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Original Article

Add-on Chinese medicine for hospitalized chronic obstructive pulmonary disease (CHOP): A cohort study of hospital registry

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A R T I C L E I N F O

Keywords:
Chronic obstructive pulmonary disease
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Chinese medicine
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A B S T R A C T

Background: Chronic obstructive pulmonary disease (COPD) is the third leading cause of death globally. The effect of Chinese medicine (CM) on mortality during acute exacerbation of COPD is unclear. We evaluated the real-world effectiveness of add-on personalized CM in hospitalized COPD patients with acute exacerbation.
Methods: This is a retrospective cohort study with new-user design. All electronic medical records of hospitalized adult COPD patients (n = 4781) between July 2011 and November 2019 were extracted. Personalized CM exposure was defined as receiving CM that were prescribed, and not in a fixed form and dose at baseline. A 1:1 matching control cohort was generated from the same source and matched by propensity score. Primary endpoint was mortality. Multivariable Cox regression models were used to estimate the hazard ratio (HR) adjusting the same set of covariates (most prevalent with significant inter-group difference) used in propensity score calculation. Secondary endpoints included the change in hematology and biochemistry, and the association between the use of difference CMs and treatment effect. The prescription pattern was also assessed and the putative targets of the CMs on COPD was analyzed with network pharmacology approach.
Results: 4325 (90.5%) patients were included in the analysis. The mean total hospital stay was 16.7 ± 11.8 days. In the matched cohort, the absolute risk reduction by add-on personalized CM was 5.2% (3.9% vs 9.1%). The adjusted HR of mortality was 0.13 (95% CI: 0.03 to 0.60, p = 0.008). The result remained robust in the sensitivity analyses. The change in hematology and biochemistry were comparable between groups. Among the top 10 most used CMs, *Poria* (Fu-ling), *Citri Reticulatae Pericarpium* (Chen-pi) and *Glycyrrhizae Radix Et Rhizoma* (Gan-cao) were associated with significant hazard reduction in mortality. The putative targets of the CM used in this cohort on COPD were related to Jak-STAT, Toll-like receptor, and TNF signaling pathway which shares similar mechanism with a range of immunological disorders and infectious diseases.

Abbreviations: CM, Chinese medicine; COPD, Chronic obstructive pulmonary disease; HR, Hazard ratio; HCPSAS, Human-machine Cooperative Phenotypic Spectrum Annotation System; FEV1, The first second forced expiratory volume; FVC, The forced vital capacity; FAH-HUCM, The Frist Affiliated Hospital of Henan University of Chinese Medicine.

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Conclusion: Our results suggest that add-on personalized Chinese medicine was associated with significant mortality reduction in hospitalized COPD patients with acute exacerbation in real-world setting with minimal adverse effect on liver and renal function. Further randomized trials are warranted.

Introduction

Chronic obstructive pulmonary disease (COPD) refers to the chronic inflammatory lung diseases that progressively obstructs airflow, causing difficulty in breathing, cough, phlegm production and wheezing which increasingly limit daily activities (Global Initiative for Chronic Obstructive Lung Disease, 2021). COPD patients experience flare-ups with acutely deteriorated symptoms. Globally, COPD is the third leading cause of death, accounting for 6% (3.23 million) of the total mortality (World Health Organization, 2020). COPD is also a risk factor of severe COVID-19 (Chan et al., 2020). Tobacco smoking; exposure to dusts, chemicals and biomass fuels; underweight, history of childhood chronic cough and tuberculosis; gender (male), aging, family history of respiratory disease, and poor education are important risk factors associated with COPD (Wang et al., 2018; Magitta et al., 2018; Lange et al., 2015). Acute exacerbation could be caused by infections, including COVID-19 (Polverino and Kheradmand, 2021), leading to hospitalization, intensive care admission and mortality (Pardhan et al., 2021).

Management of COPD depends on the disease severity based on the first second forced expiratory volume (FEV1), symptoms and the future risk of exacerbations (Global Initiative for Chronic Obstructive Lung Disease, 2021; Cooper and Barjaktarevic, 2015). Bronchodilators are commonly used as the first line pharmacological therapy among patients with less frequent and less severe exacerbations. Combinations of bronchodilators and inhaled corticosteroids can be considered for more severe exacerbation. Smoking cessation and pulmonary rehabilitation are also important non-pharmacological interventions. Nevertheless, there is a constant call for more personalized regimens for COPD (Mannino and Buist, 2007).

Chinese medicine (CM) has been used to treat respiratory disease including COPD with a long history (Chan et al., 2020; Lin et al., 2019; Shu et al., 2021; .Zhen et al., 2018). Previous meta-analyses showed that add-on CM was associated with improved lung function, oxygen partial pressure and general symptoms (Liu et al., 2019; Chan, K.H. et al., 2021). A 64% (95%CI: 0.24 to 0.53, $p < 0.001$) reduction in the risk of lung cancer was observed among the CM user ($n = 5346$) from the analysis of the National Health Insurance Research Database (Lin et al., 2019). Network pharmacology approach has been widely used to investigate the underlying mechanisms of classical herbal formulas (Chan et al., 2022). Possible mechanism of action of commonly used CM for COPD involved the modulation of acetylcholine, steroid hormone, neurotransmitter, and adrenergic receptor activity, and the T cell homeostasis, myeloid leukocyte and monocyte differentiation targeting IL-6, IL-10, IL-1β, TNF-α, interferon-γ, epidermal growth factor and the receptor and TGF-β1 (Zhang et al., 2019).

Nevertheless, current evidence from randomized trials is mostly of moderate to low quality with unclear allocation concealment, randomization and completeness of data (Chan, K.H. et al., 2021). The effect of CM on the mortality during acute exacerbation is unclear as most of the existing evidence focused on the management of stable COPD outpatients. Furthermore, CM prescription is personalized based on patients' individual clinical presentation (Chan et al., 2020; Shu et al., 2021; Jiang et al., 2012), while most randomized trials evaluated the effect of specific and fixed CM formulations which may not fully reflect the current clinical practice. In this cohort study, we evaluated the real-world effectiveness of add-on personalized CM in hospitalized COPD patients with acute exacerbation, and identified the frequently used CMs and their association with mortality.

Methods

Study design

This is a retrospective cohort study of hospital registry with new-user design, in which only patients with no previous CM exposure during the observation period of hospitalized COPD were recruited (Yoshida et al., 2015). The new-user design enables the accurate use of baseline measures to adjust for confounding factors and reduce immortal bias. The data extraction process is summarized in Fig. 1.

Setting

The data was collected from the Department of Respiratory Medicine, The Frist Affiliated Hospital of Henan University of Chinese Medicine (FAH-HUCM). All electronic medical records of hospitalized adult COPD patients ($n = 4781$) between July 2011 and November 2019 were retrieved. The data was censored on 28 November 2019. Patients who was 1) diagnosed as having COPD with post-bronchodilator FEV1/FVC $< 70\%$ (Mannino and Buist, 2007; Celli et al., 2004), 2) hospitalized for at least 3 days, and 3) with baseline prescription record were included in the analysis. Personalized treatment was given by CM physicians based on individual patient' clinical presentation with reference to the TCM Diagnosis and Treatment Guidelines for Chronic Obstructive Pulmonary Disease (2011) of the China Association of Chinese Medicine (Li et al., 2012). An analysis on the prescription pattern was conducted.

Data collection

A clinical data warehouse platform developed based on clinical reference information model and physical data model was established in FAH-HUCM since 2010 to store, integrate and analyze different information entities and their relationships in complex clinical data of both conventional and Chinese medicine (Shu et al., 2021; Zhou et al., 2010) In addition, several phenotypic clinical entities (e.g. symptoms and signs) were further extracted from the full text of electronic medical records(e.g. main complaints and medical histories) using a web tool named Human-machine Cooperative Phenotypic Spectrum Annotation System (HCPSAS) (http://www.tcmai.org) (Zou et al., 2022).

All data from the hospital system including consultation notes, demographics, medical investigations, and prescription records were retrieved. To minimize data entry error, all aforementioned data were automatically extracted and no manual data extraction were further performed. All data were validated by at least 2 researchers (Xu, N., Zhong, K.Y.) independently and a physician (Xu, N.). All incoherence was resolved through discussion.

Personalized Chinese medicine exposure

Exposure of personalized CM was defined as receiving CM that were 1) prescribed, and 2) not in a fixed form and dose at baseline. Study baseline was defined as the first day of hospitalization. To minimize the immortal bias, we excluded patients without CM exposure at baseline who subsequently received CM and avoided cross-over between groups (Yoshida et al., 2015).

Endpoint

The primary endpoint was mortality. Kaplan–Meier curves were presented and Cox regression models were used to estimate the hazard

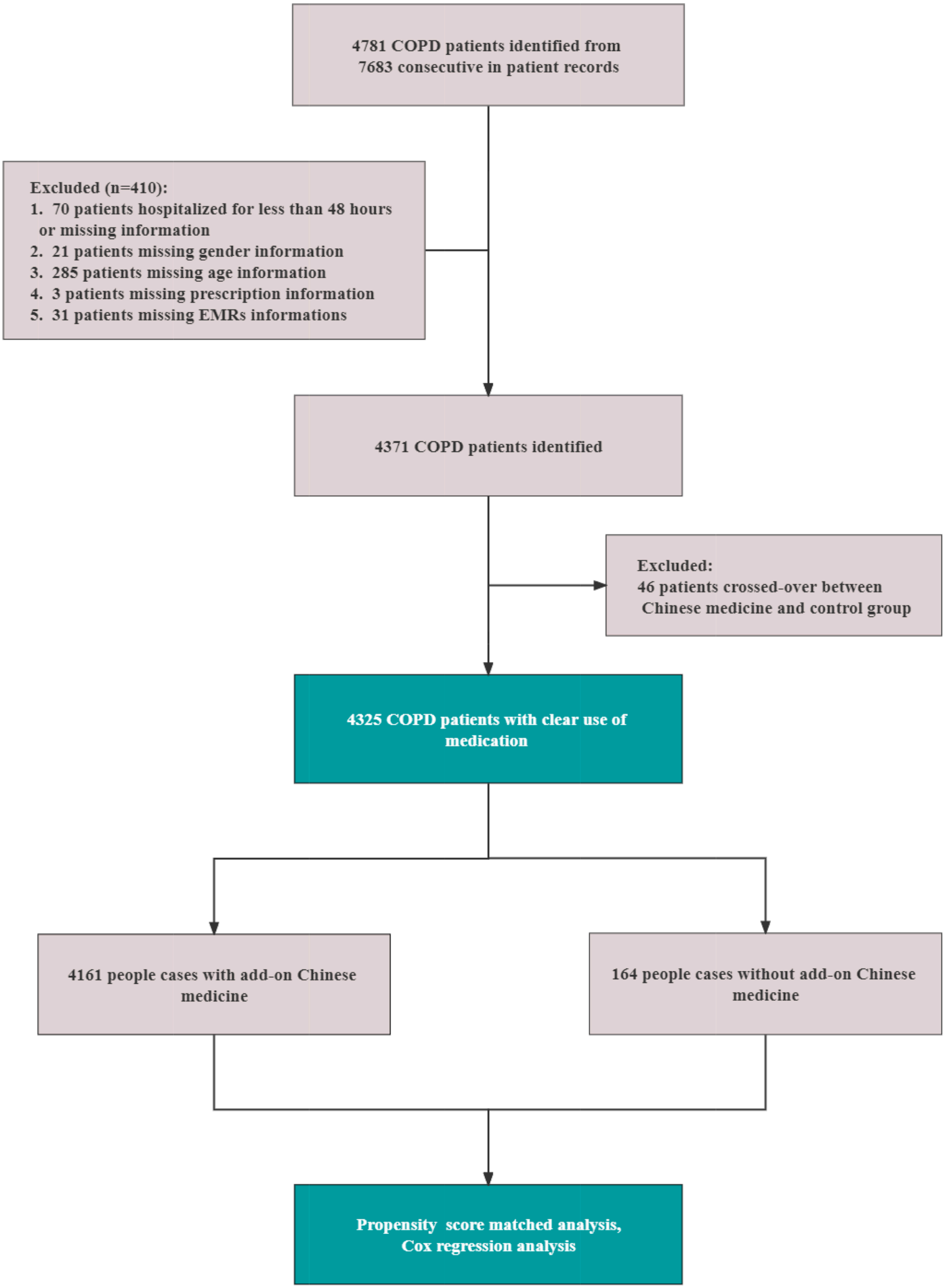


Fig. 1. Flow of data extraction.
Linked electronic medical record of all adult chronic obstructive pulmonary disease inpatients at any point during hospitalization were retrieved. 4325 (90.5%) of all cases satisfied inclusion and exclusion criteria and were included.

ratio (HR). Secondary endpoints included 1) the change in hematology and biochemistry between the point of admission and the last investigation before discharge, and 2) the association between the use of different CMs and treatment effect.

Statistical analysis

Patients who did not reach primary endpoint were censored on 28 November 2019. Cases with complete baseline data were used for analysis. The associations among baseline characteristics were assessed by bivariate correlation analyses. Propensity score was calculated to adjust for confounding factors from the non-randomized allocation of personalized CM treatment. Multivariable logistic-regression model including the same covariates of the Cox regression model was used to estimate the individual propensities for receiving CM treatment. A 1:1 matching control cohort was created by using the nearest-neighbor method. The nearest-neighbor of a CM-exposed case was defined as the control with the closest propensity score (Geldof, et al. 2020). The propensity scores of all patients were sorted, and each patient of the CM-exposed group was matched with a control patient having the closest score without replacement. A multivariable Cox regression model adjusting the most prevalent covariates with significant inter-group difference at baseline in demographics (gender, age, number of hospitalization episodes, history of coronary heart disease, stroke, asthma, emphysema, pleural effusion, congestive heart failure, diabetes, etc.), clinical presentation (sputum production, edema, fever, etc.), and the use of concomitant medication (bronchodilator, antibiotics, steroid, etc.) was subsequently used to estimate the association between the use of personalized CM and death. A full list of covariates is listed in **Supplement S1**.

The inter-group difference in the change of key hematology and biochemistry from baseline at admission to discharge was compared by t-test. Prescription analysis was performed firstly by analyzing the frequency of the use of each CMs. The frequency of use of all CMs during hospitalization was included, de-duplicated and counted, by each patient, to account for the change in prescription throughout the period. The association between each of the 10 most used individual CMs and mortality was estimated by using Cox regression in the cohort adjusting the same set of covariates used in the propensity score calculation. An exploratory analysis on the frequency of use of formulations was also performed.

Sensitivity analysis was performed by 1) estimating the adjusted hazard ratio in the unmatched cohort by using multivariable Cox regression model, 2) estimating the crude hazard ratio in the matched cohort without adjusting confounders, and 3) analysing the change of liver function test results by categorizing liver enzymes into within normal range or deranged and comparing the percentage change between groups. Statistical analyses were performed with R (version 4.0.3).

Network pharmacology

To further investigate the underlying mechanisms of clinical effectiveness of COPD related herbs, we performed network pharmacology analysis (Chan et al., 2022) using the phenotype-genotype associations and the drug targets of the related herbs for COPD. COPD-related genes were retrieved from Malacards (https://www.malacards.org) (Rappaport et al., 2017) and HPO (https://hpo.jax.org/app/) (Köhler et al., 2021). These two databases provide genotypic and phenotypic information on molecular contributions based on phenotypes. We searched the databases by using the phenotypes presented in the clinical guidelines of COPD and in our cohort. The drug targets of top 20 most used herbs of COPD in our clinical data were extracted from HIT (https://bio.tools/hit) (Ye et al., 2011) and SymMap (http://www.symmap.org) (Wu et al., 2019).

The genes and herbal targets of COPD were associated to the 314 network clusters (Xu et al., 2018) from the human protein-protein interaction (PPI) network filtered from STRING (Szklarczyk rt al., 2019) by using enrichment analysis with Fisher's exact test. The enriched clusters were imported into DAVID (https://david.ncifcrf.gov/summary.jsp) (Huang et al., 2009) for analysis to obtain the enriched pathways and GO annotations.

Results

Cohort characteristics

4781 patients from 7683 consecutive inpatient attendance records between July 2011 and November 2019 were retrievable. 4325 (90.5%) patients were included in the analysis (Fig. 1). 70 patients were hospitalized for less than 2 days or missing information, 306 patients had missing key demographics required in the propensity score calculation (285 missing age, 21 missing gender), 3 had missing exposure information, 31 were missing electronic medical records information, 46 had cross-over between exposure groups and were excluded. 4161 patients (87.03%) were prescribed personalized CM. No death was recorded from the excluded patients.

Before matching, personalized CM-exposed patients were 1) younger, 2) had lower levels of leukocyte count and neutrophil, and 3) had higher levels of hemoglobin, lymphocyte and serum albumin. There were more patients with asthma, emphysema, and less patients with congestive heart failure among the CM-user (Table 1).

154/164 of the patients with no CM exposure were included in the propensity score analysis and matched 1:1 with CM users. The baseline characteristics and distribution of propensity scores in the matched cohort was comparable between groups (Table 1**, Supplement S2, S3**). The odds ratio of receiving CM of each covariate in the propensity score regression model is summarized in **Supplement S1**. After matching, the mean age was 70.5 ± 12.5 years and 32.8% ($n = 101/308$) were female. 83.1% ($n = 256/308$), 81.5% ($n = 251/308$), 80.8% ($n = 249/308$) and 76.3% ($n = 235/308$) patients presented with chest distress, cough, sputum production and wheezing at admission. 97.1% ($n = 299/308$), 93.8% ($n = 289/308$), and 77.9% ($n = 240/308$) were on antibiotics, bronchodilators and steroids, respectively. 31.0% ($n = 93/308$), 27.3% ($n = 82/308$) and 14.0% ($n = 42/308$) had known history of coronary heart disease, hypertension and diabetes, respectively. The most presented subtypes among all cases were *Phlegm-heat lung* distress (34.4%), *Phlegm lung* congestion (22.5%) and *Lung* and *kidney qi* deficiency (14.9%) according to CM theories based on their clinical presentations (Jiang et al., 2012).

The mean total hospital stay was 16.7 ± 11.8 days and the mean hospitalization episodes was 1.0 ± 0.2 times. The mean duration of the first hospital stay was 15.9 ± 10.3 days. The crude mortality rate was 6.5% ($n = 20/308$), lower in CM-users (3.9%, $n = 6/308$).

Primary clinical outcomes

The Kaplan-Meier survival curves of propensity score-matched and unmatched cohorts are shown in Fig. 2. In the matched cohort, the absolute risk reduction of mortality by add-on personalized CM was 5.2% (3.9% vs 9.1%). The adjusted hazard ratio of mortality was 0.13 (95% CI: 0.03 to 0.60, $p = 0.008$) **(**Table 2**).** The result remained robust in the sensitivity analysis with different statistical modelling **(**Table 2**).**

Change in key biomarkers

CM-treated patients had higher lymphocyte percentage and hemoglobin, and lower neutrophil percentage after taking CM when compared with patients without CM use. The levels of alkaline phosphatase, alanine aminotransferase, alkaline phosphatase, C-reactive protein and serum creatinine were comparable between groups (Table 3**, Supplement S4**). The result remained robust in the sensitivity analysis

Table 1
Demographics.

Characteristics	Unmatched cohort Chinese Medicine + standard care (n = 4161)	Standard care (n = 164)	Total (n = 4325)	p-value	Matched cohort [1] Chinese Medicine + standard care (n = 154)	Standard care (n = 154)	Total (n = 308)	p-value
Age (yr) – mean ± sd	66.6 ± 11.9	71.2 ± 13.4	66.8 ± 12.0	< 0.001	70.3 ± 11.2	70.7 ± 13.6	70.5 ± 12.5	0.764
Female – n (%)	1236 (29.7)	52 (31.7)	1288 (29.8)	0.584	51 (33.1)	50 (32.5)	101 (32.8)	0.903
Laboratory investigations – mean ± sd								
Hemoglobin (g/L)	134.8 ± 17.1	128.8 ± 21.9	134.6 ± 17.3	< 0.001	131.2 ± 19.9	127.6 ± 21.8	129.5 ± 20.9	0.143
Leukocyte (10^9/L)	7.4 ± 3.3	8.2 ± 4.1	7.4 ± 3.4	0.031	7.5 ± 3.0	8.2 ± 4.2	7.8 ± 3.6	0.208
Neutrophils (10^9/L)	5.2 ± 3.1	6.1 ± 4.0	5.2 ± 3.1	0.005	5.4 ± 2.9	6.1 ± 4.0	5.8 ± 3.5	0.171
Neutrophils (%)	67.6 ± 12.8	71.2 ± 14.4	67.7 ± 12.9	<0.001	69.8 ± 12.9	71.3 ± 14.4	70.6 ± 13.7	0.361
Lymphocytes (10^9/L)	1.6 ± 1.2	1.4 ± 0.8	1.6 ± 1.2	0.017	1.6 ± 0.8	1.4 ± 0.7	1.5 ± 0.8	0.077
Lymphocytes (%)	24.2 ± 10.9	20.4 ± 11.7	24.1 ± 10.9	< 0.001	22.5 ± 11.4	20.1 ± 11.5	21.4 ± 11.5	0.075
Alanine aminotransferase (U/L)	24.0 ± 21.4	36.3 ± 101.1	24.4 ± 28.5	0.390	29.2 ± 30.6	37.2 ± 104.6	33.0 ± 76.1	0.381
Alkaline phosphatase (U/L)	89.8 ± 30.4	94.1 ± 53.5	89.9 ± 31.6	0.411	92.2 ± 33.2	94.2 ± 55.3	93.2 ± 45.3	0.718
C-reactive protein (mg/L)	24.1 ± 45.8	31.1 ± 44.9	24.4 ± 45.8	0.127	33.8 ± 64.1	32.8 ± 46.1	33.3 ± 56.5	0.902
Serum albumin (g/L)	39.7 ± 4.7	37.1 ± 5.5	39.7 ± 4.7	< 0.001	38.8 ± 5.0	37.1 ± 5.5	37.9 ± 5.3	0.007
Serum creatinine	67.4 ± 21.2	76.3 ± 57.1	67.7 ± 23.5	0.324	70.1 ± 24.6	75.9 ± 59.0	73.1 ± 46.2	0.509
Signs and symptoms – n (%)								
Cough	4044 (97.2)	127 (77.4)	4171 (96.4)	< 0.001	124 (80.5)	127 (82.5)	251 (81.5)	0.660
Sputum	3924 (94.3)	123 (75.0)	4047 (93.6)	< 0.001	126 (81.8)	123 (79.9)	249 (80.8)	0.664
Chest distress	3879 (93.2)	127 (77.4)	4006 (92.6)	< 0.001	130 (84.4)	126 (81.8)	256 (83.1)	0.543
Wheezing	3612 (86.8)	116 (70.7)	3728 (86.2)	< 0.001	119 (77.3)	116 (75.3)	235 (76.3)	0.688
Shortness of breath	2624 (63.1)	61 (37.2)	2685 (62.1)	< 0.001	76 (49.4)	60 (39.0)	136 (44.2)	0.066
Reduced appetite	2126 (51.1)	87 (53.1)	2213 (51.2)	0.623	80 (52.0)	83 (53.9)	163 (52.9)	0.732
Sweating	1319 (31.7)	31 (18.9)	1350 (31.2)	0.001	28 (18.2)	30 (19.5)	58 (18.8)	0.771
Dry mouth	1319 (31.7)	27 (16.5)	1346 (31.1)	< 0.001	29 (18.8)	27 (17.5)	56 (18.2)	0.768
Fatigue / malaise	1287 (30.9)	52 (31.7)	1339 (31.0)	0.833	52 (33.8)	50 (32.5)	102 (33.1)	0.809
Insomnia	1203 (28.9)	70 (42.7)	1273 (29.4)	<0.001	60 (39.0)	66 (42.9)	126 (40.9)	0.487
Dyspnea	1074 (25.8)	36 (22.0)	1110 (25.7)	0.267	41 (26.6)	36 (23.4)	77 (25.0)	0.511
Fever	875 (21.0)	37 (22.6)	912 (21.1)	0.637	38 (24.7)	36 (23.4)	74 (24.0)	0.790
Comorbidities – n (%)								
Coronary heart disease	1048 (25.4)	44 (27.9)	1092 (25.5)	0.484	51 (33.8)	42 (28.2)	93 (31.0)	0.295
Hypertension	959 (23.2)	41 (26.0)	1000 (23.3)	0.426	44 (29.1)	38 (25.5)	82 (27.3)	0.480
Asthma	919 (22.3)	21 (13.3)	940 (21.9)	0.008	19 (12.6)	21 (14.1)	40 (13.3)	0.700
Emphysema	478 (11.6)	8 (5.1)	486 (11.3)	0.011	9 (6.0)	8 (5.4)	17 (5.7)	0.825
Bronchiectasis	467 (11.3)	10 (6.3)	477 (11.1)	0.051	10 (6.6)	10 (6.7)	20 (6.7)	0.975
Bronchitis	434 (10.5)	20 (12.7)	454 (10.6)	0.389	10 (6.6)	18 (12.1)	28 (9.3)	0.104
Pulmonary fibrosis	394 (9.5)	13 (8.2)	407 (9.5)	0.581	13 (8.6)	13 (8.7)	26 (8.7)	0.972
Cor pulmonale	383 (9.3)	21 (13.3)	404 (9.4)	0.090	21 (13.9)	20 (13.4)	41 (13.7)	0.903
Diabetes	375 (9.1)	19 (12.0)	394 (9.2)	0.208	23 (15.2)	19 (12.8)	42 (14.0)	0.536
Ischemic stroke	356 (8.6)	18 (11.4)	374 (8.7)	0.225	18 (11.9)	17 (11.4)	35 (11.7)	0.890
Pulmonary bullae	298 (7.2)	6 (3.8)	304 (7.1)	0.100	8 (5.3)	6 (4.0)	14 (4.7)	0.602
Respiratory failure	272 (6.6)	16 (10.1)	288 (6.7)	0.081	16 (10.6)	16 (10.7)	32 (10.7)	0.968
Arrhythmia	227 (5.5)	13 (8.2)	240 (5.6)	0.143	14 (9.3)	12 (8.1)	26 (8.7)	0.708
Congestive Heart failure	195 (4.7)	16 (10.1)	211 (4.9)	0.002	18 (11.9)	15 (10.1)	33 (11.0)	0.608
Concurrent treatment – n (%)								
Bronchodilator	3993 (96.30)	152 (92.7)	4145 (95.8)	0.039	146 (94.8)	143 (92.9)	289 (93.8)	0.477
Antibiotics	3931 (94.5)	159 (97.0)	4090 (94.6)	0.170	150 (97.4)	149 (96.8)	299 (97.1)	1.000
Steroid	2719 (65.3)	129 (78.7)	2848 (65.9)	< 0.001	120 (77.9)	120 (77.9)	240 (77.9)	1.000

(*continued on next page*)

Table 1 (*continued*)

Characteristics	Unmatched cohort Chinese Medicine + standard care (n = 4161)	Standard care (n = 164)	Total (n = 4325)	p-value	Matched cohort [1] Chinese Medicine + standard care (n = 154)	Standard care (n = 154)	Total (n = 308)	p-value
Immunosuppressant	1743 (41.9)	59 (36.0)	1802 (41.7)	0.132	61 (39.6)	56 (36.4)	117 (38.0)	0.557
Anti-coagulant	1310 (31.5)	65 (39.6)	1375 (31.8)	0.028	68 (44.2)	62 (40.3)	130 (42.2)	0.489
Antihistamine	1033 (24.8)	27 (16.5)	1060 (24.5)	0.015	33 (21.4)	27 (17.5)	60 (19.5)	0.388
Anti-hypertensive	936 (22.5)	53 (32.3)	989 (22.9)	0.003	55 (35.7)	49 (31.8)	104 (33.8)	0.470
Diuretics	652 (15.7)	54 (32.9)	706 (16.3)	< 0.001	57 (37.0)	52 (33.8)	109 (35.4)	0.551
Chinese medicine symptom-based diagnosis – *n* (%)								
Phlegm-heat lung distress	1385 (42.3)	46 (31.5)	1431 (41.8)	0.010	45 (36.0)	45 (32.9)	90 (34.4)	0.591
Phlegm lung congestion	689 (21.0)	33 (22.6)	722 (21.1)	0.646	26 (20.8)	33 (24.1)	59 (22.5)	0.525
Lung and *kidney qi* deficiency	403 (12.3)	21 (14.4)	424 (12.4)	0.453	19 (15.2)	20 (14.6)	39 (14.9)	0.891
Prognosis								
Deceased – *n* (%)	78 (1.9)	15 (9.2)	93 (2.2)	< 0.001	6 (3.9)	14 (9.1)	20 (6.5)	0.064
Hospitalization episodes	1.6 ± 1.7	1.0 ± 0.2	1.6 ± 1.7	< 0.001	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	1.000
1st hospitalization duration (days)	15.2 ± 8.7	15.6 ± 10.9	15.2 ± 8.8	0.169	16.2 ± 9.4	15.6 ± 11.2	15.9 ± 10.3	0.598
Total length of hospitalization (days)	25.7 ± 37.0	16.3 ± 12.3	25.4 ± 36.4	< 0.001	17.0 ± 10.9	16.3 ± 12.6	16.7 ± 11.8	0.624

Baseline demographics and investigation. [1] Matched by propensity score calculated by demographic factors, clinical presentation and the use of concomitant medications (**Supplement S1**).

with categorical analysis, showing no increase in deranged liver and renal function after add-on CM.

Prescription frequency and association with mortality

The frequency of CM prescription is summarized in **Supplement S5.** The top ten most used CMs in our cohort included *Fritillariae Cirrhosae Bulbus* (Chuan-bei-mu) (Quan et al., 2022; Geng et al., 2018), *Pinelliae Rhizoma* (Ban-xia) (Wagner et al., 2011), *Poria* (Fu-ling) (Ríos, 2011; Sun, 2014), *Atractylodis Macrocephalae Rhizoma* (Bai-zhu) (Gu et al., 2019), *Citri Reticulatae Pericarpium* (Chen-pi) (Yu et al., 2018; Shi et al., 2009), *Perillae Fructus* (Zi-su-zi) (Yim et al., 2010; Ahmed, 2018), *Farfarae Flos (*Kuan-dong-hua) (Liu et al., 2020), *Asteris Radix Et Rhizoma (*Zi-wan) (Zhang et al., 2018), *Glycyrrhizae Radix Et Rhizoma (*Gan-cao) (Wang et al., 2015) and *Armeniacae Semen Amarum (*Xing-ren) (Do et al., 2006).

Among the 10 most prescribed CMs, the use of *Poria* (Fu-ling) (HR: 0.56, 95% CI: 0.32 to 1.00, p = 0.050), *Citri Reticulatae Pericarpium* (Chen-pi) (HR: 0.56, 95% CI: 0.27 to 0.87, p = 0.015) and *Glycyrrhizae Radix Et Rhizoma* (Gan-cao) (HR: 0.56, 95% CI: 0.29 to 0.89, p = 0.018) was associated with significant mortality reduction, statistically and clinically. A total of 29241 CM prescription records were identified, of which 3441 records contained *Er-chen-tang* and 8740 records contained more than half (50%) of *Xing-su-san.* In addition, 8331 different CM prescriptions were obtained, of which the most frequent prescription appeared 30 times in total.

Network pharmacology analysis

Two molecular network modules were both enriched for COPD genes and the drug targets of the 20 top related herbs, which totally contain 348 genes (Fig. 3, **Supplement S6**). From KEGG analysis, the putative targets of the CM used in this cohort on COPD were related to Jak-STAT, Toll-like receptor, and TNF signaling pathway which shares similar mechanism with a range of immunological disorders and infectious diseases (**Supplement S7**). For example, hesperidin is one of the main components of *Citri Reticulatae Pericarpium* and is used as an official indicator to monitor the quality of *Citri Reticulatae Pericarpium* (Yu et al., 2018). Through the HIT database, we know that the targets of hesperidin include PTGS2 and ICAM1, and according to the KEGG analysis results, these two targets are involved in the TNF signaling pathway.

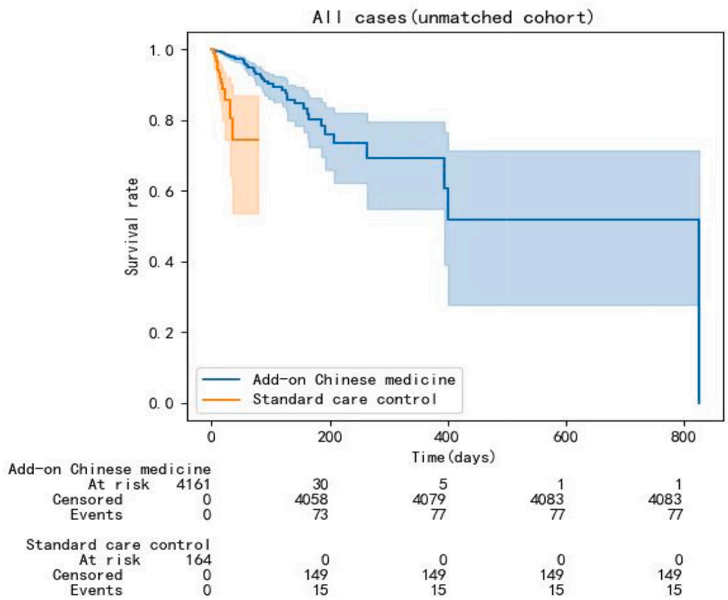
Disscusion

We investigated 4325 consecutive inpatient COPD cases to assess the effectiveness of add-on personalized CM. Our findings show that add-on CM was associated with an 87% significant risk reduction of mortality with minimal adverse effect on liver and renal function. On the drug level, *Poria* (Fu-ling), *Citri Reticulatae Pericarpium* (Chen-pi) and *Glycyrrhizae Radix Et Rhizoma (*Gan-cao) were associated with reduced hazard of mortality. The putative targets involved Jak-STAT, Toll-like receptor, and TNF signaling pathways.

Existing evidence and limitation

Previous meta-analyses showed that add-on CM was associated with improved lung function, oxygenation and general symptoms in COPD patients (Liu et al., 2019; Chan, K.H. et al., 2021). A recent cohort study from Taiwan showed that long-term CM use for was associated with reduced mortality in COPD patients (Hung et al., 2022). *Fritillaria thunbergii* (Zhe-bei-mu), *Platycodon grandiflorum* (Jie-gen), *Prunus armeniaca ansu* (Xing-ren), *Houttuynia cordata* (Yu-xing-cao), *Salvia miltiorrhiza* (Dan-shen), *Ophiopogon japonicus* (Mai-men-dong), *Rheum palmatum* (Da-huang), *Scutellaria baicalensis* (Huang-qin), *Schisandra chinensis* (Wu-wei-zi) and *Magnolia officinalis* (Hou-po) were most used CMs in the Taiwan cohort.

Nevertheless, the effect of CM use for hospitalized acute exacerbation is unclear as most of the current evidence focused on the management of stable COPD patients in the outpatient setting. A late randomized controlled trial showed that protocolized Chinese medicine treatment leads to less severe presentation (less scores in COPD Assessment Test and modified Medical Research Council Dyspnea Scale and COPD-Patient Reported Outcome scale), shorter hospitalization and less readmission in COPD patients with acute exacerbation (Li et al., 2020). However, the effect of CM on the mortality during acute exacerbation remains unclear.



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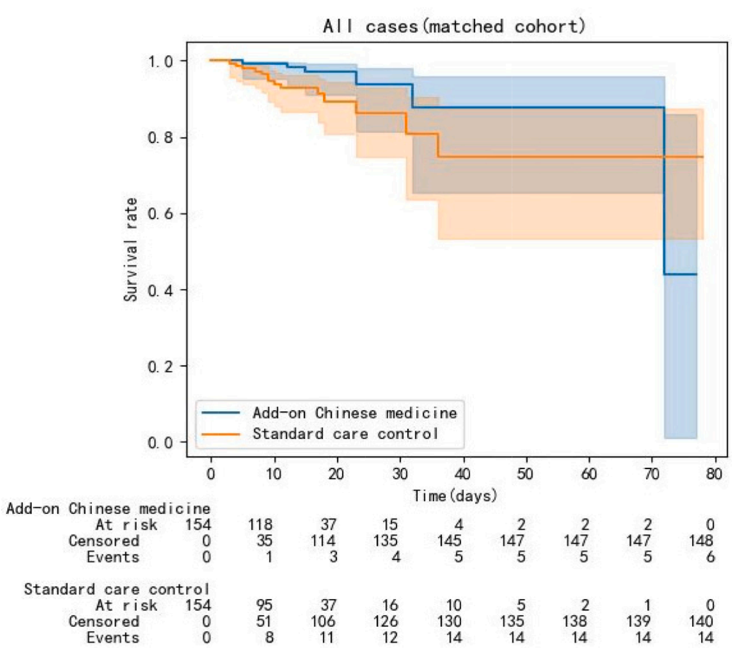

b

Fig. 2. Survival of COPD patients.
Kaplan Meier survival curves of all chronic obstructive pulmonary disease inpatients with add-on personalized Chinese medicine (exposed) and standard care alone (unexposed). Patients with add-on Chinese medicine had a significantly better survival when compared to non-user, in both unmatched (adjHR = 0.18, 95% CI: 0.09 to 0.37, $p < 0.001$) and propensity score matched cohort (adjHR = 0.13, 95%CI: 0.03 to 0.60, p = 0.008).

CM prescription is personalized based on clinical presentation (Chan et al., 2020; Shu et al., 2021; Jiang et al., 2012; Li et al., 2020). Most existing CM trials used single formulation, herb or extract in the disease population without personalization which is not reflecting the CM clinical practice, or had only recruited a specific phenotype-based subset of patients which is not representative to the disease population (Chan, K.H. et al., 2021; Chan, K.W., et al. 2021). Therefore, real-world evidence assessing the effectiveness of CM in mortality reduction during acute exacerbation of COPD is limited (Chan, K.H. et al., 2021).

In this study, we show that the use of add-on CM was associated with significant mortality reduction. CM-treated patients also had higher lymphocyte and lower neutrophil percentages, which indicated possible anti-inflammatory and immune-modulating effect from the CM used. This is further supported by our network pharmacology inferences showing key inflammation and immune mechanisms including Jak-STAT, Toll-like receptor, and TNF signaling pathways were likely involved. The level of hemoglobin was higher in CM-treated patients. Although anemia is a known important comorbidity and independent mortality predictor of COPD (Oh et al., 2017), the mechanism is unclear. To summarize, CM used in this cohort may exert anti-inflammatory and immune-modulating effect to reduce the risk of mortality of patients.

Table 2
Association between the use of personalized Chinese medicine and mortality.

Analysis on mortality Mortality / Patient at risk (%)	All cases (n = 4325)	Matched cohort (n = 308)
Personalized Chinese medicine user	78/4161 (1.9)	6/154 (3.9)
Personalized Chinese medicine non-user	15/164 (9.2)	14/154 (9.1)
Crude hazard ratio (unadjusted Cox regression)	0.09 (0.05 to 0.16) $p < 0.001$	0.38 (0.14 to 0.98) $p = 0.046$
Adjusted hazard ratio (multivariable Cox regression) [1]	0.18 (0.09 to 0.37) $p < 0.001$	0.13 (0.03 to 0.60) $p = 0.008$

Multivariable Cox regression model adjusting demographic factors, clinical presentation and the use of concomitant medications (**Supplement S1**) was used to estimate the association between the use of personalized CM and death.

Table 3
Endpoint hematology and biochemistry.

Hematology	Chinese Medicine + standard care (n = 154) Mean ± SD	Standard care (n = 154) Mean ± SD	Difference Mean ± SE	p-value
Hemoglobin (g/l)	**124.2 ± 19.7**	**116.8 ± 22.2**	**7.4 ± 3.4**	**0.033**
Leukocyte (10^9/l)	**7.2 ± 4.2**	**8.0 ± 4.0**	**-0.8 ± 0.7**	**0.221**
Neutrophils (10^9/l)	**5.1 ± 4.2**	**6.2 ± 4.0**	**-1.0 ± 0.7**	**0.123**
Neutrophils percentage (%)	**67.5 ± 14.0**	**73.3 ± 15.0**	**-5.8 ± 2.4**	**0.016**
Lymphocytes (10^9/l)	**1.4 ± 0.7**	**1.3 ± 0.7**	**0.2 ± 0.1**	**0.128**
Lymphocytes percentage (%)	**23.2 ± 11.9**	**18.7 ± 12.6**	**4.5 ± 2.0**	**0.026**
Platelet (10^9/l)	**197.4 ± 79.9**	**191.7 ± 80.9**	**5.7 ± 13.1**	**0.664**
Biochemistry				
Alkaline phosphatase (U/l)	**101.6 ± 56.8**	**93.0 ± 60.3**	**8.6 ± 10.8**	**0.431**
Alanine aminotransferase (U/l)	**34.3 ± 41.0**	**71.4 ± 261.4**	**-37.1 ± 33.2**	**0.308**
Aspartate aminotransferase (U/l)	**29.6 ± 21.5**	**60.8 ± 219.8**	**-31.2 ± 25.5**	**0.287**
C-reactive protein (mg/l)	**34.5 ± 60.5**	**39.8 ± 73.1**	**-5.3 ± 13.9**	**0.703**
Serum albumin (g/l)	**35.2 ± 4.8**	**34.7 ± 5.4**	**0.5 ± 0.9**	**0.601**
Serum creatinine (μmol/l)	**64.0 ± 17.0**	**75.7 ± 50.0**	**-11.7 ± 10.4**	**0.342**

Adjusting the selection bias

To adjust for the potential bias arise from non-randomized allocation of personalized CM use in this retrospective cohort, propensity score was used for matching. The propensity score was calculated based on key demographic factors, clinical presentation, and the use of concomitant medication that were 1) prevalent, 2) with baseline inter-group difference, and 3) previously reported to correlate with prognosis of acute exacerbation of COPD. The hazard ratio of mortality was estimated by Cox regression adjusting the same set of covariates as that used for propensity score calculation. An analysis of crude hazard ratio without adjustment was conducted as sensitivity analysis. We also performed the same set of analysis on the unmatched cohorts as sensitivity analysis. We further assessed the change of key biochemistry and biomarkers to potential adverse effect of CM on the liver and renal function.

Comparison to other studies

The significant mortality reduction and the general trend of improved hematology laboratory investigation found in our study using real-world data is coherent to the symptomatic improvement reported earlier from a randomized trial on hospitalized COPD patients with acute exacerbation (Li et al., 2020) in Henan, China. The trial used semi-personalized treatment protocol based on fluid clearing and cold repelling (San-han-hua-yin), phlegm and hear clearing (Qing-re-hua-tan) and dampness and phlegm clearing (Zao-shi-hua-tan) CMs.

Our cohort has more comorbidities (e.g., coronary heart disease, hypertension, asthma, diabetes), more use of concomitant medications (bronchodilator and steroid) with less patients presented with external cold and internal fluid (Wai-han-nei-yin). Prescription analysis showed that the most used CMs in hospitalized acute exacerbated COPD patients in our cohort are related to *lung* releasing and regulating *qi* (Xuan-fei-li-qi): 1) *Perillae Fructus (*Zi-su-zi), 2) *Farfarae Flos (*Kuan-dong-hua), 3) *Asteris Radix Et Rhizoma (*Zi-wan), and 4) *Armeniacae Semen Amarum (*Xing-ren), and dampness, phlegm and heat clearing (Zao-shi-hua-tan-qing-re): 1) *Pinelliae Rhizoma* (Ban-xia), 2) *Poria* (Fu-ling), 3) *Atractylodis Macrocephalae Rhizoma* (Bai-zhu), 4) *Citri Reticulatae Pericarpium* (Chen-pi) and 5) *Fritillariae Cirrhosae Bulbus* (Chuan-bei-mu) which is also coherent to the reported intervention protocol. From our further drug-based analysis, *Poria* (Fu-ling) and *Citri Reticulatae Pericarpium* (Chen-pi) were the 2 CMs with most consistent and significant risk reduction of mortality, indicating dampness and phlegm clearing is core component of treatment leading to mortality reduction. Further prescription analysis showed that our CM prescription was personalized based on clinical presentation as only 30 patients had repeating prescription.

The prescription pattern of our cohort is different from the report of the Taiwan cohort. Only *Armeniacae Semen Amarum* (Xing-ren) was the overlapped in both cohorts as the most commonly used CMs. Although the two cohorts had similar demographics, the Taiwan cohort used more *Salvia miltiorrhiza* (Dan-shen), *Rheum palmatum* (Da-huang) and *Ophiopogon japonicus* (Mai-men-dong) suggesting a substantial focus is on the maintenance with mild exacerbation. Nevertheless, there is limited information on the duration of inpatient and outpatient treatment and the generalizability to the inpatient setting remains unclear.

As the patients were given CM in formulations with multiple chemical ingredients exerting systemic effects (Zhang et al., 2019), we used network pharmacology analysis to explore the possible mechanisms underpinning the observed clinical effect from a whole-system approach based on current *in vivo* and *in vitro* studies (Zhang et al., 2019; Hopkins, 2008). From the network inference, the putative targets involved numerous interleukins and both the TNF and Toll-like receptor singling pathway. These targets shared similar mechanisms with inflammatory bowel disease, supporting a potential repurpose of the CM used for COPD in this cohort for inflammatory bowel disease. This is consistent with the CM theory that *lung* is connected with *bowel* (Zhong et al., 2013), and the gut-lung axis linked through immunomodulating effect of the microbiota (Anand and Mande, 2018).

Implication to further research

Based on our findings, we believe further large-scale prospective randomized trials are warranted to ascertain the effect of CM in mortality reduction in COPD patients with acute exacerbation. The intervention could be fully personalized as supported by our data, or semi-personalized for easier translation. Also, the three CMs that were most related to the treatment effect worth further investigation and development into new drugs. Further exploratory drug repurposing studies could also assess the effect of these CMs on gastrointestinal conditions.

Strengths and limitations

To our knowledge, this is the first real-world study demonstrating the

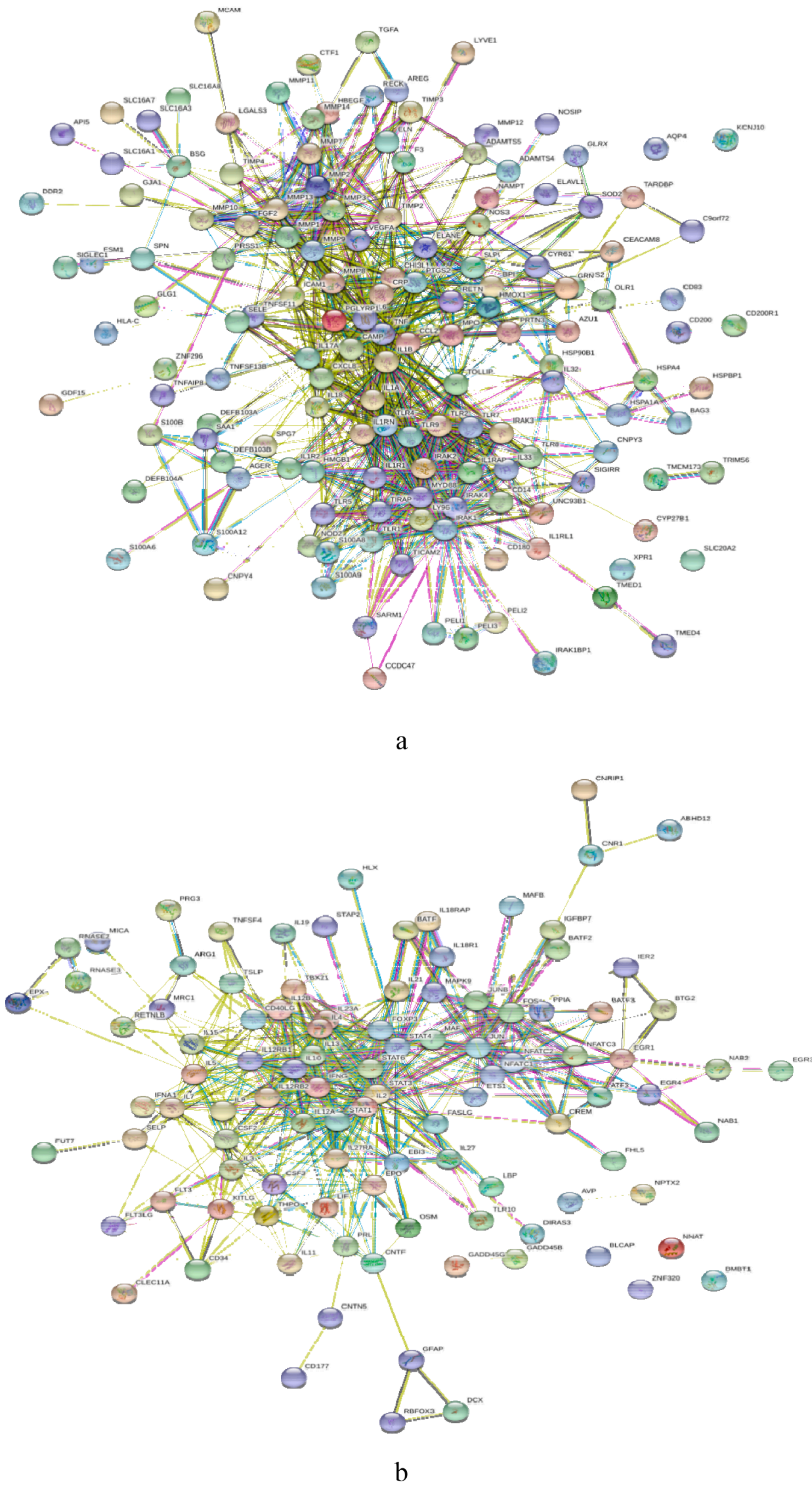

Fig. 3. PPI network of two enrich molecular network modules.
Screen protein-protein interaction (PPI) network graphs with a minimum required interaction score of high confidence (0.700). In the network graph, nodes represent proteins, and nodes are labeled with the names of these proteins. The pattern in the node represents the three-dimensional structure of the protein. If it is empty, the structure is currently unknown. If there is an interaction between two proteins, they are connected by wires, the color of which reflects the type of interaction. The disconnected nodes in the network were hidden.

effective of add-on personalized CM in reducing mortality among hospitalized COPD patients with acute exacerbation by using a representative total population sampling. The demographics are comparable to other inpatient COPD cohorts. Coherent findings on symptomatic improvement were previously reported from randomized trials and we further found a substantial reduction in mortality with minimal adverse effects on liver and renal function building on the existing studies. Besides, we analysed the effect of 1) CM as an overall intervention, and 2) most used CMs individually to explore the effect at different levels. We also used network pharmacology analysis to explore the putative targets of the CMs used.

This study has several limitations. First, this is a non-randomized observational cohort and potential unknown confounding factors may introduce selection bias that were not adjusted or matched. Also, since CM has been used widely used in our center for COPD inpatients, the non-user group was small. Nevertheless, our results remained robust in both the adjusted Cox regression model and propensity score matched cohort. Besides, the network pharmacology analysis on possible mechanism was only based on the molecular chemistry level of all CM used, which does not inform the overall mechanisms of a specific CM and clinical prescription.

Conclusion

Our results suggest that add-on personalized Chinese medicine was associated with significant mortality reduction in hospitalized COPD patients with acute exacerbation in real-world setting, with minimal adverse effect on liver and renal function. Chinese medicine should be considered as an add-on regimen for the current multidisciplinary COPD management. *Poria* (Fu-ling) and *Citri Reticulatae Pericarpium* (Chen-pi) were associated with significant reduced risk of mortality in the survival analysis at drug level and could be considered in new drug development.

Additional Information

Ethics

This study was approved by the ethics review board of The First Affiliated Hospital of Henan University of Chinese Medicine (AF/SG-17/03.1). Written consent was waived due to the retrospective nature. This study is reported according to STROBE (The Strengthening the Reporting of Observational Studies in Epidemiology).

Conflict of Interest Disclosure

This study is partially supported by the National Natural Science Foundation of China (81830116 and 82174533) and the Natural Science Foundation of Beijing (Nos. M21012). The funding organizations had not participate in the study design, conduct, management, data collection, analysis, interpretation, and dissemination. There is no financial relationships with any organizations that might have foreseeable interest in this study for the previous three years, and no other relationships or activities that influenced the related work.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Transparency declaration

The lead authors (N. Xu, K. Zhong, H. Yu, X. Zhou, K.W. Chan and J. Li) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Authors' Contribution

J. Li, H. Yu, K.W. Chan, X. Zhou and B. Liu conceived the study. N. Xu, W. Wang and Y. Qu collected the data. N. Xu, K. Chang, L. Zhou, W. Wang and Y. Qu processed the data. N. Xu, K. Zhong, Z. Shu and Q. Zheng performed data analysis. K. Zhong, H. Yu, K.W. Chan, X. Zhou and J. Li designed statistical analysis and advised data interpretation. K.W. Chan and X. Zhou drafted the manuscript. All authors proofread the manuscript. All data were generated in-house, and no paper mill was used. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

Supplementary file

S1Odds ratios of receiving personalized Chinese medicine treatment for variables included in the propensity score model

S2Distribution of propensity score for receiving personalized Chinese medicine

S3Standardized mean differences in risk factors in the matched and unmatched sample

S4Change of key hematology and biochemistry investigations

S5Top 10 most used Chinese medicines in the cohort

S6Genes overlapped between chronic obstructive pulmonary disease

S7Function of the putative targets of Chinese medicine on chronic obstructive pulmonary disease

Declaration of Competing Interest

No financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Funding

This study is partially supported by the National Natural Science Foundation of China (81830116 and 82174533) and the Natural Science Foundation of Beijing (Nos. M21012). The funding organizations had not participate in the study design, conduct, management, data collection, analysis, interpretation, and dissemination.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.phymed.2022.154586.

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