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Original Article

Clinical Analysis of the Association Between Chinese Medicine Syndromes and Risk Factors for Hypertension

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Abstract

Background and objectives: The application of Chinese medicine in clinic is based on the classical theory of traditional Chinese medicine (TCM) syndrome differentiation, which remains not fully understood. This study aims to explore and interpret the associations between TCM syndromes and multiple clinical risk factors of hypertension.

Methods: A total of 203 patients with hypertension were retrospectively studied. After the regression analysis of confounding factors for different types of hypertension, the potential association between TCM syndrome and risk factors were analyzed.

Results: The univariate and multivariable regression for the confounding factors for different types of hypertension revealed that the comorbidity of left ventricular hypertrophy was probably an independent risk factor for different types of hypertension. The correlation analysis indicated that the disease course was positively correlated with the syndrome differentiation degree (Spearman's coefficient = 0.185, $p < 0.05$) and blood stasis syndrome (Spearman's coefficient = 0.291, $p < 0.05$), the hypertension risk group was positively correlated with the blood stasis syndrome (Spearman's coefficient = 0.207, $p < 0.05$), and age was positively correlated with the blood stasis syndrome (Spearman's coefficient = 0.231, $p < 0.05$) and qi-deficiency syndrome (Spearman's coefficient = 0.187, $p < 0.05$), but this was negatively correlated with the liver-yang hyperactivity syndrome (Spearman's coefficient = −0.167, $p < 0.05$).

Conclusions: There are correlations between TCM syndromes and the clinical risk factors of hypertension. These findings may help to interpret the TCM syndrome differentiation theory.

Introduction

Hypertension is the leading cause of cardiovascular disease and premature death worldwide, and the incidence of hypertension in patients continues to increase.[1,2] The most appropriate antihypertensive drug should be selected, according to the actual situation of the patient, which is in line with the overall concept of traditional Chinese medicine (TCM) syndrome differentiation.[3,4] However, the TCM syndrome remains not fully understood.

TCM has a history of more than two-thousand years in China, and is increasingly being welcomed by a number of developed countries, such as Australia and the United States. Hypertension can be categorized as headache or dizziness in TCM. The treatments for headache or dizziness are guided by the TCM syndrome differentiation based on the factors of qi, blood stasis, yang, yin, phlegm and others. These dialectical diagnoses and treatments reflect the individualization of TCM syndromes for hypertension for a certain relationship with clinical risk factors, such as age, disease course, hypertension grade, blood homocysteine, coagulation parameters, risk stratification of hypertension and others,[5–7] and are consistent with the individual modern medicated selection of antihypertensive drugs.[8]

Keywords: Hypertension; Traditional Chinese medicine syndrome; Correlation analysis; Risk factors; Retrospective study.

Abbreviations: BMI, body mass index; BNP, brain natriuretic peptide; CHD, coronary heart disease; Cr, creatinine; HCY, homocysteine; INR, international normalized ratio; LDL, low density lipoprotein cholesterol; TCM, traditional Chinese medicine.

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The present study aimed to explore and interpret the potential associations between TCM syndromes and multiple clinical risk factors of hypertension. The present retrospective study revealed the correlations between TCM syndromes and the clinical risk factors of hypertension, which can help to interpret the process of classifying and distinguishing TCM syndromes with common clinical risk factors, and individually guide the clinical medication. These present findings may help bridge the gap between Chinese medicine and Western medicine.

Methods

Study design and ethics approval

A retrospective study was conducted in the Department of Cardiology, Guangdong Provincial Hospital of Chinese Medicine. All TCM diagnostic information, demographic characteristics and clinical data of hypertensive patients, who were screened based on the inclusion and exclusion criteria for the present study, were collected. The present study was approved by Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (No. ZE2019-079-01).

Inclusion and exclusion criteria for the participants

According to the Guidelines for the Prevention and Treatment of Hypertension in China[9] and the latest guidelines,[10,11] patients with a systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg in the resting non-medication state for three times within three days were diagnosed with hypertension. Hypertension was classified as level 1, 2 and 3, based on the level of blood pressure. All patients were local residents of Guangzhou. Patients diagnosed with hypertension, but had normal blood pressure, were excluded. Furthermore, pregnant or lactating women were excluded. All hypertensive patients who met the above inclusion criteria were included for the present study.

TCM syndrome definition, risk factors and bias elimination

According to the Diagnostics of TCM edited by Tietao Deng,[12] the four TCM syndromes were defined, as follows:

1. Qi deficiency syndrome was defined as a syndrome with shortage of qi, and disinclination to talk, lassitude, dizziness, spontaneous sweating, worse when active and weak pulse;
2. Blood stasis syndrome was defined as a syndrome with stabbing pain, pain with fixed locations, lump, hemorrhage, cyanotic lips, tongue and nails, and rough pulse;
3. Phlegm-dampness syndrome was defined as a syndrome with cough and vomiting or spitting sputum, chest distress, nausea, lumps, greasy tongue coating and slippery pulse, or a syndrome with edema, retention of urine, and enlarged tongue with white slippery coating;
4. Liver-yang hyperactivity syndrome was defined as a syndrome with vertigo and tinnitus, headache, red face, irritability, palpitation and forgetfulness, insomnia and dreams, lumbar and knee soreness, heavy head and decreased foot sensation, red tongue with slight coating, and strong pulse string.

Since TCM syndrome differentiation is mainly based on symptoms, this would easily lead to measurement bias. In order to reduce the measurement bias, the syndrome differentiations for hypertension were completed by two attending physicians, who are Chinese medicine practitioners, based on the above-mentioned criterions, and according to the recorded case data. If there were disagreements in the syndrome differentiation for hypertension, a chief physician would carry out the syndrome differentiation for hypertension.

The patient demographics, such as age, gender and clinical data, as well as the course of hypertension, grade of hypertension, risk stratification of hypertension, and diagnosis of comorbidities, were obtained. The highest blood pressure in the previous measurements and the blood pressure measured during the hospitalization were recorded, and the highest values were used for grading. The cardiovascular risks were stratified by risk factor, target organ damage and complication. According to the Chinese Guidelines for the Prevention and Treatment of Hypertension, the risk stratification was assessed based on the following: hypertension (grades 1–3), age >55 years old (male) or >65 years old (female), smoking, impaired glucose tolerance (two-hour postprandial blood glucose of 7.8–11.0 mmol/L) and/or fasting blood glucose (6.1–6.9 mmol/L), dyslipidemia (total cholesterol of ≥5.7 mmol/L [220 mg/dl], low-density lipoprotein cholesterol of >3.3 mmol/L [130 mg/dl], or high-density lipoprotein cholesterol of <1.0 mmol/L [40 mg/dl]), family history of early onset of cardiovascular disease (first-degree relative age of onset of <55 years old [male] or <65 years old [female]), abdominal obesity (waist circumference of ≥90 cm [male] or ≥85 cm [female], or obese (body mass index of ≥28 kg/m^2), and blood homocysteine (HCY) increase of more than 10 umol/L. Homocysteine was collected after admission. In order to avoid errors between the research data and original clinical data, two researchers recorded the data obtained from the database.

Statistical analysis

A database was established for the present study, and all statistical analyses of the data were conducted using the SPSS statistical software (version 21.0). Demographic data were statistically analyzed using descriptive analysis. Quantitative data were expressed as mean±standard deviation (SD), and categorical data were expressed in composition ratio. The relationship between TCM syndromes and potentially related clinical biochemistry indexes for different types of hypertension was analyzed by multivariable regression. The potential correlation among quantitative values was analyzed by Pearson's bivariate correlation after the normality test using the Kolmogorov-Smirnov method, and the counting data was analyzed by Spearman's bivariate correlation. A correlation coefficient of >0 was considered a positive correlation, while correlation coefficient of <0 was considered a negative correlation. A p-value of <0.05 was considered statistically significant.

Results

Characteristics of patients with hypertension

A total of 203 hypertensive patients were enrolled for the present study. The demographic and clinical data are presented in Table 1. These patients included 89 male and 114 female patients, with an average age of 67.84±12.45 years old. The average age of women was 68.38±10.82 years old, with a minimum age of 39 years old and a maximum age of 92 years old. The average age of men was 67.15±14.30 years old, with a minimum age of 22 years old and a maximum age of 91 years old.

The disease course is detailed in Table 2. That is, 103 of 203 hypertensive patients had a disease course of 0–5 years, accounting for 50.74% of all patients, 65 patients had a disease course of 6–10 years, accounting for 32.02% of all patients, 24 patients had a disease course of 11–20 years, accounting for 11.82% of all patients,

Table 1. Gender and age composition for the 203 hypertensive patients

	Number (*n*)	Minimum age (years)	Maximum age (years)	Mean age	Standard deviation
Male	89	22	91	67.15	14.30
Female	114	39	92	68.38	10.82
Total	203	22	92	67.84	12.45

and 11 patients had a disease course of >20 years, accounting for 5.42% of all patients.

The severity of hypertension for this population is presented in Table 2. That is, 18 patients had hypertension grade 1, accounting for 8.87% of all patients, 65 patients had hypertension grade 2, accounting for 32.02% of all patients, and 120 patients had hypertension grade 3, accounting for 59.11% of all patients.

The stratification of various risk factors and the target organ damage revealed the following: 172 patients were assigned to the very high-risk group, which had the largest proportion (84.73%); one patient was assigned to the low-risk group, which had the smallest proportion (0.49%); 12 patients were assigned to the intermediate risk group, accounting for 5.91% of all patients; 18 patients were assigned to the high-risk group, accounting for 8.87% of all patients (Table 2).

Furthermore, 107 patients developed heart failure or coronary heart disease (CHD), 65 patients had diabetes mellitus, and 36 patients had impaired glucose tolerance. In addition, 111 patients developed cerebrovascular disease, 86 patients had high homocysteine, and one patient had single or multiple conditions (Table 2). The data is summarized in Figure 1.

Distribution of TCM syndromes for hypertension

There were a total of 469 patients: 156 (33.26%) patients had qi-deficiency syndrome, 180 (38.38%) patients had phlegm-dampness syndrome, 108 (23.03%) patients had blood stasis syndrome, and 25 (5.23%) patients had liver-yang hyperactivity syndrome (Fig. 2 and Table 3).

Table 2. Characteristics of the 203 hypertension patients

Variable	Number (*n*)	Proportion (%)
Disease course (years)		
0–5	103	50.74
6–10	65	32.02
11–20	24	11.82
>20	11	5.42
Total	203	100.00
Hypertension grade		
Grade 1	18	8.87
Grade 2	65	32.02
Grade 3	120	59.11
Total	203	100.00
Risk stratification		
Low risk	1	0.49
Intermediate risk	12	5.91
High risk	18	8.87
Very high risk	172	84.73
Total	203	100.00
Combined disease		
Left ventricular hypertrophy	93	45.81
Heart failure or coronary heart disease	107	26.42
Diabetes	65	16.05
Abnormal glucose tolerance	36	8.89
Cerebrovascular disease	111	27.41
Hyperhomocysteinemia	86	21.23
Total	405	100.00

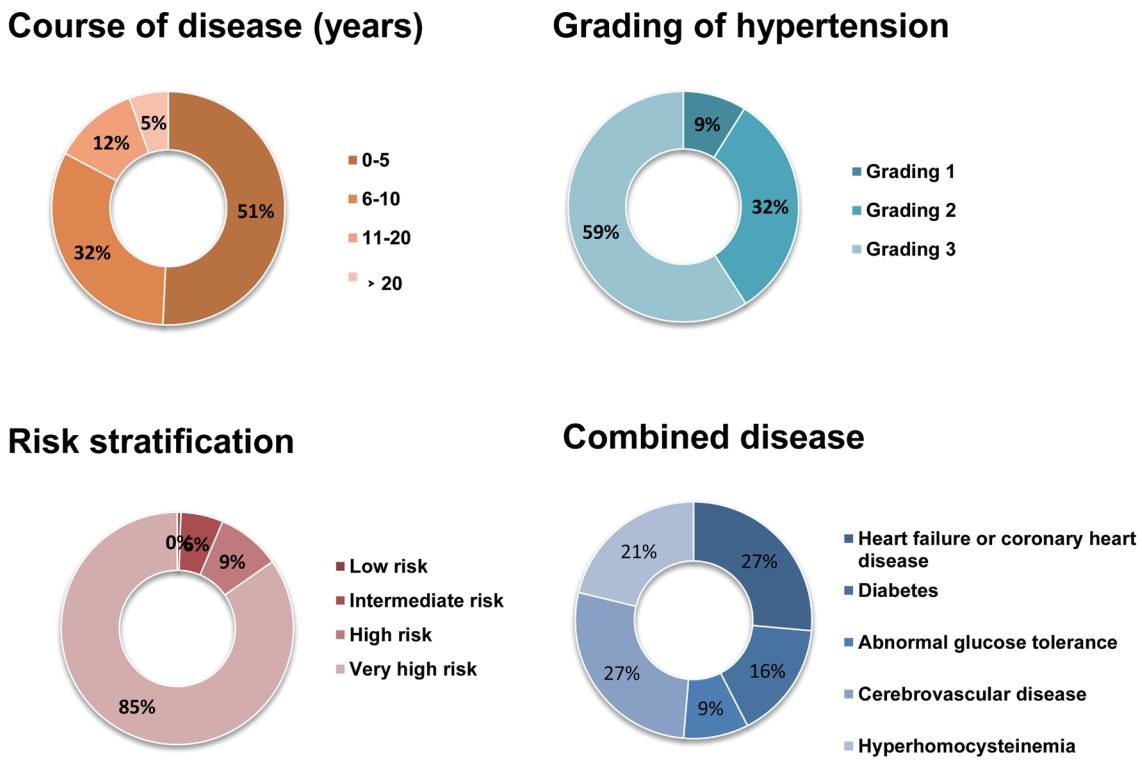

Fig. 1. Basal level characteristics of hypertension patients.

Multivariable regression for hypertension, TCM syndromes and biochemistry indexes

The univariate and multivariable regression analysis for hypertension classification indicated that age, days of hospitalization, years of hypertension, family history, and the comorbidities of left ventricular hypertrophy, cerebrovascular disease and heart disease are associated with the development of hypertension, and that the comorbidities of left ventricular hypertrophy is an independent risk factor for hypertension in this population (Table 4).

The further multivariable regression analysis revealed that abnormal HbA1c levels are associated with the qi-deficiency type of hypertension, but there was no significant association of biochemistry with the other TCM syndromes (Supplementary Tables 1–2).

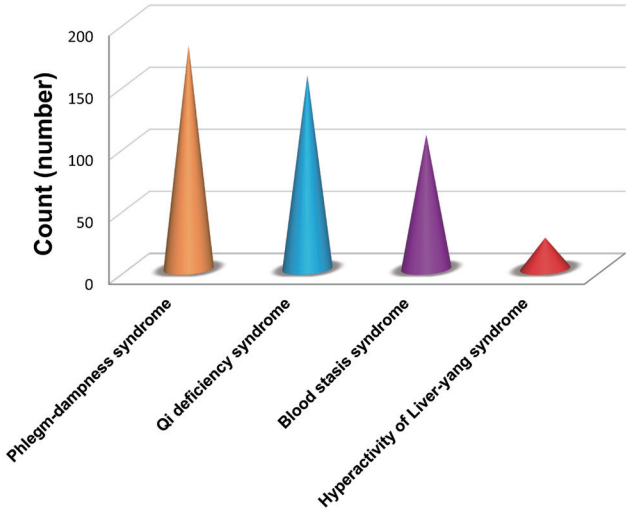

Fig. 2. Distribution of TCM syndromes in hypertension patients. TCM, traditional Chinese medicine.

The correlation between TCM syndromes and risk factors of hypertension

The correlation between the disease course and TCM syndromes was determined by Spearman's correlation analysis. The Spearman's correlation coefficient between the disease course and complexity of the TCM syndromes was 0.185, indicating a positive correlation ($p < 0.05$). Furthermore, the Spearman's correlation coefficient between the disease course and blood stasis syndrome was 0.291, indicating a positive correlation ($p < 0.05$) (Fig. 3 and Table 5).

The further Spearman's analysis revealed that age is positively correlated with blood stasis syndrome (Spearman's correlation co-

Table 3. Distribution of TCM syndromes in hypertension patients

TCM syndromes	Frequency (*n*)	Proportion (%)
Qi-deficiency syndrome	156	33.26
Phlegm-dampness syndrome	180	38.38
Blood stasis syndrome	108	23.03
Liver-yang hyperactivity syndrome	25	5.33
Total	469	100.00

TCM, traditional Chinese medicine.

Table 4. Multivariable regression for hypertension classification and the related confounding

Variable	Model fitting standard value	X^2	*p*
Age	185.006	184.856	0.000*
Gender	0.206	0.056	0.972
Hospitalization days	218.719	218.569	0.000*
Hypertension years	531.453	531.303	0.000*
Smoking	3.702	3.552	0.169
Family history	11.565	11.415	0.003*
Impaired sugar tolerance	0.181	0.031	0.985
Abnormal blood lipid	0.684	0.534	0.766
Left ventricular hypertrophy	107.580	107.430	0.000*
Impaired renal function	0.419	0.268	0.874
Cerebrovascular disease	105.585	105.435	0.000*
Heart disease	133.383	133.233	0.000*
Peripheral vascular disease	1.376	1.226	0.996
Diabetes	3.934	3.784	0.151
Qi-deficiency syndrome	1.428	1.278	0.528
Phlegm-dampness syndrome	3.315	3.164	0.206
Hyperactivity of liver-yang	3.969	3.819	0.148
Complexity of syndrome	0.261	0.110	1.000

Note: *$p < 0.05$ indicates that the difference is statistically significant.

efficient = 0.231, $p < 0.05$) or qi-deficiency syndrome (Spearman's correlation coefficient = 0.187, $p < 0.05$), but not with phlegm-dampness syndrome (Spearman's correlation coefficient = −0.018, $p > 0.05$) in this population. In addition, there was a negative correlation between age and liver-yang hyperactivity syndrome (Spearman's correlation coefficient = −0.167, $p < 0.05$) (Fig. 4 and Table 6).

However, the correlation analysis revealed that there was no statistically significant difference between the blood pressure grade and TCM syndrome. Furthermore, there was no significant

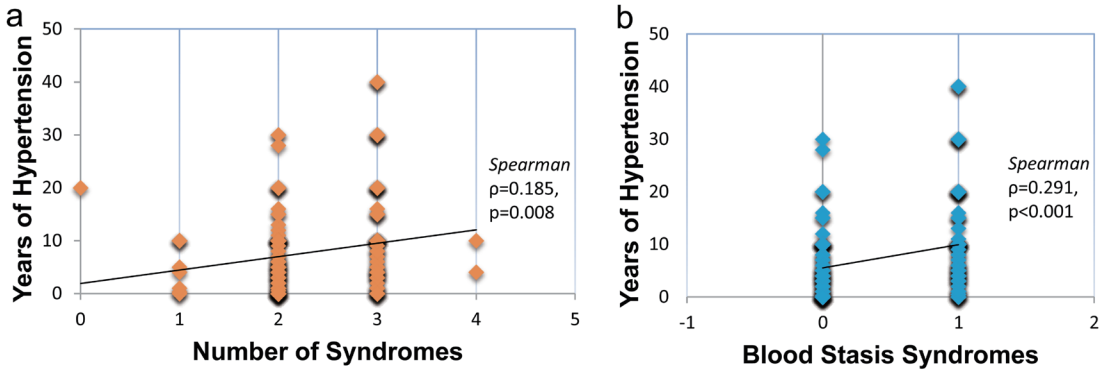

Fig. 3. Correlations between the disease course and complexity of TCM syndromes or blood stasis syndrome. (a) Correlations between the disease course and complexity of TCM syndromes. (b) Correlations between the disease course and blood stasis syndrome. TCM, traditional Chinese medicine.

Table 5. The correlation between the disease course, and complexity of syndrome differentiation or blood stasis syndrome in hypertension patients

Variable		Syndrome differentiation	Blood stasis syndrome
Disease course	Spearman's correlation coefficient	0.185	0.291
	p	0.008*	0.000*

Note: *the difference was statistically significant.

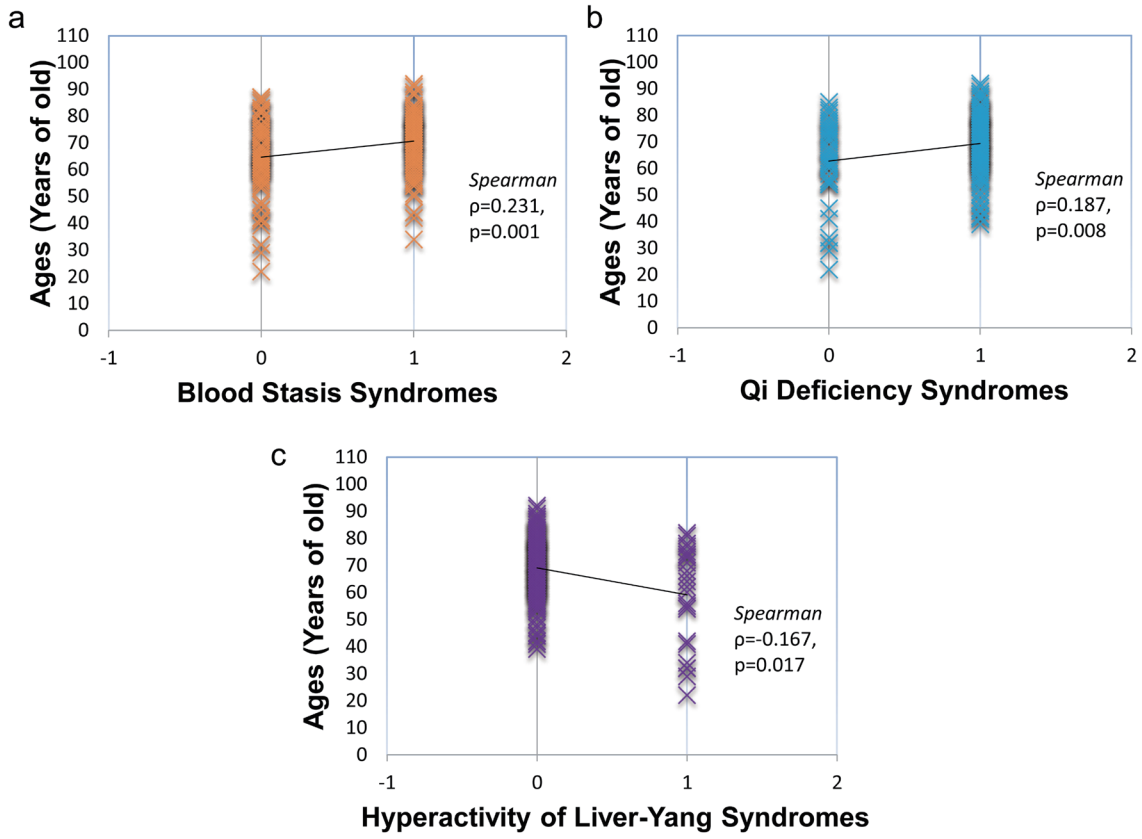

Fig. 4. Correlations between age and TCM syndromes in hypertension. (a) Correlations between age and blood stasis syndrome. (b) Correlations between age and Qi deficiency syndrome. (c) Correlations between age and hyperactivity of Liver-Yang syndrome. TCM, traditional Chinese medicine.

difference in the correlation between the hypertension risk group, and qi-deficiency syndrome (Spearman's correlation coefficient = 0.066, $p > 0.05$) and phlegm-dampness syndrome (Spearman's correlation coefficient = −0.021, $p > 0.05$), suggesting that the correlation between the hypertension risk group, and qi-deficiency syndrome or phlegm-dampness syndrome cannot be considered. Next, the correlation between the hypertension risk group and blood stasis syndrome (Spearman's correlation coefficient = 0.207, $p < 0.05$) was statistically significant, indicating that there may be a positive correlation between the hypertension risk group and blood stasis syndrome. Furthermore, the correlation between the hypertension risk group and liver-yang hyperactivity syndrome

Table 6. The correlation between syndrome differentiation and various variables in hypertensive patients

Variable		Blood stasis syndrome	Qi-deficiency syndrome	Phlegm-dampness syndrome	Liver-yang hyperactivity syndrome
Hypertension grading	Spearman's correlation coefficient	0.061	0.013	0.057	−0.031
	p	0.387	0.856	0.419	0.664
Hypertension risk grouping	Spearman's correlation coefficient	0.207	0.066	−0.021	−0.135
	p	0.003*	0.347	0.764	0.55 (one-tailed test, 0.028*)
Age	Spearman's correlation coefficient	0.231	0.187	−0.018	−0.167
	p	0.001*	0.008*	0.804	0.017*
Combined with diabetes	Spearman's correlation coefficient	0.030	0.101	−0.021	−0.129
	p	0.671	0.150	0.764	0.067 (one-tailed test, 0.034*)
Combined heart disease	Spearman's correlation coefficient	0.160	0.252	0.004	−0.216
	p	0.023*	0.000*	0.957	0.002*

Note: *$p < 0.05$ indicates that the difference was statistically significant. Heart disease refers to heart failure or coronary heart disease.

(Spearman's correlation coefficient = −0.135, one-tailed test, $p < 0.05$) suggested a possible negative correlation.

Discussion

The correlation between TCM syndromes and the hypertension grade

The data indicated that there was no significant correlation between the different types of TCM syndromes and hypertension grade in hypertension patients. The reason for this may be because the present study used the method of splitting complex syndromes into several single syndromes to determine the correlation between each single syndrome and the blood pressure grade. In contrast, previous studies were conducted through cluster analysis, and the single syndrome type and blood pressure grade were not analyzed, which may lead to different conclusions.[8]

The stratification of higher hypertension risk factors revealed that more risk factors existed in hypertensive patients.[13] The correlation between different TCM syndromes and hypertension risk factors indicated that the higher the risk stratification of hypertension, the greater the probability for blood stasis syndrome, and the smaller the probability for liver-yang hyperactivity syndrome in this population. It can be inferred that the liver-yang hyperactivity syndrome mostly occurred in the early stage of hypertension, which is consistent with the reports of other studies,[3] and that TCM for the treatment of hypertension in patients with the liver-yang hyperactivity syndrome can effectively reduce blood pressure.[14]

The correlation between TCM syndromes and disease course of hypertension

The present study revealed that the disease course for hypertension was positively correlated with the complexity of the syndrome differentiation. That is, the longer the disease course, the more complicated the syndrome differentiation. The type of syndrome differentiation is a complex of multiple single syndromes. This may be correlated to the old age of hypertensive patients in the selected sample, and the combination of other geriatric diseases. The development of hypertension would easily damage the target organs, such as the heart,[15,16] brain,[17,18] kidney and eyes, and various comorbidities would interact with each other,[19] thereby increasing the complexity of syndrome differentiation after the change in disease course.

Furthermore, the present study revealed that there is positive correlation between the disease course and blood stasis syndrome. That is, the longer the disease course of hypertension, the more probable the blood stasis syndrome. This coincides with the TCM theory that there would probably be stasis in most chronic diseases. Based on this observations, it can be noted that hypertension is a risk factor for CHD, and that a long-term disease course of hypertension would more easily lead to CHD.[20] In terms of treatment, the existing evidence revealed that the application of TCM, which has the property of promoting blood circulation and removing blood stasis, can effectively treat hypertension and its complications.[21–24]

The correlation between TCM syndromes and age in patients with hypertension

The present study revealed that older patients have a higher chance to develop blood stasis syndrome and qi-deficiency syndrome. Furthermore, the older the patient, the smaller the probability of occurrence of liver-yang hyperactivity syndrome. Similarly, studies have revealed that qi-deficiency is the basic pathogenesis and common syndrome of hypertension in the elderly. Hypertensive patients become weaker as they become older, which is consistent with the results of the present study. Furthermore, as age increases, the disease course of hypertension would become longer. Thus, it can be concluded that the longer the disease course of hypertension, the greater the probability for blood stasis syndrome, and the more complicated the syndrome differentiation.

The correlation between TCM syndromes and plasma homocysteine in hypertension

Studies have revealed that homocysteine is one of the risk factors for cardiovascular and cerebrovascular diseases in the Chinese population.[25–27] However, the present study revealed that there was no correlation between the individual syndrome of hypertensive patients and plasma homocysteine levels. This may be correlated to the small sample size of the study, or the small proportion of hyperhomocysteinemia patients. Another reason may be that the present study was performed based on a single syndrome, instead of complex syndrome differentiations for hypertension. Further investigations are needed to confirm the relationship between the homocysteine level and TCM syndromes for hypertension.

The present data indicates that the syndromes for hypertension were differentially distributed in the distinct ages of patients. In the elderly, the most common syndromes for hypertension were blood stasis syndrome and qi-deficiency syndrome, while liver-yang hyperactivity syndrome mostly occurred in young patients. The complexity of TCM syndromes, particularly blood stasis syndrome, would accumulate as the disease course of hypertension is prolonged. The present data is consistent to some reports on the different distributions of TCM syndromes in hypertension patients.[3,28] Thus, the syndrome differentiation and treatment of TCM should be carried out based on the age of the patient and duration of the disease course (years), in order to help in the administration of Chinese medication after individual treatment.

Future directions

Future studies would focus in illustrating the underlying mechanisms and determining why these TCM syndromes were correlated with hypertension risk factors, thereby providing evidences to understand Chinese medicine theories.

Conclusions

Overall, the present study revealed that the distribution of TCM syndromes in patients with hypertension, from more to less is, as follows: qi-deficiency syndrome, phlegm-dampness syndrome, blood stasis syndrome and liver-yang hyperactivity syndrome. The univariate and multivariable regression for the confounding of the hypertension classification revealed that the comorbidity of left ventricular hypertrophy was probably an independent risk factor for hypertension classification. The correlation analysis revealed that the disease course is positively correlated with the complexity of the TCM syndrome or blood stasis syndrome, and that age is positively correlated with blood stasis syndrome or qi-deficiency syndrome, while age is negatively correlated with liver-yang hyperactivity syndrome.

Compared to several studies that discussed the correlation between Chinese medicine syndromes and hypertension, the present study selected elderly patients with a mean age of >65 years old, in

order to determine the relationship between the geriatric disease, and TCM syndrome differentiation and treatment. The present retrospective study revealed the relationship between TCM syndromes and the clinical risk factors of hypertension. This would be helpful in interpreting the process for classifying and distinguishing TCM syndromes with common clinical risk factors, which may provide guidance for individual clinical medications, helping to bridge the gap between Eastern and Western medicine, to some extent.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/JERP.2022.00071.

Supplementary Table 1. A single sample in the normality test using the Kolmogorov-Smirnov method.

Supplementary Table 2. Multivariable regression for the TCM syndrome for qi-deficiency and related biochemistry indexes.

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Conflict of interest

The authors declare that there are no competing interests.

Author contributions

The study was designed by QL. The initial search, data analysis and manuscript writing were performed by ZZ. The critical comments and typesetting correction on the final version were made by QL and RY. The manuscript was finalized by QL. All authors have critically read and revised the manuscript.

Ethical statement

The study was approved by the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (No. ZE2019-079-01).

Data sharing statement

The technical appendix, statistical code, and dataset are available from the corresponding author on reasonable request (E-mail: 851757626@qq.com).

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