). A comparison of the basic characteristics between the two groups showed no statistically significant differences (Table 1).

Table 1 Demographics and characteristics

Variable	TCM syndrome		p-value
	QYLX (N =42)	FPQX (N =108)	
Age(years) [a]	35.78±17.93	41.52±17.50	0.450
Sex,			0.150
- Male [b]	7(5)	30(20)	
- Female	35(23)	78(52)	

[a] Mean ± standard deviation, [b] number, percent

Table 2 Symptoms among the QYLX and FPQX groups

Symptom	N (%)	QYLX (n=42)	FPQX(n=108)
Breathlessness	130(87)	39	91
Forgetful	105(70)	26	79
Fatigue	100(67)	24	76
Thirsty	66(44)	30	36
Myalgia	66(44)	15	51
Irritable	60(40)	19	41
Insomnia	56(37)	19	37
Headache	53(35)	19	34
Hair loss	51(34)	19	32
Frequent sickness	45(30)	13	32

Table 3 Comparison of FSS and spirometry results (mean difference) of FSS and spirometry results between the two syndromes of TCM

Variable	Group	N	Mean	SD	p-value	95 %Confidence interval	
						Lower	Upper
FSS	QYLX [c]	42	5.261	2.173	0.267	0.439	0.393
	FPQX [d]	108	4.822	2.134			
FVC	QYLX	42	2.786	0.564	0.176	-0.157	0.115
	FPQX	108	2.942	0.784			
FEV_1	QYLX	42	2.506	0.573	0.854	-0.203	0.110
	FPQX	108	2.526	0.688			
FEV_1/FVC	QYLX	42	89.697	7.088	0.006*	3.656	1.302
	FPQX	108	86.040	7.348			

*Significant at α level ≤ 0.05

[c] QYLX = deficiency of both Qi and Yin Syndrome

[d] FPQX = Lung and spleen Qi deficiency Syndrome

Table 2 presents the prevalence of self-reported symptoms among the 150 study subjects. Dyspnea emerged as the most prevalent symptom, affecting 87% of the subjects, and was also the dominant symptom in both FPQX and QYLX groups. This was followed by forgetfulness (70%), fatigue (67%), thirst, and myalgia (44%). Other frequently reported symptoms included irritability, headache, hair loss, and frequent sickness.

4.2 Fatigue Severity Scale (FSS)

The data from Table 3 indicates that the average FSS score for the QYLX syndrome group was 5.26 ± 2.17, while the FPQX syndrome group had an average score of 4.82 ± 2.13. Statistical analysis revealed no significant difference ($p > 0.05$) in FSS scores between the two groups.

4.3 Spirometry

Table 3 presents a comparison of the spirometry test results between the QYLX and FPQX groups. The QYLX group displayed a mean FVC of 2.78 ± 0.56 Liters and a mean FEV_1/FVC ratio of 89.69 ± 7.08. The FPQX group exhibited a mean FVC of 2.94 ± 0.78 Liters and a mean FEV_1/FVC ratio of 86.04 ± 7.34. Notably, the QYLX group had a statistically significant ($p=0.006$) higher mean FEV_1/FVC ratio compared to the FPQX group.

5. Discussion

This cross-sectional study investigated TCM syndromes of post-COVID-19 respiratory symptoms in Thailand and assessed the suitability of spirometry and FSS in differentiating these syndromes. Among the 150 subjects, the study identified FPQX Syndrome and QYLX Syndrome as the two dominant TCM patterns associated with post-COVID respiratory symptoms, with FPQX Syndrome being the most prevalent (72%), consistent with recent studies (Tian et al., 2020; Niu et al., 2021; Li et al., 2020). Our findings revealed that symptoms such as dyspnea, forgetfulness, fatigue, thirst, muscle soreness, irritability, headache, and hair loss were the most commonly reported, aligning with recent research (Fernández-de-las-Peñas et al., 2021; Han et al., 2022; Lenz et al., 2024). Additionally, malaise and frequent sickness were commonly observed in Qi deficiency syndrome, consistent with previous studies (Chiang et al., 2012). These findings can serve as a foundation for guidelines to diagnose post-COVID-19 persistent respiratory symptoms in Thailand, specifically for TCM practitioners. This will enhance the accuracy and effectiveness of TCM diagnoses and treatments for post-COVID conditions.

According to TCM principles, COVID-19 is considered an "epidemic" due to its highly contagious nature. The causative factor, referred to as "Yili" or epidemic Qi (pathogenic factors), is believed to be transmitted through the respiratory mucosa and contact, as described in the Huangdi Neijing (The Yellow Emperor's Classic of Medicine: 黄帝内经). These pathogenic factors ("邪", or "evil"), often associated with external elements like coldness, dampness, and dryness, tend to converge on the lungs, leading to a deficiency of lung Qi. This can manifest as fatigue, weakness, shortness of breath (Ai et al., 2020). This deficiency can subsequently weaken the spleen, hindering its ability to nourish the lungs, creating a vicious cycle of lung and spleen Qi deficiency (FPQX) (Yang et al., 2012).

From the perspective of TCM principles, the lung governs respiration and distributes Wei Qi (卫气), the body's protective energy. When lung Qi is deficient, the lung's ability to take in and distribute air weakens, manifesting as shortness of breath (dyspnea) (Ren et al., 2021a). Weak Wei Qi can also make individuals more susceptible to catching colds. The spleen plays a vital role in digestion, nutrient absorption, and producing Qi. When spleen Qi is deficient, the body lacks the energy needed for optimal functioning, resulting in fatigue, pale complexion, dizziness, forgetfulness, hair loss, and weakness. Subsequently, the functions of other organs, especially the brain, are impeded, such as cognitive dysfunction, sleep disorders, and mood fluctuation. Recently research also found that spleen Qi deficiency had a psychological and neural basis at least in the cognitive control aspect (Lin et al., 2017; Ying, & Yuan, 2023). Recent studies have also found that spleen Qi deficiency has a psychological and neural basis, particularly in cognitive control (Lin et al., 2017; Ying, & Yuan, 2023).

In some cases, not only is there Qi deficiency, but there can also be Yin deficiency. Yin represents the body's fluids, essence, and cooling principle. Yin deficiency occurs when these fluids are insufficient. The deficiency of both Qi and Yin, known as Qi and Yin Deficiency Syndrome (QYLX), presents symptoms of Qi deficiency along with additional symptoms of Yin deficiency, leading to issues such as dry mouth, dry throat, dry skin, night sweats, a sensation of internal heat, and irritability. Recent research suggests a potential link between Yin deficiency and disturbances in the hypothalamus-pituitary-adrenal (HPA) axis, the hypothalamus-pituitary-thyroid (HPT) axis, the cyclic nucleoside system, and immune function (Wang et al., 2010).

Spirometry results indicated a statistically significant decrease in the FEV_1/FVC ratio within the FPQX group compared to the QYLX group, although both groups-maintained ratios within the normal range ($FEV_1/FVC > 80\%$). This finding suggests that while spirometry can differentiate between these TCM syndromes, it may not fully capture the extent of respiratory impairment in post-COVID patients. Although spirometry is a valuable tool for distinguishing between healthy individuals and those with compromised lung function, it may lack sensitivity in identifying issues in this population. Recent research indicates that many post-COVID-19 patients present with normal spirometry results, implying that not all individuals will experience long-term pulmonary impairment (Sousa et al., 2023).

The FSS scores did not reveal a statistically significant difference between the two groups, yet fatigue remained prevalent in both. This suggests that while the FSS is a reliable tool for measuring fatigue, it may not directly correlate with lung function (Aronson et al., 2023). Neurophysiological studies propose that post-COVID fatigue may stem from GABAergic dysfunction, potentially accounting for the cognitive and psychological symptoms often

observed in these patients (Ortelli et al., 2021). Moreover, the high prevalence of symptoms such as forgetfulness, irritability, sleep disorders, and headaches in both TCM groups suggests potential neurological contributions to post-COVID conditions with respiratory symptoms. This insight highlights the complexity of post-COVID conditions, suggesting that fatigue may arise from multifaceted mechanisms beyond mere respiratory issues.

TCM provides a personalized and holistic approach to managing post-COVID syndrome, addressing both physical and emotional health. For FPQX syndrome, the focus is on tonifying lung and spleen Qi. This is typically achieved through dietary modifications that favor easily digestible foods and herbal formulas like Yuping Feng San. These interventions aim to boost overall vitality and support respiratory health. In contrast, QYLX syndrome treatment emphasizes tonifying Qi and nourishing Yin fluids. This approach includes dietary adjustments, gentle exercise, and herbal formulas such as Sha Shen Mai Dong Tang, all designed to replenish vital fluids and promote recovery. Recent research highlights the efficacy of TCM in this context. A randomized controlled trial demonstrated that a comprehensive TCM rehabilitation program significantly reduced clinical symptoms for COVID-19 patients with both FPQX and QYLX syndrome types. The results showed notable improvements in TCM syndrome scores compared to pre-treatment scores and a control group ($P<0.01$) (Sun et al., 2022). Based on these findings, promoting TCM as part of post-COVID-19 management could be beneficial for patients, addressing their unique needs and enhancing their recovery process.

This study's reliance on self-reported symptoms and its cross-sectional design present notable limitations. To enhance the validity of future research, it is essential to include larger and more diverse populations and to utilize objective measures of respiratory function. Moreover, further investigations should prioritize the identification of specific biomarkers associated with post-COVID respiratory symptoms, especially those that may indicate a neurological component (Stefanou et al., 2022). This could involve exploring markers of inflammation, neurotransmitter imbalances, or other relevant factors that may influence the cognitive and emotional dimensions of this condition.

6. Conclusion

This study examined the prevalence of TCM patterns in patients experiencing post-COVID respiratory symptoms in Thailand. The findings suggest that Lung and Spleen Qi deficiency syndrome and deficiency of both Qi and Yin syndrome are prevalent patterns associated with this condition. However, limitations in spirometry and the FSS highlight the need for more comprehensive assessment methods in future TCM-based research on post-COVID respiratory symptoms.

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