European Journal of Integrative Medicine 32 (2019) 101001

Contents lists available at ScienceDirect

European Journal of Integrative Medicine

journal homepage: www.elsevier.com/locate/eujim

Research paper

A retrospective database analysis of traditional Chinese medicine syndromes in patients with chronic obstructive pulmonary disease and asthma

Qing Kong[a,1], Rongrong Jiang[b,1], Mihui Li[a], Fei Xu[a], Yuanhao Zhang[a], Zihui Tang[a,c,*], Jingcheng Dong[a,*]

[a] Department of Integrative Medicine, Huashan Hospital, Fudan University, Shanghai, China
[b] Department of Cardiothoracic Surgery, Huashan Hospital, Fudan University, Shanghai, China
[c] Department of Biomedical Informatics and Statistics, Institutes of Integrative Medicine, Fudan University, Shanghai, China

ARTICLE INFO

Keywords:
Real-world evidence
Traditional Chinese medicine
Electronic health records
Syndrome
Chronic obstructive pulmonary disease
Asthma
Logistic regression
Generalized linear model
Registry study

ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) and asthma have common characteristics both in terms of their pathology and clinical symptoms, but whether they share the same traditional Chinese medicine syndromes (TCMS) is unclear. This study compared the distribution of TCMS for chronic obstructive pulmonary disease (COPD) and asthma by using a large data set of clinical records which would reflect real world practice.
Methods: Electronic medical records were used from five hospitals in China between 2012 and 2016. A total of 26,074 subjects with complete medical records were available for data analysis. Frequencies and multinomial logistic regressions (LR) were conducted to determine independent and significant TCMS associated with COPD or asthma compared to a shared reference of other respiratory diseases. Bivariate association analyses were conducted to estimate shared TCMS for the two diseases by using general linear model.
Results: Multinomial LR showed that Tan_Re_Yong_Fei was independently and significantly associated with both COPD and asthma ($P < 0.001$ for both). Similarly, Fei_Shen_Qi_Xu had a significant, independent, and respective association with the two diseases ($P < 0.001$ for both). Bivariate associated analyses indicated that the Shi TCMS (excess syndrome) of Tan_Re_Yong_Fei was associated with the two diseases ($P < 0.001$) and Xu TCMS (deficiency syndrome) of Fei_Shen_Qi_Xu was associated with both outcomes ($P < 0.001$).
Conclusion: The shared core Shi TCMS (excess syndrome) for both COPD and asthma was Tan_Re_Yong_Fei, and the shared core Xu TCMS (deficiency syndrome) was Fei_Shen_Qi_Xu.
(Trial registration, ClinicalTrials.gov ID: NCT03274908, Registered September 8, 2017.)

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease that affects 5%–10% of people 45 years of age are older worldwide [1]. Globally, almost three million people die from COPD, making it the fourth leading cause of mortality. It is generally accepted that protease-antiprotease autoimmunity, balance, mucus hypersecretion, airway remodeling, and chronic respiratory infection all contribute to the disease [1]. Asthma is also a common chronic disease, affecting over 300 million people throughout the world [2]. Moreover, the prevalence of asthma is rising, particularly in developing countries. The characteristic pathology of asthma is airway inflammation, which is manifested by the infiltration of the eosinophils and increasing the number of activated T helper (Th) 2 cells, all of which promote airway inflammation by releasing multiple cytokines [3,4].

Traditional Chinese medicine (TCM) is becoming increasingly recognized and popular worldwide, and is a style of traditional medicine built on a foundation of more than 2500 years of medical practice in China, however recently also influenced by modern medicine [5]. Traditional Chinese medicine syndrome (TCMS), also called Zheng, has been used to classified patients into various categories on the basis of the TCM four diagnostic categories [6]. In China, the TCM treatment of

Abbreviations: TCM, traditional Chinese medicine; TCMS, traditional Chinese medicine syndrome; COPD, chronic obstructive pulmonary disease; LR, logistic regressions; EMR, electronic medical records; HIS, hospital information systems; LIS, laboratory information systems; RDs, respiratory diseases; PACS, picture archiving and communication systems

* Corresponding authors at: Department of Integrative Medicine, Huashan Hospital, Fudan University, No. 12 Urumqi Middle Road, Shanghai, 200040, China.
E-mail addresses: kq2016829@163.com (Q. Kong), 0456152@fudan.edu.cn (R. Jiang), perfectlmh@sina.com (M. Li), xufeigaomi@163.com (F. Xu), shengdan210811@sina.com (Y. Zhang), dr_zhtang@yeah.net (Z. Tang), dongjcfdu@yeah.net (J. Dong).
[1] Q.K. and R.J. have contributed equally to this work.

https://doi.org/10.1016/j.eujim.2019.101001
Received 8 April 2019; Received in revised form 27 October 2019; Accepted 27 October 2019

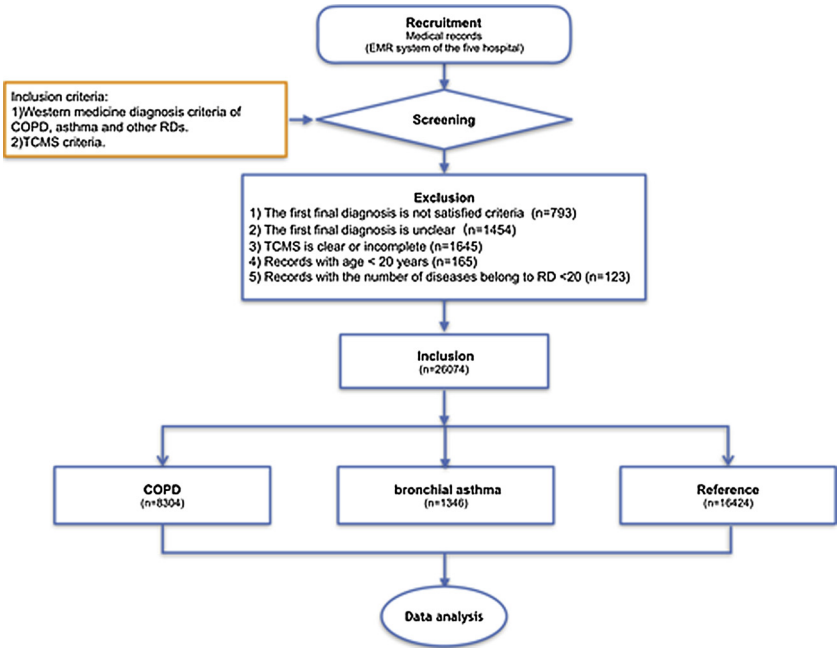

Fig. 1. The flow chart of the included and excluded records.

COPD and asthma has a long history, which is based on TCMS differentiation. In ancient times, COPD and asthma were called gasp syndrome and wheezing disease. As we all know, though they belong to different diseases, they have common symptoms. According to the TCM differentiation method, COPD and asthma possess common syndromes. Nevertheless, previous studies on the TCMS of COPD and asthma have usually been implemented separately, or have a small sample size [7–9]. In modern medicine, COPD and asthma both show the pathological characteristics of airway inflammation, which is influenced by the increased expression of multiple inflammatory proteins, including cytokines, adhesion molecules, chemokines, and airway remodeling [3]. Both severe asthma and COPD patients have an increased number of neutrophils in the sputum and an increased amount of CXCL8, as well as a poor response to corticosteroids and increased oxidative stress. In addition, there is a co-existence of Th1 andTh2, and more CD8 + T cells were observed in the bronchial biopsies in cases of severe asthma and COPD [10,11].

As mentioned above, evidence from basic medical science shows a shared underlying pathophysiology for the two diseases, and clinical evidence indicates shared signs and syndromes for the two diseases. We hypothesized that some TCMS are associated with both COPD and asthma and that shared TCMS might be linked to both COPD and asthma. Our previous real-world study was carried out to assess the distribution of TCMS and its elements for entire respiratory disease by using machine learning algorithms and big data approaches [12]. However, few investigations of TCMS or shared ones associated with COPD and asthma have been done. This work was aimed at comparing the distribution of TCMS in COPD and asthma to identify the shared TCMS of both COPD and asthma, and provide solid evidence for TCM principles regarding the treatment of different diseases with the same method.

2. Methods

2.1. Study design and participants

As was detailed in our previous study [12], a real-world study was conducted using electronic medical records to evaluate the relationships between TCMS found with COPD and asthma. A total of 26,074 subjects with complete medical record were available for data analysis. In this multicenter, retrospective, hospital-based, observational study, a total of 30,254 records of respiratory disease were extracted from five hospitals between 2012 and 2016. To be included in the study, a patient's first final diagnosis had to satisfy the diagnostic criteria of modern medicine for respiratory diseases and subjects had to be over the age of 18 [12].

2.2. Data collection and preparation

Data from medical records were extracted from the EMR systems of the five hospitals and loaded into the integrative medical data warehouse in our institute [12]. Respiratory diseases (RDs) included COPD, bronchial asthma, and other RDs were used as reference. The diagnosis criteria of COPD and asthma and the other RDs were based on clinical guidelines of RD in China and the book *Harrison's Principles of Internal Medicine* [13,14]. The definition criteria of these TCMS were based on the National Standard for Clinical Diagnosis and Treatment of Traditional Chinese Medicine Syndrome - Respiratory system disease syndrome (Supplementary file - National_Standard _TCM_ Syndrome.pdf). As was mentioned in our previous study [12], we excluded records with the first finial diagnosis not satisfying the diagnostic criteria of RDs (n = 793), and records with unclear the first final diagnosis for RDs (n = 1454), and records with unclear or incomplete TCMS (n = 1645), records with age < 20 years (n = 165) and records with the number of diseases belong to RD < 20 (n = 123). A total of 26,074 subjects with complete medical records were available for data analysis. The flow chart detailing the inclusion exclusion of records is shown in Fig. 1.

2.3. Data analysis

Differences in the continuous variables among subjects categorized by COPD, asthma, and reference were assessed by one-way analysis of variance. Differences in properties among the groups were detected by $\chi 2$ analysis. We employed univariate logistic regression to estimate the variables associated with diseases to estimate the confounding factors that might disturb the associations between a TCMS and COPD or asthma. As was mentioned in our previous study [15], we carried out multinomial logistic regression to evaluate the associations between the different outcome categories and candidate predictors that allows to assess the probability of COPD and asthma compared with the reference

category, simultaneously. Multinomial logistic regression includes several logistic regression models simultaneously to evaluate the relationships between predictors and each of the outcomes as compared to the reference category simultaneously so that the regression coefficients may differ per outcome [16]. Multivariable logistic regression controlling for confounding factors was conducted to evaluate the associations of the independent variables to COPD or asthma. We employed generalized linear model to perform bivariate association analysis that may treat correlations of outcomes so as to be more power to identify the shared contributors to outcomes compared with univariate association analysis [17]. The generalized linear model detects shared predictors to simultaneously include the dependencies of both COPD and asthma. In addition, odds ratios (OR) with 95% confidence intervals (CI) were computed for the relative risk of a TCMS with COPD or asthma. The results were analyzed using the Statistical Package for the Social Sciences for Windows version 16.0 (SPSS, Chicago, IL, USA). The tests were two-sided and a P-value of < 0.05 was considered significant.

3. Results

3.1. Characteristics of individuals

The characteristics of the 26,074 individuals were detailed in previous study [12]. The proportion of males (n = 15,350) was 58.87% and the mean age was 65.70 years in the entire sample. The improvement and cure rate for patients was 95.16%. The mean hospitalization duration was 11.86 days.

3.2. Frequency analysis of TCMS for COPD and asthma

The distributions of COPD, asthma, and reference in the entire sample are showed in Table 1. The proportions of COPD and asthma were 32.05% and 5.16%, respectively. The distributions of TCMS for COPD, asthma, and reference are showed in Table 1. The top four proportions of Shi TCMS (excess syndrome) were 27.61%, 25.60%, 10.49%, and 6.81%, respectively, please see Table 2. The top four proportions of Xu TCMS (deficiency syndrome) were 5.80%, 5.60%, 1.22%, and 0.69, respectively.

In the entire sample, the proportions of Tan_Re_Yong_Fei in COPD, asthma, and reference were 29.72%, 30.76%, and 26.28%, respectively (Fig. 2), while in Shi TCMS (excess syndrome), the proportions of Tan_Re_Yong_Fei were 37.64%, 33.99%, and 32.72%, respectively (Fig. 3). The other three TCMS in COPD, asthma, and reference for the entire sample are showed in Fig. 2, and for Shi TCMS (excess syndrome) are listed in Fig. 3. For Xu TCMS (deficiency syndrome) analysis, the proportions of Fei_Qi_Xu in COPD, asthma, and reference in the entire sample were 0.81%, 0.67%, and 0.64%, respectively (Fig. 4), and in Xu TCMS (deficiency syndrome), the proportions of Fei_Qi_Xu were 5.35%, 8.41%, and 4.72%, respectively (Fig. 5). The proportions of Fei_Shen_Qi_Xu in COPD, asthma, and reference were 13.21%, 2.82%, and 2.30%, respectively. The proportions of Fei_Shen_Qi_Xu in COPD, asthma, and reference were 87.55%, 35.51%, and 16.99%, respectively. The distributions of the other two TCMS are shown in Figs. 4 and 5.

Multinomial logistic regression analysis of Shi TCMS (excess syndrome) for COPD and asthma

In the entire sample, there were significant differences in the distribution of the TCMS for the four Shi TCMS (excess syndrome) in COPD and asthma compared to reference by using multinomial logistic regression ($P < 0.001$ for all, Table 2). In Tan_Re_Yong_Fei TCMS, the OR of COPD was 1.186 and the OR of asthma was 1.246 ($OR > 1.0$ for both). In addition, the ORs of COPD and asthma were less than 1.0 in the other three TCMS (see Table 2).

In the Shi TCMS (excess syndrome) group, the distributions of the four Shi TCMS (excess syndrome) in COPD and asthma compared to reference had significant differences according to multinomial logistic regression ($P < 0.001$ for all, Table 2). In the Tan_Re_Yong_Fei TCMS, the OR of COPD was 1.241 and the OR of asthma was 1.059 ($OR > 1.0$ for both). However, in the other three TCMS, the ORs of COPD and asthma were less than 1.0 (see Table 2).

Multinomial logistic regression analysis of Xu TCMS (deficiency syndrome) for COPD and asthma

Table 1
Distribution of traditional Chinese medicine syndrome for chronic obstructive pulmonary disease, asthma and reference group.

Model	TCM syndrome	COPD (%)	Asthma (%)	Reference(%)	Total(%)
Shi	Tan_Re_Yong_Fei	2468(29.72)	414(30.76)	4316(26.28)	7198(27.61)
	Tan_Zhuo_Zu_Fei	3521(42.4)	188(13.97)	2965(18.05)	6674(25.6)
	Feng_Re_Fan_Fei	63(0.76)	19(1.41)	2652(16.15)	2734(10.49)
	Feng_Han_Xi_Fei	61(0.73)	187(13.89)	1528(9.3)	1776(6.81)
	Shui_Ling_Xin_Fei	216(2.6)	7(0.52)	676(4.12)	899(3.45)
	Tan_Yu_Zu_Fei	79(0.95)	113(8.4)	257(1.56)	449(1.72)
	Wai_Han_Nei_Yin	52(0.63)	201(14.93)	21(0.13)	274(1.05)
	Qi_Zhi_Xue_Yu	11(0.13)	3(0.22)	239(1.46)	253(0.97)
	Gan_Huo_Fan_Fei	2(0.02)	2(0.15)	242(1.47)	246(0.94)
	Biao_Han_Fei_Re	22(0.26)	3(0.22)	145(0.88)	170(0.65)
	Tan_Meng_Shen_Qiao	60(0.72)	1(0.07)	20(0.12)	81(0.31)
	Feng_Tan_Zu_Fei	0(0)	58(4.31)	22(0.13)	80(0.31)
	Qi_Zhi_Xin_Xiong	1(0.01)	0(0)	77(0.47)	78(0.3)
	Re_Du_Yong_Fei	1(0.01)	22(1.63)	31(0.19)	54(0.21)
Xu	Fei_Shen_Qi_Xu	1097(13.21)	38(2.82)	378(2.3)	1513(5.8)
	Fei_Yin_Xu	28(0.34)	55(4.09)	1376(8.38)	1459(5.6)
	Fei_Shen_Qi_Yin_Liang_Xu	48(0.58)	4(0.3)	265(1.61)	317(1.22)
	Fei_Qi_Xu	67(0.81)	9(0.67)	105(0.64)	181(0.69)
	Qi_Xue_Kui_Xu	4(0.05)	0(0)	60(0.37)	64(0.25)
	Fei_Pi_Qi_Xu	9(0.11)	1(0.07)	39(0.24)	49(0.19)
Mix	Fei_Pi_Qi_Xu_Tan_Shi_Yun_Fei	216(2.6)	13(0.97)	129(0.79)	358(1.37)
	Fei_Shen_Qi_Xu_Tan_Yu_Zu_Fei	24(0.29)	4(0.3)	328(2)	356(1.37)
	Fei_Pi_Qi_Xu_Tan_Yu_Zu_Fei	0(0)	0(0)	304(1.85)	304(1.17)
	Fei_Shen_Qi_Xu_Tan_Shi_Yun_Fei	127(1.53)	3(0.22)	42(0.26)	172(0.66)
	Qi_Yin_Liang_Yu_Xue_Nei_Zu	5(0.06)	0(0)	144(0.88)	149(0.57)
	Fei_Shen_Qi_Xu_Tan_Re_Yong_Fei	71(0.86)	0(0)	46(0.28)	117(0.45)
	Fei_Pi_Qi_Xu_Tan_Re_Yong_Fei	51(0.61)	1(0.07)	17(0.1)	69(0.26)
	Total	8304(100)	1346(100)	16,424(100)	26,074(100)

Note: TCM - traditional Chinese medicine, Shi syndrome - excess syndrome, Xu syndrome - deficiency syndrome.

Table 2
Multinomial logistic regression to include Shi traditional Chinese medicine syndrome (excess syndrome) for chronic obstructive pulmonary disease and asthma.

Group	TCM syndrome	Disease	Bate	S.E	P value	OR	95% CI for OR
Entire	Tan_Re_Yong_Fei	COPD	0.171	0.03	< 0.001	1.186	1.119-1.258
		Asthma	0.22	0.062	< 0.001	1.246	1.104-1.406
	Tan_Zhuo_Zu_Fei	COPD	1.206	0.03	< 0.001	3.342	3.150-3.545
		Asthma	−0.305	0.081	< 0.001	0.737	0.629-0.864
	Feng_Re_Fan_Fei	COPD	−3.226	0.128	< 0.001	0.040	0.031-0.051
		Asthma	−2.599	0.232	< 0.001	0.074	0.047-0.117
	Feng_Han_Xi_Fei	COPD	−2.629	0.131	< 0.001	0.072	0.056-0.093
		Asthma	0.453	0.083	< 0.001	1.573	1.336-1.852
Shi	Tan_Re_Yong_Fei	COPD	0.216	0.032	< 0.001	1.241	1.167-1.32
		Asthma	0.057	0.023	0.0436	1.059	1.011-1.107
	Feng_Re_Fan_Fei	COPD	−3.256	0.128	< 0.001	0.039	0.030-0.050
		Asthma	−2.765	0.232	< 0.001	0.063	0.04-0.099
	Feng_Han_Xi_Fei	COPD	−2.636	0.131	< 0.001	0.072	0.055-0.093
		Asthma	0.325	0.084	< 0.001	1.384	1.174-1.632
	Tan_Zhuo_Zu_Fei	COPD	1.386	0.032	< 0.001	4.000	3.754-4.262
		Asthma	−0.463	0.082	< 0.001	0.630	0.536-0.739

Note: multiple variable adjusted for age, gender, duration of hospitalization; TCM - traditional Chinese medicine, COPD - chronic obstructive pulmonary disease, Shi syndrome- excess syndrome.

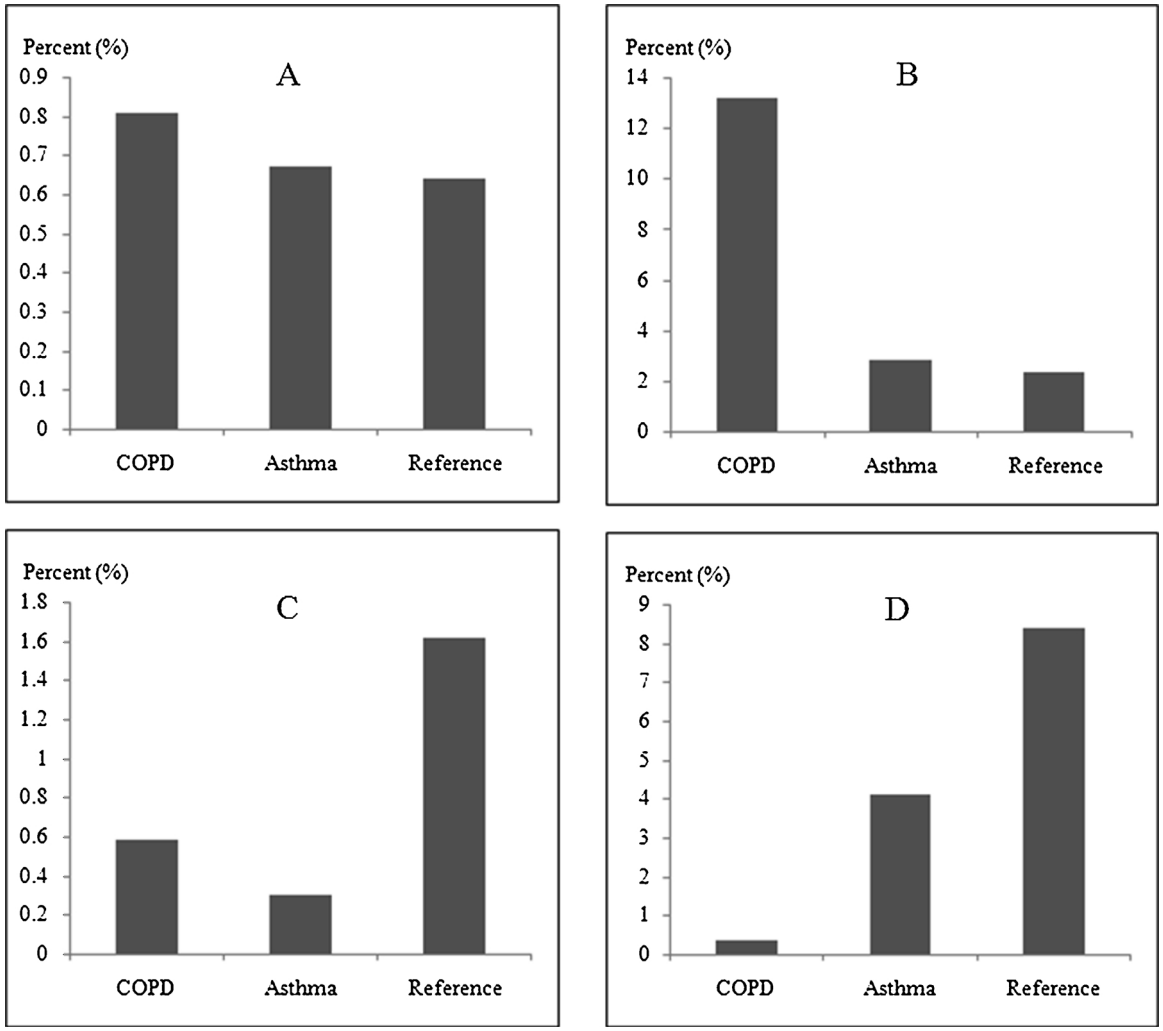

Fig. 2. The distribution of Shi TCMS (excess syndrome) in COPD, asthma and reference in entire sample. TCMS - traditional Chinese medicine syndrome, COPD - chronic obstructive pulmonary disease.
A: the proportion of Tan_Re_Yong_Fei in COPD, asthma and reference were 29.72%, 30.76% and 26.28%; B: the proportion of Tan_Zhuo_Zu_Fei in COPD, asthma and reference were 42.40%, 13.97% and 18.05%. C: the proportion of Feng_Re_Fan_Fei in COPD, asthma and reference were 0.76%, 1.41% and 16.15%; D: the proportion of Feng_Han_Xi_Fei in COPD, asthma and reference were0.73%, 13.89% and 9.30%.

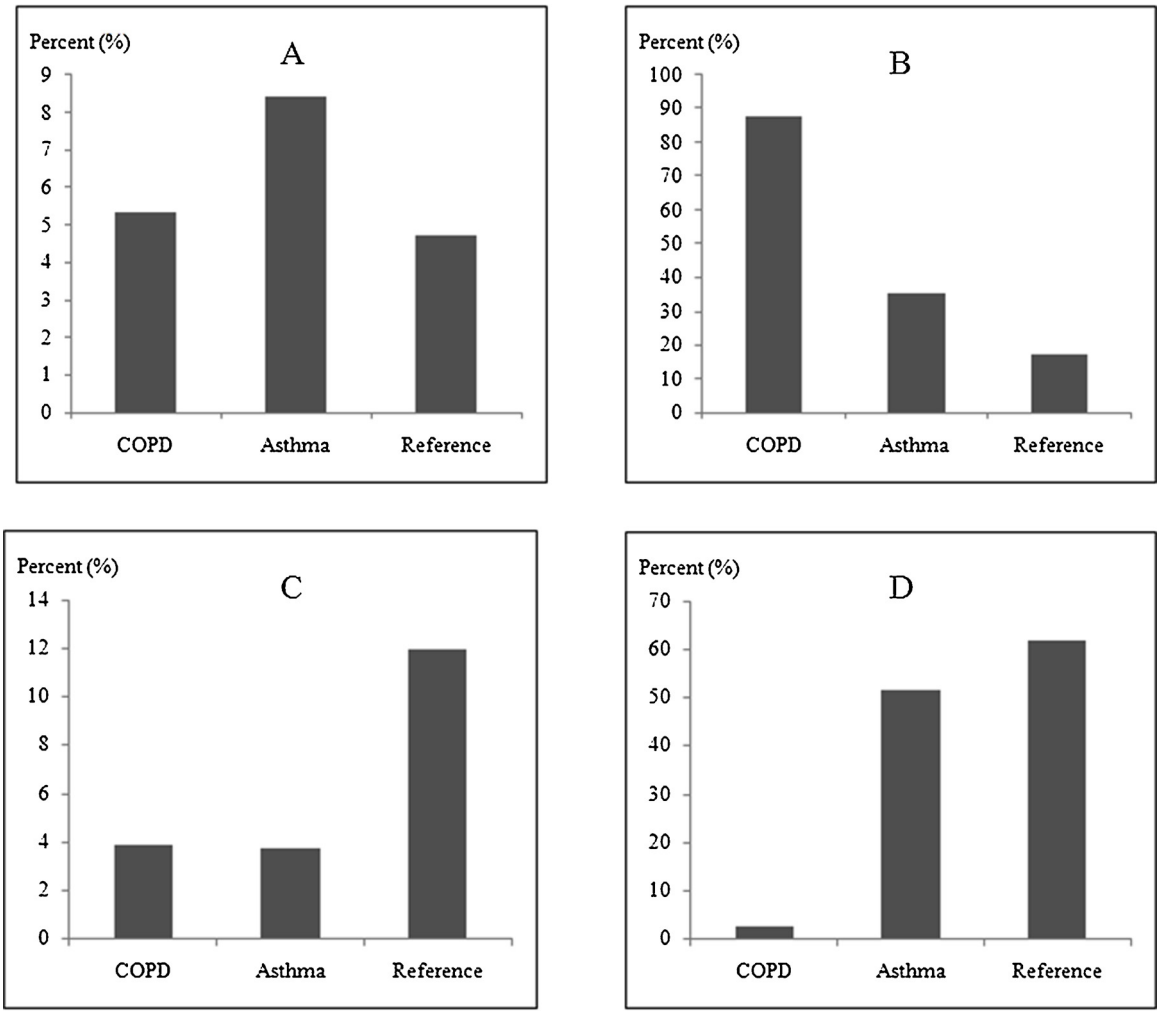

Fig. 3. The distribution of Shi TCMS (excess syndrome) in COPD, asthma and reference in Shi TCMS (excess syndrome) sample. TCMS - traditional Chinese medicine syndrome, COPD - chronic obstructive pulmonary disease.
A: the proportion of Tan_Re_Yong_Fei in COPD, asthma and reference were 37.64%, 33.99% and 32.72%; B: the proportion of Tan_Zhuo_Zu_Fei in COPD, asthma and reference were 53.70%, 15.44% and 22.48%.C: the proportion of Feng_Re_Fan_Fei in COPD, asthma and reference were0.93%, 15.35% and 11.58%; D: the proportion of Feng_Han_Xi_Fei in COPD, asthma and reference were0.96%, 1.56% and 20.10%.

After controlling for confounding factors, there were significant differences in the distributions of the TCMS syndromes for the three Xu TCMS (deficiency syndrome) in COPD and asthma as compared with reference according to multinomial logistic regression ($P < 0.001$ for three, Table 3). In the Fei_Shen_Qi_Xu TCMS, the OR of COPD was 6.461 and the OR of asthma was 1.233(OR > 1.0 for both). However, in the other two TCMS, the ORs of COPD and asthma were less than 1.0 (see Table 3).

The distribution of the three Xu TCMS (deficiency syndrome) in COPD and asthma compared to reference were significantly different according to multinomial logistic regression in the Xu TCMS (deficiency syndrome) group ($P < 0.001$ for three, Table 3). In Fei_Shen_Qi_Xu TCMS, the ORs of COPD and asthma were greater than 1.0. However, in the other two TCMS, the ORs of COPD and asthma were less than 1.0 (see Table 3).

3.3. Bivariate association analysis for COPD and asthma

The bivatiate association analysis in Shi TCMS (excess syndrome) for both COPD and asthma showed that Tan_Re_Yong_Fei was a shared predictor of both outcomes (in the entire sample: Wilks'$\lambda = 0.998$, $P < 0.001$; in the Shi TCMS (excess syndrome) sample: Wilks'$\lambda = 0.998$, $P < 0.001$; Table 4). In Xu TCMS (deficiency syndrome) sample, Fei_Shen_Qi_Xu was a shared contributor to both COPD and asthma (in the entire sample: Wilks'$\lambda = 0.953$, $P < 0.001$; in the Xu TCMS (deficiency syndrome) sample: Wilks'$\lambda = 0.543$, $P < 0.001$; Table 5).

4. Discussion

The term real-world study (RWS) has been increasingly used in clinical studies to integrate experience-based medicine with evidence-based medicine [18]. The advantage of RWS lies in the large sample databases and the close connection with the real world. To the best of our knowledge, this is the first study to evaluate the shared TCMS for COPD and asthma that were related to so many cases in the real world. In China, TCM treatment of COPD and asthma has been based on the various symptoms for thousands of years. In TCM, a syndrome reveals the intrinsic nature of a disease and reflects the nature of pathological changes at certain stages [19]. TCM practitioners usually classify the patterns of symptoms based on eight major parameters. There is also zang-fu syndrome differentiation and qi, blood, and body fluid syndrome differentiation [8]. Because syndrome differentiation is the core of disease diagnosis, patients with the same disease may exhibit different syndromes and should receive different treatments [20]. In contrast, patients with different diseases may show the same symptoms

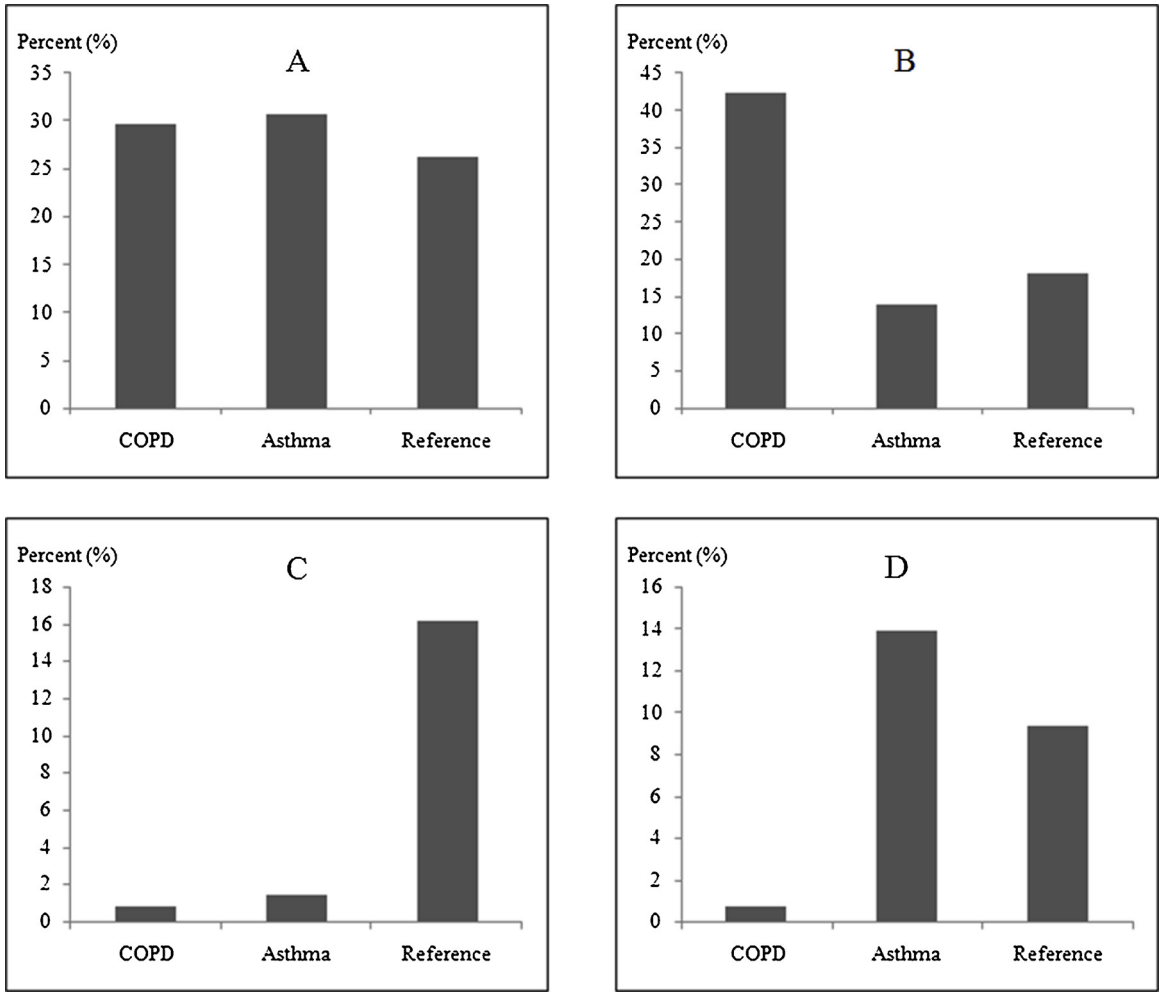

Fig. 4. The distribution of Xu TCMS (deficiency syndrome) in COPD, asthma and reference in entire sample. TCMS - traditional Chinese medicine syndrome, COPD - chronic obstructive pulmonary disease.
A: the proportion of Fei_Qi_Xu in COPD, asthma and reference were 0.81%, 0.67% and 0.64%; B: the proportion of Fei_Shen_Qi_Xu in COPD, asthma and reference were 13.21%, 2.82% and 2.30%; C: the proportion of Fei_Shen_Qi_Yin_Liang_Xu in COPD, asthma and reference were 0.58%, 0.30% and 1.61%; D: the proportion of Fei_Shen_Yin_Xu in COPD, asthma and reference were 0.34%, 4.09% and 8.38%.

and syndromes, so they should receive the same treatment, which is called treatment of different diseases with the same method. It is so important for TCM physicians to understand and clarify the relationship of TCMS with COPD and asthma, especially the TCMS associated with both outcomes.

The interesting finding of this work was that the core Shi syndrome (excess syndrome) for COPD and asthma was Tan_Re_Yong_Fei. A multinomial logistic regression analysis showed that Tan_Re_Yong_Fei was significantly associated with COPD and asthma. Moreover, the proportion of Tan_Re_Yong_Fei was significantly higher in COPD and asthma as compared to reference. A bivariate association analysis confirmed that the shared core Shi TCMS (excess syndrome) was associated with both COPD and asthma. The Tan_Re_Yong_Fei symptoms are: cough, yellow phlegm, fever, flushing, red tongue, yellow and grease fur, and floating rapid pulse [21]. The TCM pathogenesis of Tan_Re_Yong_Fei is that the exogenous pathogenic factors attack the human body, resulting in pathological products of phlegm and heat obstructing the lung, which damage the qi function of the lung, leading to the symptoms of the exacerbation of COPD and asthma [22]. TCM classifies a series of symptoms of heat, phlegm, and lung symptoms to Tan_Re_Yong_Fei syndrome. In Western medicine, the most typical symptoms of the exacerbation of COPD and asthma are also cough, dyspnea, sputum purulence, and sometimes fever [23,24].

Another interesting finding was that during the exacerbation of COPD and asthma. Multinomial logistic regression showed that the proportion of Tan_Re_Yong_Fei was significantly higher in COPD and asthma as compared with reference. Bivariate association analysis showed that Fei_Shen_Qi_Xu is the most typical shared core TCMS among all the Xu syndromes (deficiency syndrome). In TCM, lung and kidney have a close connection with each other physiologically and pathologically. According to the TCM five elements theory, the lungs are the mothers of the kidneys, which easily leads to a lung disorder passing to the kidneys [25]. In the human body, the lung plays a leading role and the kidney plays a foundation role in Qi movement. The pathogenesis of Fei_Shen_Qi_Xu is that the Qi function is damaged because of congenital constitution or macronosia, which manifests as cough, shortness of breath, fatigue, soreness, and weakness of the waist and knees [26].

TCM have been used widely in China and have good effects on lung disease, including COPD and asthma. Despite the existence of effective therapies, including corticosteroids (ICS) and ß$_2$-agonists (LABA); in China, over half of the patients with asthma are poorly controlled and there is a high mortality in the exacerbation of COPD due to its comorbidities [27–29]. With TCM, the immune state can be balanced, which decreases acute asthma attacks, relieves symptoms, improves the life quality of patients, and attenuates the symptoms of the exacerbation of COPD and asthma [22]. According to TCM rules, during the exacerbation of COPD and asthma, TCM attaches importance to treating

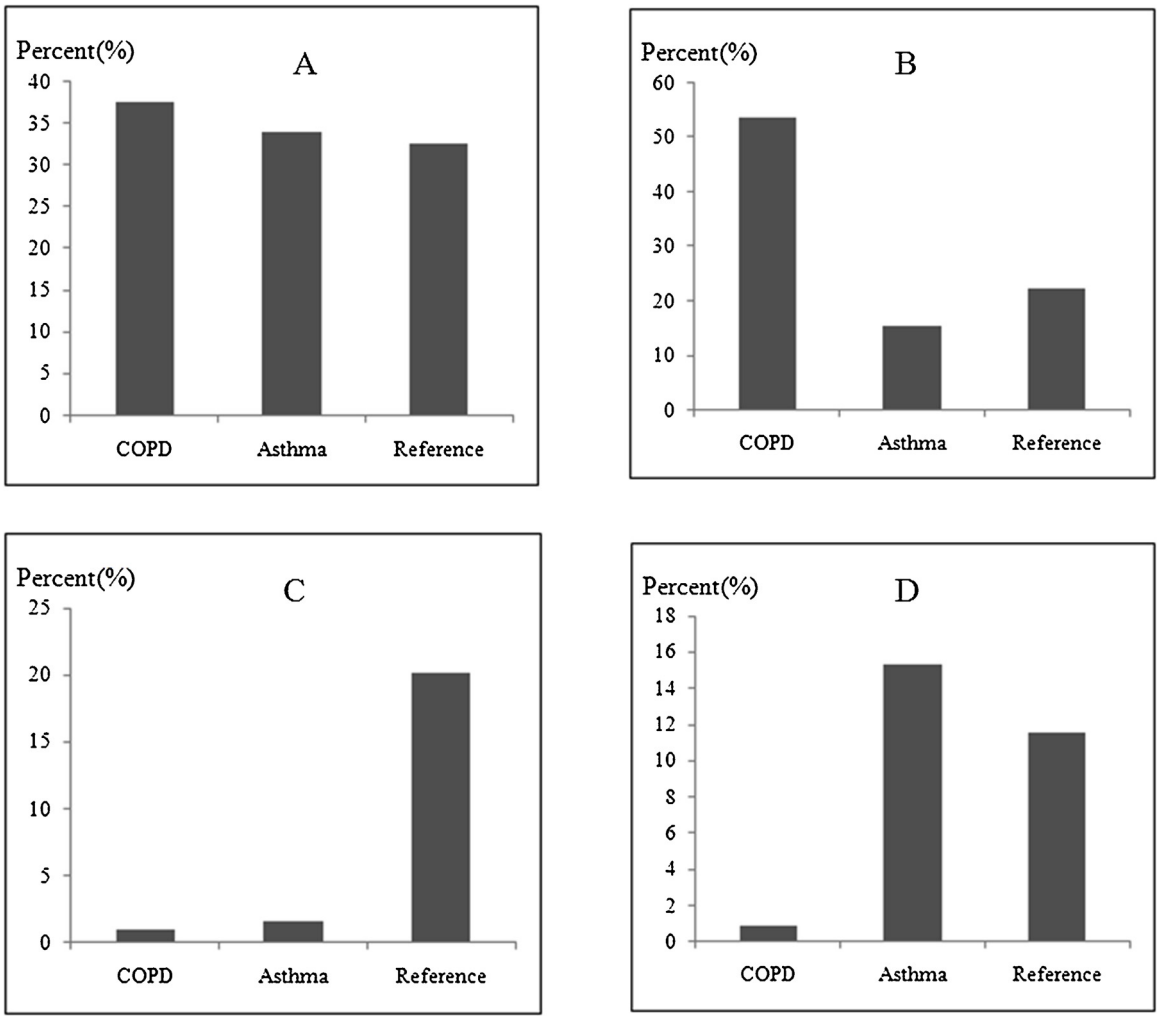

Fig. 5. The distribution of Xu TCMS (deficiency syndrome) in COPD, asthma and reference in Xu TCMS (deficiency syndrome) sample. TCMS - traditional Chinese medicine syndrome, COPD - chronic obstructive pulmonary disease.
A: the proportion of Fei_Qi_Xu in COPD, asthma and reference were 5.35%, 8.41% and 4.72%; B: the proportion of Fei_Shen_Qi_Xu in COPD, asthma and reference were 87.55%, 35.51% and 16.99%; C: the proportion of Fei_Shen_Qi_Yin_Liang_Xu in COPD, asthma and reference were 3.83%, 3.74% and 11.91%; D: the proportion of Fei_Shen_Yin_Xu in COPD, asthma and reference were 2.23%, 51.40% and 61.87%.

Table 3
Multinomial logistic regression to include Xu traditional Chinese medicine syndrome (deficiency syndrome) for chronic obstructive pulmonary disease and asthma.

Group	TCM syndrome	Disease	Beta	S.E	P value	OR	95% CI for OR
Entire	Fei_Qi_Xu	COPD	0.234	0.157	0.135	1.264	0.929-1.719
		Asthma	0.045	0.348	0.897	1.046	0.528-2.071
	Fei_Shen_Qi_Xu	COPD	1.866	0.061	< 0.001	6.461	5.730-7.286
		Asthma	0.210	0.103	0.042	1.233	1.008-1.509
	Fei_Shen_Qi_Yin_Liang_Xu	COPD	−1.037	0.157	< 0.001	0.355	0.260-0.483
		Asthma	−1.705	0.505	0.001	0.182	0.068-0.489
	Fei_Yin_Xu	COPD	−3.297	0.191	< 0.001	0.037	0.025-0.054
		Asthma	−0.764	0.141	< 0.001	0.466	0.354-0.614
Xu	Fei_Qi_Xu	COPD	0.131	0.161	0.416	1.14	0.832-1.561
		Asthma	0.617	0.362	0.089	1.852	0.911-3.769
	Fei_Shen_Qi_Xu	COPD	3.536	0.103	< 0.001	34.323	28.075-41.961
		Asthma	0.989	0.21	< 0.001	2.688	1.782-4.055
	Fei_Shen_Qi_Yin_Liang_Xu	COPD	−1.223	0.161	< 0.001	0.294	0.215-0.404
		Asthma	−1.248	0.514	0.015	0.287	0.105-0.785
	Fei_Yin_Xu	COPD	−4.264	0.196	< 0.001	0.014	0.010-0.021
		Asthma	−0.429	0.198	0.03	0.651	0.441-0.960

Note: multiple variable adjusted for age, gender, duration of hospitalization; TCM - traditional Chinese medicine, Xu syndrome - deficiency syndrome.

Table 4
Bivariate association analysis to include Shi traditional Chinese medicine syndrome (excess syndrome) for both chronic obstructive pulmonary disease and asthma by using general linear model.

Group	TCM syndrome	Parameter	Value	F value	P value
Entire	Tan_Re_Yong_Fei	Pillai's Trace	0.002	19.90×10^3	< 0.001
		Wilks' Lambda	0.998	19.90×10^3	< 0.001
		Hotelling's Trace	0.002	19.90×10^3	< 0.001
		Roy's Largest Root	0.002	19.90×10^3	< 0.001
Shi	Tan_Re_Yong_Fei	Pillai's Trace	0.002	23.59×10^5	< 0.001
		Wilks' Lambda	0.998	23.59×10^5	< 0.001
		Hotelling's Trace	0.002	23.59×10^5	< 0.001
		Roy's Largest Root	0.002	23.59×10^5	< 0.001

Note: multiple variable adjusted for age, gender, duration of hospitalization; TCM - traditional Chinese medicine, Shi syndrome - excess syndrome.

Table 5
Bivariate association analysis to include Xu traditional Chinese medicine syndrome deficiency syndrome for both chronic obstructive pulmonary disease and asthma by using general linear model.

Group	TCM syndrome	Parameter	Value	F value	P value
Entire	Fei_Shen_Qi_Xu	Pillai's Trace	0.047	642.00	< 0.001
		Wilks' Lambda	0.953	642.00	< 0.001
		Hotelling's Trace	0.049	642.00	< 0.001
		Roy's Largest Root	0.049	642.00	< 0.001
Xu	Fei_Shen_Qi_Xu	Pillai's Trace	0.457	1505.00	< 0.001
		Wilks' Lambda	0.543	1505.00	< 0.001
		Hotelling's Trace	0.841	1505.00	< 0.001
		Roy's Largest Root	0.841	1505.00	< 0.001

Note: multiple variable adjusted for age, gender, duration of hospitalization; TCM - traditional Chinese medicine, Xu syndrome - deficiency syndrome.

the lung and also gives consideration to the kidney. In contrast, during the remission stage, TCM theory emphasizes treating the kidney and incorporates treatment for the lung [25]. In modern medicine, COPD and asthma not only have some similarities in inflammation but also have overlap in disease characteristics. A patient can manifest the symptoms of both COPD and asthma, which is called asthma-COPD overlap syndrome (ACOS), now being thought to affect up to a quarter of the patients previously thought to have COPD and up to a third of the patients previously thought to have asthma [30,31]. It also proved that COPD and asthma share some common pathogenesis and symptoms.

Although this study has profound significance for clinical practice, the strengths and limitations of this study should be listed. As selection bias could not be avoided in an observational study, we collected a multi-center study with large numbers of cases in order to reduce the bias. Because the associations among the symptoms and syndromes are very complicated and the diagnostic criteria of syndromes may be subjective and differ between clinicians and hospitals and in different countries, the syndromes may not be fully accurate. Experts may need to review syndrome identification in order to improve the quality of diagnosis. Additionally, there is currently no molecular basis to differentiate the syndromes, but this I will be investigated in our further research.

In TCM, Shi syndrome (excess syndrome) is described as violent struggle between pathogenic factor and healthy qi. That is why it is a syndrome of excess nature. Shi syndrome (excess syndrome) is often seen at the early and medium stages of disease caused by Feng、Han、Re、Tan、Yu and so on. Xu syndrome (deficiency syndrome) is marked by deficiency of healthy qi. Though pathogenic factors are not eliminated, they are not strong enough to damage healthy qi. So, the struggle between pathogenic factors and healthy qi is mild with hypofunction of the viscera. This deficiency syndrome is often seen at the advanced stage of exogenous diseases, which results in weakness of body and chronic disease. Meantime, the severity grade of COPD and asthma is very important for choosing appropriate medications in western medicine guidelines. Therefore, the relationship between TCM syndromes and severity grades or between TCM syndromes and exacerbation/ remission status will be interesting and significant. Unfortunately, the severity grades of COPD and asthma is deficiency in medical records enrolled in this study. A further study with appropriate analysis between TCM syndromes and severity grades of COPD and asthma will compensate for this limitation.

In conclusion, we can find an inner, close connection between COPD and asthma compared with the reference population of other respiratory diseases, both diseases show that the common core Shi syndrome (excess syndrome) was Tan_Re_Yong_Fei, the common core Xu syndromes (deficiency syndrome) was Fei_Shen_Qi_Xu. In addition, our big data research would provide evidence for the similar principles of TCM treatment for different diseases. This not only brings vitality to the long history of TCM, but also provides a new direction for the contemporary treatment of COPD and asthma.

Ethical approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/ or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all patients before the study, and this study was approved by the Ethics Committee of Huashan Hospital, Shanghai, China. The methods were carried out in accordance with the approved guidelines.

Consent for publication

All authors read and approved the final manuscript.

Availability of data and material

The datasets generated and/or analyzed during the current study are not publicly available due to private information but are available from the corresponding author on reasonable request. Dataset are from the study whose authors may be contacted at Instituion of Bioinformatics and Biostatistics, Institutes of Integrative Medicine, Fudan University.

Funding

Grants from the Institutes of Integrative Medicine of Fudan University, ClinicalTrials.gov Identifier: NCT03274908; and Shanghai Development Project of Shanghai Peak Disciplines-Integrative Medicine (20150407); and China Postdoctoral Science Foundation funded project (2017M611461); Science and Technology Innovation Projects of Traditional Chinese Medicine of Shanghai Municipal Commission of Health and Family Planning (ZYKC201602001).

Author's contributions

Q.K, and R.J, drafted the manuscript. M.L, F.X and Y.Z participated in the design of the study and performed the statistical analysis. Z.T and J.D conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Acknowledgments

We thank the grant from Institutes of Integrative Medicine of Fudan University for supporting the study.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eujim.2019.101001.

References

[1] A. Tam, D.D. Sin, Pathobiologic mechanisms of chronic obstructive pulmonary disease, Med. Clin. North Am. 96 (4) (2019) 681–698.
[2] P.J. Barnes, New therapies for asthma: is there any progress? Trends Pharmacol. Sci. 31 (7) (2019) 335–343.
[3] P.J. Barnes, Immunology of asthma and chronic obstructive pulmonary disease, Nat. Rev. Immunol. 8 (3) (2019) 183–192.
[4] R.W. Harper, A.A. Zeki, Immunobiology of the critical asthma syndrome, Clin. Rev. Allergy Immunol. 48 (1) (2019) 54–65.
[5] J. Dong, The relationship between traditional chinese medicine and modern medicine, Evid. Complement. Alternat. Med. (2013) 153148.
[6] Z. Xu, N.L. Zhang, Y. Wang, et al., Statistical validation of Traditional Chinese Medicine syndrome postulates in the context of patients with cardiovascular disease, J. Altern. Complement. Med. 19 (10) (2019) 799–804.
[7] M. Liu, X. Zhong, Y. Li, et al., Xuan Bai Cheng Qi formula as an adjuvant treatment of acute exacerbation of chronic obstructive pulmonary disease of the syndrome type phlegm-heat obstructing the lungs: a multicenter, randomized, double-blind, placebo-controlled clinical trial, BMC Complement. Altern. Med. 14 (2019) 239.
[8] Z. Wang, J. Li, Y. Xie, X. Yu, Z. Zhang, Traditional Chinese medicine ZHENG identification of bronchial asthma: clinical investigation of 2500 adult cases, Complement. Ther. Med. 30 (2019) 93–101.
[9] D. Chen, F. Zhang, S. Tang, et al., A network-based systematic study for the mechanism of the treatment of zhengs related to cough variant asthma, Evid. Complement. Altern. Med. (2013) 595924.
[10] E.L.J. van Rensen, J.K. Sont, C.E. Evertse, et al., Bronchial CD8 cell infiltrate and lung function decline in asthma, Am. J. Respir. Crit. Care Med. 172 (7) (2019) 837–841.
[11] K. Kurashima, M. Fujimura, S. Myou, Y. Ishiura, N. Onai, K. Matsushima, Asthma severity is associated with an increase in both blood CXCR3+ and CCR4+ T cells, Respirology 11 (2) (2019) 152–157.
[12] F. Xu, W. Cui, Q. Kong, Z. Tang, J. Dong, A real-world evidence study for distribution of traditional chinese medicine syndrome and its elements on respiratory disease, Evid. Complement. Altern. Med. 12 (December 2018) (2018) 8305892.
[13] X. Nie, G. Cai, Q. Li, Bronchoscopy in China: the chinese society of respiratory diseases survey, Chest 136 (4) (2019) 1186–1187.
[14] M.T. Simonson, Product review. Harrison's online, National Netw. 25 (1) (2019) 28–29.
[15] Z.H. Tang, L. Wang, F. Zeng, K. Zhang, Association and predictive value analysis for metabolic syndrome on systolic and diastolic heart failure in high-risk patients, BMC Cardiovasc. Disord. 14 (2019) 124.
[16] C. Kwak, A. Clayton-Matthews, Multinomial logistic regression, Nurs. Res. 51 (6) (2019) 404–410.
[17] R.D. Riley, K.R. Abrams, P.C. Lambert, A.J. Sutton, J.R. Thompson, An evaluation of bivariate random-effects meta-analysis for the joint synthesis of two correlated outcomes, Stat. Med. 26 (1) (2019) 78–97.
[18] Z.S. Huang, Y.T. Luo, J.L. Liu, Method and practice of real world study, J. Evid.-Based Med. 14 (6) (2019) 364–368.
[19] P. Wang, Z. Chen, Traditional Chinese medicine ZHENG and Omics convergence: a systems approach to post-genomics medicine in a global world, OMICS 17 (9) (2019) 451–459.
[20] Z. Chen, P. Wang, Clinical distribution and molecular basis of traditional chinese medicine ZHENG in cancer, Evid. Complement. Altern. Med. (2012) 783923.
[21] H. DONG, w Zhang, The clinical effect of reding injection on treating acute exacerbation of chronic obstructive pulmonary syndrome of phlegm heat obstructing in the lung, J. Emergency Tradit. Chin. Med. 24 (8) (2019) 1433–1435.
[22] W. Qian, W. Zhang, X. Cai, The rule of cleaning heat and phlegm to treat bronchial asthma, Chin. J. Ethnomed. Ethnopharm. 18 (2019) 85–86.
[23] A. Zhou, Z. Zhou, Y. Zhao, P. Chen, The recent advances of phenotypes in acute exacerbations of COPD, Int. J. Chron. Obstruct. Pulmon. Dis. 12 (2019) 1009–1018.
[24] L. Brussino, P. Solidoro, G. Rolla, Is it severe asthma or asthma with severe comorbidities? J. Asthma Allergy 10 (2019) 303–305.
[25] L. Yubai, M. Shuming, D. Jingcheng, Development of th TCM theory "Inter-relationship of lung and kidney" in modern times, World Chin. Med. 8 (7) (2019) 734–737.
[26] X. Rui, Z. Mingdan, Q. Nini, Clinical observation of the combined treatment with modified duqiwan and tiotropium bromide in treatment of chronic obstructive pulnoary disease (Lung and kidney deficiency) at stable stage, World J. Integr. Tradit. Western Med. 12 (3) (2019) 365–368.
[27] M.R. Partridge, T. van der Molen, S.E. Myrseth, W.W. Busse, Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study, BMC Pulm. Med. 6 (2019) 13.
[28] K.H. Cho, Y.S. Kim, J.A. Linton, C.M. Nam, Y. Choi, E.C. Park, Effects of inhaled corticosteroids /long-acting agonists in a single inhaler versus inhaled corticosteroids alone on all-cause mortality, pneumonia, and fracture in chronic obstructive pulmonary disease: a nationwide cohort study 2002-2013, Respir. Med. 130 (2019) 75–84.
[29] P. Rogliani, V. Brusasco, L. Fabbri, et al., Multidimensional approach for the proper management of a complex chronic patient with chronic obstructive pulmonary disease, Expert Rev. Respir. Med. (2019) 1–10.
[30] J.M. Leung, D.D. Sin, Asthma-COPD overlap syndrome: pathogenesis, clinical features, and therapeutic targets, BMJ 358 (2019) j3772.
[31] A. Alshabanat, Z. Zafari, O. Albanyan, M. Dairi, J.M. FitzGerald, Asthma and COPD overlap syndrome (ACOS): a systematic review and Meta analysis, PLoS One 10 (9) (2019) e0136065.