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Add-On Chinese Medicine for Coronavirus Disease 2019 (ACCORD): A Retrospective Cohort Study of Hospital Registries

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Abstract: Chinese medicine (CM) was extensively used to treat COVID-19 in China. We aimed to evaluate the real-world effectiveness of add-on semi-individualized CM during the outbreak. A retrospective cohort of 1788 adult confirmed COVID-19 patients were recruited from 2235 consecutive linked records retrieved from five hospitals in Wuhan during 15 January to 13 March 2020. The mortality of add-on semi-individualized CM users and non-users was compared by inverse probability weighted hazard ratio (HR) and by propensity score matching. Change of biomarkers was compared between groups, and the frequency of CMs used was analyzed. Subgroup analysis was performed to stratify disease severity and dose of CM exposure. The crude mortality was 3.8% in the semi-individualized CM user group and 17.0% among the non-users. Add-on CM was associated with a mortality reduction of 58% (HR = 0.42, 95% CI: 0.23 to 0.77, $p = 0.005$) among all COVID-19 cases and 66% (HR = 0.34, 95% CI: 0.15 to 0.76, $p = 0.009$) among severe/critical COVID-19 cases demonstrating dose-dependent response, after inversely weighted with propensity score. The result was robust in various stratified, weighted, matched, adjusted and sensitivity analyses. Severe/critical patients that received add-on CM had a trend of stabilized D-dimer level after 3–7 days of admission when compared to baseline. Immunomodulating and anti-asthmatic CMs were most used. Add-on semi-individualized CM was associated with significantly reduced mortality, especially among severe/critical cases. Chinese medicine could be considered as an add-on regimen for trial use.

Keywords: Coronavirus Disease 2019; COVID-19; Integrative Medicine; Chinese Medicine; Cohort; Effectiveness; Mortality.

Introduction

By 30 December 2020, Coronavirus disease 2019 (COVID-19) had infected 81.4 million people, and the death tolls reached 1.78 million (GitHub, 2020). The current strategy against COVID-19 focuses on non-pharmacological public health interventions, trial treatment with licensed drugs and development of new therapies and vaccines (Chan *et al.*, 2020b; Jackson *et al.*, 2020; Li and De Clercq, 2020). Social distancing was shown effective in reducing the transmission of COVID-19 (Chu *et al.*, 2020). Although remdesivir (Beigel *et al.*, 2020) and cocktail interferon/ribavirin therapy (Hung *et al.*, 2020) have demonstrated a trend of shortened clinical course, their reduction in mortality was modest, and the efficacy varied across different populations (Beigel *et al.*, 2020; WHO Solidarity Trial Consortium, 2020). Preliminary results from the RECOVERY trial added dexamethasone to the toolbox for patients receiving invasive mechanical ventilation with 36% reduction in mortality (The RECOVERY Collaborative Group, 2020). Nevertheless, more interventions that are licensed and readily available for repurposing are needed to provide timely therapeutic options in different clinical settings to prepare for the subsequent waves while we are waiting for vaccines to become widely accessible.

Chinese medicine (CM) has been extensively used in China during the COVID-19 outbreak in the form of proprietary and semi-individualized prescribed CMs (Chan *et al.*, 2020b; National Health Comission *et al.*, 2020; Shu *et al.*, 2020). Recent network pharmacology and previous *in vitro* studies showed that many of the CMs listed in the Chinese national guideline of COVID-19 management (Guideline) (National Health Comission *et al.*, 2020) have antiviral, anti-inflammatory and immunomodulating effects with good affinity to angiotensin-converting enzyme 2 (ACE2) receptor and coronavirus 3CL hydrolase that could prevent cytokine storm (Ren *et al.*, 2020; Runfeng *et al.*, 2020; Zhong *et al.*, 2020). A recent randomized controlled trial (RCT) of a licensed proprietary CM (Lian-hua-qing-wen Capsule) demonstrated shorter clinical recovery time, higher lung recovery rate, and lower progression rate from mild to severe cases among COVID-19 patients (Hu *et al.*, 2020). Another RCT using two add-on proprietary CMs also reported an 85.6% (1.6% vs. 11.1%) relative risk reduction of severity progression in COVID-19 patients (Xiao *et al.*, 2020).

In addition to proprietary CMs, COVID-19 patients in China were also treated with semi-individualized CM formulations, which were prescribed according to patients' severity and key symptoms based on the guideline (Table S6). A recent meta-analysis on existing clinical trials of prescribed CMs showed that add-on CMs could improve clinical recovery, shorten length of hospital stay, and alleviate symptoms, although the methodological quality of the included trials was generally unsatisfactory and of small scale (Xiong *et al.*, 2020). The CMs used in the guideline mainly formed by three classical CM formulations that is composed of 17 herbal CMs (Table S6). The majority of the CMs recommended are licenced and commercially available in standardized granule form globally. Nevertheless, the effectiveness of semi-individualized CM in real-world setting remains uncharacterized.

We aimed to evaluate the real-world effectiveness of add-on semi-individualized CM based on the registry data from Wuhan and identify the CMs that were frequently used.

Methods

Study Design

Retrospective cohort study on the registry of five hospitals in Wuhan. The flow of data extraction is summarized in Fig. 1.

Setting

We collected data from five hospitals in Wuhan, namely Hubei Provincial Hospital of Traditional Chinese Medicine (n = 325), Wuhan Huangpi District Hospital of Traditional Chinese Medicine (n = 529), Hubei 672 Orthopaedics Hospital of Integrated Chinese & Western Medicine (n = 378), Wuhan Hospital of Traditional Chinese Medicine (n = 273), and Wuhan Hospital of Traditional Chinese and Western Medicine (n = 730). The electronic medical records of all admitted adult COVID-19 patients (n = 2235) at any point during

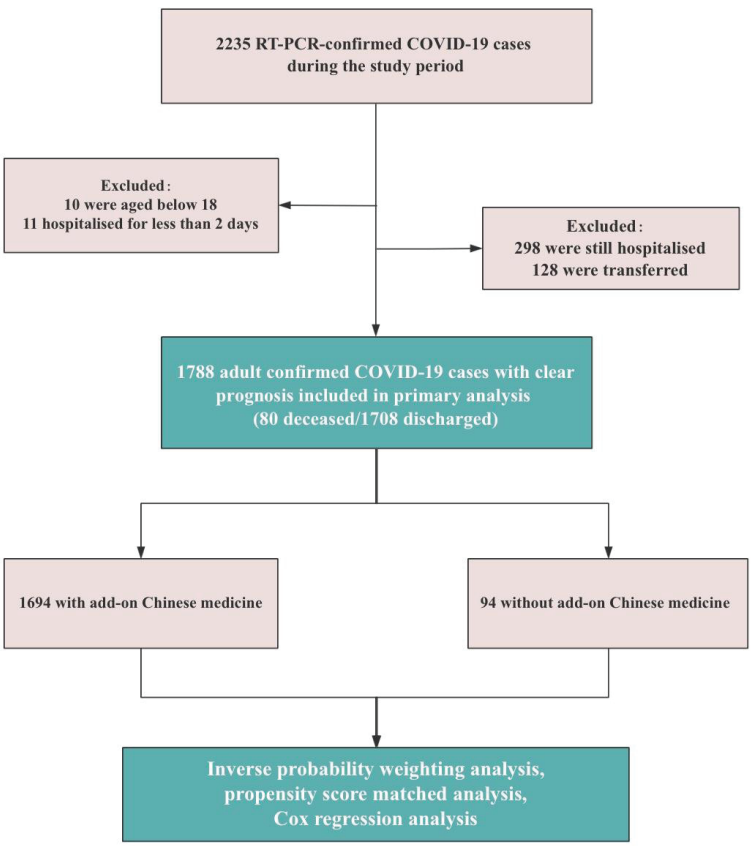


Figure 1. Flow of data extraction. Electronic medical record of all admitted adult COVID-19 patients at any point during hospitalization from five hospitals were retrieved with extraction–transformation–loading tool to integrate and normalize data from different operational sources, followed by clinicians' validation. 1788 (80%) of all cases satisfied inclusion/exclusion criteria and were included.

hospitalization from 15 January to 13 March 2020 were retrieved. Follow-ups continued through 18 March 2020. We included all patients (1) aged 18 or above, (2) with confirmed COVID-19 diagnosis by positive reverse transcription polymerase chain reaction (RT-PCR) assay result of nasopharyngeal or oropharyngeal swab and (3) hospitalized for at least two days in the analysis. Patients were further stratified into mild and severe/critical cases (severe cases were defined as respiratory rate >30 breaths/min, oxygen saturation = < 93% or PaO2/FiO2 ratio = < 300 mmHg. Critical cases were defined as including > = 1 of the following criteria: shock; respiratory failure requiring mechanical ventilation; combination with other organ failures; and admission to intensive care unit) for subgroup analysis.

Semi-individualized CM was prescribed by physicians based on patients' clinical presentation individually according to the recommendation of the guideline and their professional judgement. The prescription pattern was analysed.

Data Collection

Prior to the outbreak of COVID-19, we developed a clinical data warehouse that used clinical reference information model and physical data model to manage the various information entities and their relationships in complex clinical data involving both conventional and Chinese medicine (Zhou *et al.*, 2010). The platform incorporated data integration, pre-processing and data analysis components to process and explore the various clinical relationships.

We obtained data from the five hospitals and transferred them to the clinical data warehouse. This warehouse contains all the clinical data available on all inpatient and outpatient visits of the five hospitals, including patient demographics, consultation notes, laboratory/radiological investigations, pharmacy records and discharge status. We did not manually extract data from the electronic medical record, except for the definition of case severity. Case severity was defined by two researchers (Z. Shu, K. Chang) independently according to the predefined criteria listed in the guideline. Dissonance was resolved by discussion. All data were validated by at least two researchers independently and a physician (Z. Shu).

Semi-Individualized Chinese Medicine Exposure and Dose-Response Effect

Patients were defined as semi-individualized CM users if they had received any prescribed CMs that were not in a fixed dose and form at any point during hospitalization. To assess the dose-response effect, we further stratified patients into three subgroups of different prescription-to-hospitalization duration (*P*:*H*) ratio (< 0.6, 0.6 < = *P*:*H* < 0.8, > = 0.8). A *P*:*H* ratio of 1 refers to full use of semi-individualized CM throughout the hospitalization period, and a *P*:*H* ratio of 0 refers to a semi-individualized CM non-user. The *P*:*H* ratio provided a 3-level gradient of exposure for the assessment of dose-response. Study baseline was defined as the point of ward admission.

Endpoint

The primary endpoint was the time from study baseline to death. Kaplan–Meier curve and hazard ratio (HR) of Cox regression models were reported. We analyzed all patients with definite clinical outcomes of either death or discharged ($n = 1788$), to ensure outcome accuracy.

Statistical Analysis

Patients without a primary end-point event had their data censored on 22 March 2020. Missing values were handled by multiple imputation. We performed bivariate correlation analyses to examine the associations among baseline characteristics. Propensity score methods were used to adjust for potential confounders to account for the non-randomized allocation of semi-individualized CM treatment. The individual propensities for receiving semi-individualized CM treatment were estimated with a multivariable logistic-regression model that included the same set of covariates as the Cox regression model, except for chronic kidney disease and biomarkers due to the small strata size. Associations between semi-individualized CM use and death were subsequently estimated by multivariable Cox regression models with propensity score methods. Primary propensity score analysis was based on inverse probability weighting. In the inverse-probability-weighted analysis, the predicted probabilities from the propensity score model were used to calculate the stabilized inverse-probability-weighting weight. In the propensity score matching analysis, the nearest-neighbor method was applied to create a 1:1 matched control sample.

Cox proportional-hazards regression models were also used to estimate the association between the use of semi-individualized CM and death as a secondary analysis. We used a multivariable Cox regression model to adjust demographic factors (age, gender, history of hypertension, diabetes, coronary artery disease, chronic kidney disease) and laboratory tests (C-reactive protein and lymphocyte count). The differences in the change of key biomarkers at 3–7 days from baseline (0–2 days) after hospitalization were compared by Mann–Whitney U test between groups. The prescription pattern of CMs was analyzed by the frequency of utilization of each CM used among patients.

Assessment on Severity-Stratified Effect

Disease severity was stratified into mild and severe/critical groups in the subgroup analysis to assess effect modification and minimize the risk of selection bias due to the imbalance in disease severity between groups. The demographics of the stratified groups were analyzed. Sensitivity analysis was performed with different definitions of CM exposure, including both at least 30% and 60% *P*:*H* ratio, respectively. Statistical analyses were performed with *R* (version 4.0.0).

Results

Cohort Characteristics

A total of 2235 consecutive confirmed COVID-19 patients were admitted to the five hospitals during 15 January and 13 March 2020. 1788 patients (80%) were included in the analysis (Fig. 1). Ten pediatric patients, 11 patients hospitalized for less than two days, and 426 patients with unclear prognosis (298 still hospitalized at censoring and 128 transferred to other hospital) were excluded. 1694 patients (94.7%) used semi-individualized CM.

In the unmatched cohort, semi-individualized CM users were younger, had a lower level of neutrophil count, alkaline phosphatase, and urea, and had a higher level of serum albumin (Table 1). 1409/1694 (83.2%) of the semi-individualized CM users and 62/94 (66.0%) of the

Table 1. Patient Characteristics of All Cases in the Retrospective Cohort

Characteristics	Unmatched Cohort		Matched Cohort[a]	
	Chinese Medicine + Standard Care ($n = 1694$)	Standard Care ($n = 94$)	Chinese Medicine + Standard Care ($n = 93$)	Standard Care ($n = 93$)
Age (yr) — median [IQR]	57.0 [46.0–67.0]	66.0 [56.2–72.8]**	65.0 [56.0–74.0]	66.0 [56.0–72.0]
n (%):				
<40 yr	264 (15.6)	10 (10.6)	10 (10.8)	10 (10.8)
40–59 yr	684 (40.3)	19 (20.2)	19 (20.4)	19 (20.4)
60–79yr	653 (38.5)	50 (53.2)	49 (52.7)	50 (53.8)
> = 80 yr	93 (5.5)	15 (16.0)	15 (16.1)	14 (15.1)
Female — *n* (%)	859 (50.7)	50 (53.2)	45 (48.4)	49 (52.7)
Comorbidities — *n* (%)				
Diabetes	859 (50.7)	50 (53.2)	13 (14.0)	17 (18.3)
Hypertension	481 (28.4)	33 (35.1)	34 (36.6)	33 (35.5)
Chronic lung disease[b]	70 (4.1)	4 (4.3)	6 (6.5)	4 (4.3)
Chronic kidney disease	37 (2.2)	4 (4.3)	3 (3.2)	4 (4.3)
Coronary heart disease	130 (7.7)	9 (9.6)	9 (9.7)	9 (9.7)
Cerebrovascular disease	73 (4.3)	3 (3.2)	10 (10.8)	3 (3.2)
Tumor	28 (1.7)	3 (3.2)	1 (1.1)	3 (3.2)
Time from symptom onset to admission (day) —median [IQR]	10.0 [7.0–15.0]	10.0 [7.0–15.0]	10.0 [7.0–15.0]	10.0 [7.0–15.0]
Prognosis — *n* (%)				
Deceased	1630 (96.2)	78 (83.0)**	89 (95.7)	78 (83.9)*
Discharged	64 (3.8)	16 (17.0)**	4 (4.3)	15 (16.1)*

(*Continued*)

Table 1. (*Continued*)

Characteristics	Unmatched Cohort		Matched Cohort[a]	
	Chinese Medicine + Standard Care ($n = 1694$)	Standard Care ($n = 94$)	Chinese Medicine + Standard Care ($n = 93$)	Standard Care ($n = 93$)
Signs and Symptoms — *n* (%)				
Fever	1222 (72.1)	54 (57.4)	66 (71.0)	53 (57.0)
Cough	946 (55.8)	54 (57.4)	49 (52.7)	54 (58.1)
Fatigue/malaise	149 (8.8)	7 (7.4)	11 (11.8)	7 (7.5)
Shortness of breath	168 (9.9)	15 (16.0)	11 (11.8)	15 (16.1)
Sore throat	23 (1.4)	1 (1.1)	1 (1.1)	1 (1.1)
Sputum	82 (4.8)	5 (5.3)	5 (5.4)	5 (5.4)
Myalgia	20 (1.2)	0 (0)	2 (2.2)	0 (0)
Diarrhea	43 (2.5)	5 (5.3)	2 (2.2)	5 (5.4)
Laboratory Investigations — Median [IQR]				
Hemoglobin (g/L)	128.0 [118.0–139.0]	126.5 [117.0–137.2]	126.0 [118.2–136.5]	127.0 [117.5–137.5]
Leukocyte (10^9/L)	5.0 [3.9–6.3]	5.9 [4.0–7.3]*	5.4 [4.1–6.7]	5.9 [4.0–7.3]
Neutrophils (10^9/L)	3.1 [2.3–4.2]	4.0 [2.7–5.9]**	3.7 [2.6–4.6]	4.1 [2.7–5.9]
Lymphocytes (10^9/L)	1.2 [0.9–1.6]	1.2 [0.8–1.8]	1.1 [0.7–1.5]	1.2 [0.8–1.8]
Platelets (10^9/L)	210.0 [163.0–268.0]	231.5 [155.5–278.0]	219.5 [177.0–265.5]	232.0 [155.0–279.0]
D-dimer (mg/L)	0.4 [0.2–0.8]	0.3 [0.0–1.7]	0.4 [0.2–0.9]	0.3 [0.0–1.7]
Alanine aminotransferase (U/L)	25.0 [17.0–40.0]	21.0 [16.0–32.0]	20.8 [13.8–36.5]	21.5 [16.0–32.0]
Alkaline phosphatase (U/L)	65.0 [52.0–83.0]	71.0 [58.8–100.2]**	65.0 [54.0–80.0]	71.0 [58.5–98.0]*
C-reactive protein (mg/L)	9.9 [3.1–43.7]	5.3 [3.8–47.2]	8.9 [3.1–33.8]	5.3 [3.7–47.9]

Lactate dehydrogenase (U/L)	206.6 [163.0–274.0]	184.0 [152.0–303.0]	220.0 [164.0–266.5]	184.0 [152.0–303.0]
Bilirubin (μmol/L)	10.8 [8.3–13.9]	11.6 [9.1–15.0]	10.9 [9.2–15.4]	11.7 [9.2–15.0]
Creatinine (μmol/L)	66.0 [56.0–80.2]	65.0 [54.0–83.5]	65.0 [54.5–79.5]	65.5 [54.0–83.8]
Urea (mmol/L)	4.4 [3.5–5.5]	4.6 [3.6–6.7]*	4.6 [3.8–5.7]	4.6 [3.6–6.8]
Serum albumin (g/L)	37.4 [34.8–40.1]	36.0 [32.4–38.6]**	36.6 [33.4–40.1]	36.3 [32.3–38.6]
Creatine kinase (U/L)	60.0 [41.0–95.0]	59.0 [44.0–98.0]	62.6 [47.0–96.0]	59.0 [44.0–98.0]
Radiological Investigations (Chest CT) — *n* (%)				
No identifiable abnormalities	134 (7.9)	6 (6.4)	9 (9.7)	6 (6.5)
Bilateral infiltrate	1418 (83.7)	84 (89.4)	78 (83.9)	83 (89.2)
Right lobe infiltrate	89 (5.3)	2 (2.1)	4 (4.3)	2 (2.2)
Left lobe infiltrate	53 (3.1)	2 (2.1)	2 (2.2)	2 (2.2)
Concurrent Treatment — *n* (%)				
ACE inhibitor/ARB	171 (10.1)	11 (11.7)	5 (5.4)	11 (11.8)
Antivirals	1609 (95.0)	84 (89.4)*	89 (95.7)	83 (89.2)
Antibiotics	1193 (70.4)	59 (62.8)	67 (72.0)	58 (62.4)
Glucocorticoids	481 (28.4)	32 (34.0)	35 (37.6)	32 (34.4)
IV immunoglobin	283 (16.7)	17 (18.1)	22 (23.7)	17 (18.3)

[a]Matched by gender, age, hypertension, diabetes, coronary artery disease. [b]Including chronic obstructive pulmonary disease, asthma and chronic bronchitis.

Notes: *$p < 0.05$, **$p < 0.01$ between add-on semi-individualized Chinese medicine user (exposed) and non-user.

non-users were mild cases. Demographics of mild and severe/critical subgroups are summarized in Table S1. After stratifying the disease severity, demographics of semi-individualized CM users and non-users were comparable in both mild and severe/critical subgroups.

During the observation period (median: 20 days), the crude mortality among all cases was 4.5% (80/1788). There were 64 deaths (3.8%) in the semi-individualized CM group and 16 deaths (17.0%) among the non-semi-individualized CM users. The median duration of semi-individualized CM use was 20 days. 318, 315 and 1061 of CM users had a prescription-to-hospitalization duration ratio of <0.6, 0.6< = *P*:*H*<0.8 and > = 0.8, respectively. 93/94 of the non-CM users were included in the propensity score analysis and 1:1 matched. The distribution of propensity scores between groups in the matched cohort was comparable (Fig. S2). The baseline characteristics between groups were balanced by propensity score matching (Table 1, Fig. S3). The odds ratio of receiving individualized CM of each factor in the propensity score model is summarized in Table S3. In the severity subgroup analyses, 62/62 (mild) and 31/32 (severe/critical) of the standard care cases were matched with semi-individualized CM users.

Primary Clinical Outcomes

The Kaplan–Meier survival curves of all cases and severe/critical cases of both unmatched, and propensity score-matched cohorts are shown in Fig. 2. The absolute risk reduction by add-on semi-individualised CM was 13.2% (3.8% vs. 17.0%). From the inverse probability weighted analysis with propensity scores, the hazard ratio of mortality was 0.42 (95% CI: 0.23 to 0.77, $p = 0.005$), 0.73 (95% CI: 0.09 to 5.77, $p = 0.763$), 0.34 (95% CI: 0.15 to 0.76, $p = 0.009$) among all, mild and severe/critical cases, respectively (Tables 2 and S4). Propensity score matched analysis provided comparable results. The stratified HR of mortality with prescription-to-hospitalization duration ratio of <0.6, 0.6< = *P*:*H*<0.8 and > = 0.8 were 0.67, 0.61 and 0.23, respectively, demonstrating a dose-dependent response (Fig. 2, Table 2).

In the multivariable Cox regression model adjusting age, gender, history of hypertension, diabetes, coronary artery disease, chronic kidney disease and levels of C-reactive protein and lymphocyte count (Table S2), the adjusted HR of mortality was 0.27 (95% CI: 0.15 to 0.48, $p < 0.001$), 0.82 (95% CI: 0.07 to 9.43, $p = 0.87$), 0.32 (95% CI: 0.17 to 0.60, $p < 0.001$) among all, mild and severe/critical cases, respectively (Table 2). In the sensitivity analysis, the result remained robust when the definition of individualized CM exposure was changed to either at least 30% or 60% of the individual hospitalized duration (Table S5).

Change in Key Biomarkers

Patients that received add-on CM had a trend of greater C-reactive protein and lactate dehydrogenase reduction after 3–7 days of admission when compared to baseline (0–2 days), though not statistically significant. The levels of serum creatinine, alanine aminotransferase and alkaline phosphatase were comparable between groups, except that severe/critical patients with CM exposure had a trend of less increased D-dimer compared to non-users (Fig. S1).

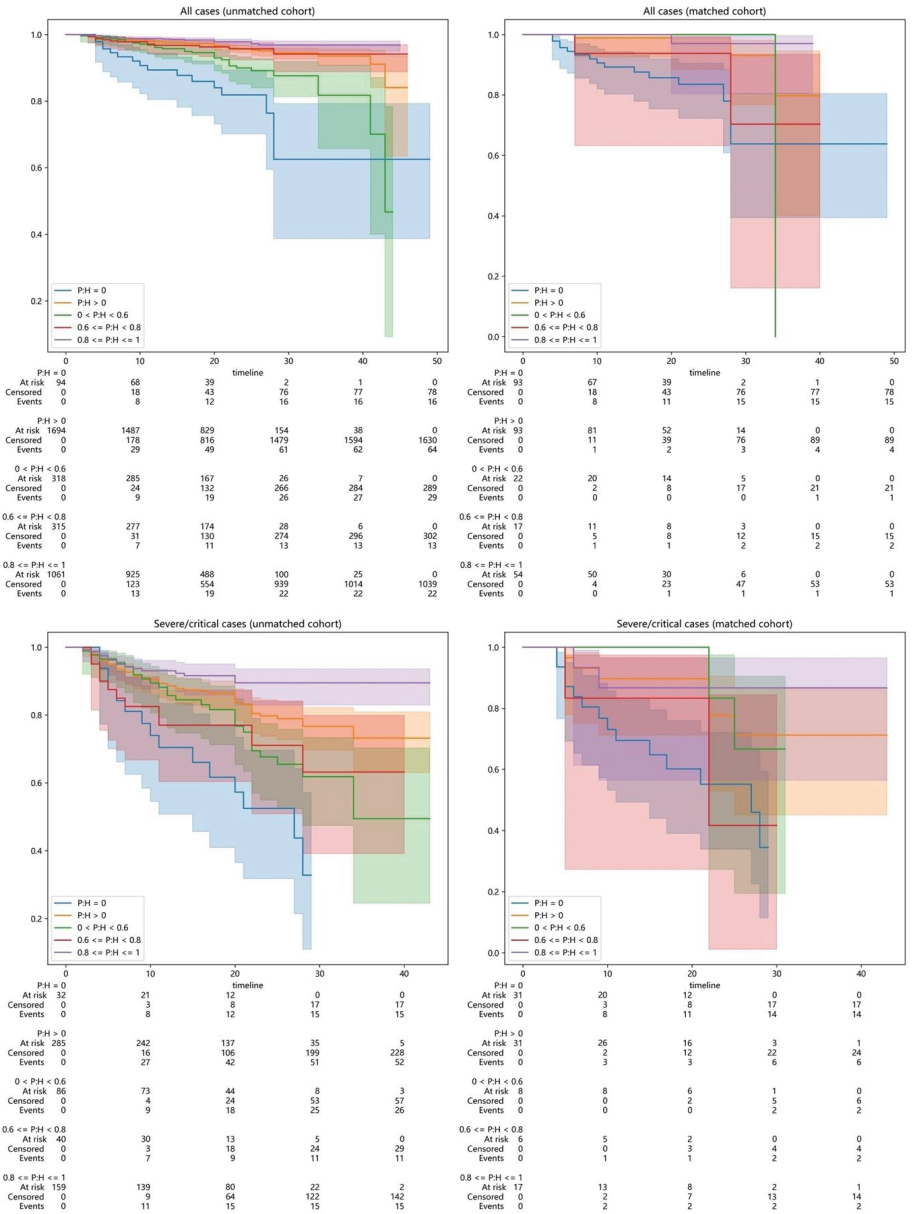


Figure 2. Survival of COVID-19 patients. The Kaplan–Meier survival curves with 95% confidence intervals of all COVID-19 patients with add-on semi-individualized Chinese medicine (exposed) and non-user (unexposed). *P*:*H* refers to prescription-to-hospitalization duration ratio, *P*:*H* = 0 refers to unexposed group, *P*:*H* > 0 refers to exposed group. The exposure was further divided into less than 60% (0 < *P*:*H* < 0.6), 60% to 80% (0.6 < = *P*:*H* < 0.8), and over 80% (0.8 < = *P*:*H* < = 1) prescription of Chinese medicine during hospitalization as subgroup analysis. The survival was significantly better with add-on Chinese medicine when compared to non-user, in both unmatched (adjHR = 0.42, 95% CI: 0.23 to 0.77) and propensity score matched cohort (HR = 0.23, 95%CI: 0.06 to 0.68).

Table 2. Association Between the Use of Semi-Individualized Chinese Medicine and Mortality

Analysis on Mortality	All Cases (Mild + Severe/Critical) ($n = 1788$)	Mild Cases ($n = 1471$)	Severe/Critical Cases[b] ($n = 317$)
Mortality/Patient at Risk (%)			
Semi-individualized Chinese medicine	64/1694 (3.8)	12/1409 (0.9)	52/285 (18.2)
Non-semi-individualized Chinese medicine	16/94 (17.0)	1/62 (1.6)	15/32 (46.9)
Crude Hazard Ratio (Unadjusted Cox Regression) of Unmatched Cohort	0.19 (0.11 to 0.33) $p < 0.001$	0.50 (0.06 to 3.84) $p = 0.50$	0.31 (0.18 to 0.55) $p < 0.001$
Adjusted Hazard Ratio (Multivariable Cox Regression) of Unmatched Cohort[a]	0.27 (0.15 to 0.48) $p < 0.001$	0.82 (0.07 to 9.43) $p = 0.87$	0.32 (0.17 to 0.60) $p < 0.001$
Propensity Score Matched Hazard Ratio			
By inverse probability weighting (All users vs. non-users)[c]	0.42 (0.23 to 0.77) $p = 0.005$	0.73 (0.09 to 5.77) $p = 0.763$	0.34 (0.15 to 0.76) $p = 0.009$
Subgroup: prescription to hospitalization ratio < 0.6	0.67 (0.34 to 1.31) $p = 0.245$	0.89 (0.09 to 8.80) $p = 0.923$	0.59 (0.24 to 1.47) $p = 0.261$
Subgroup: prescription to hospitalization ratio = 0.6 to 0.8	0.61 (0.26 to 1.40) $p = 0.245$	0.77 (0.07 to 8.72) $p = 0.831$	0.45 (0.15 to 1.34) $p = 0.159$
Subgroup: Prescription to hospitalization ratio > = 0.8	0.23 (0.11 to 0.49) $p < 0.001$	0.52 (0.06 to 4.37) $p = 0.547$	0.16 (0.06 to 0.42) $p < 0.001$
By propensity score matching[d]	0.23 (0.06 to 0.68) $p = 0.013$	0.00 [NA, Inf] $p = 0.996$	0.29 (0.09 to 0.88) $p = 0.034$

[a]Adjusted for age, gender, C-reactive protein, lymphocyte count, history of diabetes, hypertension, coronary artery disease, chronic kidney diseases.

[b]Severe cases were defined as respiratory rate >30 breaths/min, oxygen saturation = < 93% or PaO2/FiO2 ratio = < 300 mmHg. Critical cases were defined as including > = 1 of the following criteria: shock; respiratory failure requiring mechanical ventilation; combination with other organ failures; and admission to intensive care unit.

[c]Included all cases ($n = 1788$ for all cases, $n = 1471$ for mild cases, $n = 317$ for sever/critical cases).

[d]Matched by age, gender, history of diabetes, hypertension, coronary heart disease. Included disease severity in the matching for all cases ($n = 93$).

Prescription Frequency of Individual Chinese Medicines

Prescription frequency of CMs is summarized in Table 3. *Rhizoma Pinelliae* (ban-xia) (Wagner *et al.*, 2011), Poria (fu-ling) (Ríos, 2011; Sun, 2014), *Armeniacae Semen Amarum* (xing-ren) (Do *et al.*, 2006), *Agastache Rugosa* (huo-xiang) (Zielińska *et al.*, 2014), *Pericarpium Citri Reticulatae* (chen-pi) (Shi *et al.*, 2009; Yu *et al.*, 2018), *Licorice* (gan-cao) (Wang *et al.*, 2015), *Radix Scutellariae* (huang-qin) (Wang *et al.*, 2018), *Rhizoma Atractylodis Macrocephalae* (bai-zhu) (Gu *et al.*, 2019), *Herba Ephedrae* (ma-huang) (Wei *et al.*, 2019) and *Bupleurum Chinense Dc.* (chai-hu) (Law *et al.*, 2014) were most used. These CMs were recommended by the guideline for patients presented with clinical subtype 4 (mild) and 5 (severe) (Table S6). The symptom-based indications for subtype 4 were: mild/no fever, cough with little sputum, malaise, chest tightness, abdominal distention, and loose stool, and that of subtype 5 were: fever, cough with little yellowish/sticky sputum or hemoptysis, malaise, dyspnea, anorexia, poor appetite, and unsmooth defecation.

Discussion

We analyzed 1788 consecutive confirmed COVID-19 cases with definite prognosis from five hospitals in Wuhan to determine the real-world effectiveness of add-on semi-individualized CM. Our analyzes showed that add-on CM was associated with significant mortality reduction.

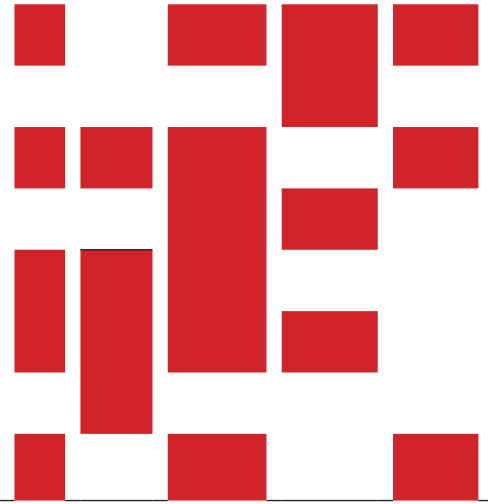
Existing Evidence

The prescription of CM is mainly guided by symptom-based diagnosis, and therefore, CM treatment strategy was formulated promptly for COVID-19 since the early stage of outbreak, when the virology understanding of SARS-CoV-2 was inadequate (Chan *et al.*, 2020a). Nevertheless, the clinical effectiveness of the CM treatments requires evaluation with empirical evidence. A RCT showed that Lian-hua-qing-wen Capsule, a proprietary CM used extensively in China for various infectious diseases, shortened the clinical recovery time, improved lung recovery, and reduced the progression from mild to severe cases among COVID-19 patients (Hu *et al.*, 2020). Another RCT using two add-on proprietary CMs highly comparable to the CMs used in our cohort also reported an 85.6% (1.6% vs. 11.1%) risk reduction of progression to severe presentation in COVID-19 patients (Xiao *et al.*, 2020). Meta-analysis on existing clinical trials of prescribed CMs showed that add-on prescribed CMs may shorten hospital stay, improve clinical recovery and alleviate symptoms (Xiong *et al.*, 2020). These effects could be explained by the antiviral, antibacterial, anti-inflammatory, immunomodulating and anti-asthmatic effect in many of the CMs used which was previously documented *in vitro* and *in vivo* (Do *et al.*, 2006; Ríos, 2011; Shi *et al.*, 2009; Sun, 2014; Wagner *et al.*, 2011; Wang *et al.*, 2018; Yu *et al.*, 2018; Zhong *et al.*, 2020).

Table 3. List of Key Chinese Medicines Used in the Cohort

English	Latin	Ping-yin	Chinese (Simplified)	Major Related Ingredients	Documented Effects and Hypothesized Mechanism on COVID-19					Frequency of Use[a]
					Anti-viral	Anti-bacterial	Anti-inflam-matory	Immuno-modulating	Anti-asthmatic	
***Processed rhizoma Pinelliae Ternatae*	*Rhizoma Pinelliae*	*Zhi-ban-xia*	制半夏 (制半夏)	*3-acetoamino-5-methylisooxazole, butyl-ethyleneether, 3-methyleicosane*			■		■	75.6%
Indian Bread	*Poria*	*Fu-ling*	茯苓 (茯苓)	*Pachymic acid, tumulosic acid, pachymic acid methyl ester*			■	■		74.0%
Ansu Apricot Seed	*Armeniacae Semen Amarum*	Xing-ren	杏仁 (杏仁)	Amygdalin, emulsin, amygdalase				■	■	73.3%
Herba Agastaches Seu Pogostemi	*Agastache Rugosa*	*Huo-xiang*	廣藿香 (广藿香)	*Pogostemonis herba*	■		■			66.1%
Dried Tangerine Peel	*Pericarpium Citri Reticulatae*	Chen-pi	陳皮 (陈皮)	Hesperidin, nobiletin			■	■	■	65.8%
Liquorice Root	*Licorice*	*Gan-cao*	甘草 (甘草)	*Glycyrrhizin, glycyrrhetic acid, glycuronic acid*	■	■	■	■		64.6%
Baical Skullcap Root	*Radix Scutellariae*	*Huang-qin*	黄芩 (黄芩)	*Baicalein, baicalin, wogonin*	■	■	■	■		64.3%
Largehead Atractylodes Rhizome	*Rhizoma Atractylodis Macrocephalae*	Bai-zhu	白朮 (白术)	Atractylol, atractylon	■		■			58.8%
Ephedra	*Herba Ephedrae*	*Ma-huang*	麻黄 (麻黄)	*Ephedrine, pseudo-ephedrine*	■	■	■		■	54.6%
Chinese Thorowax Root	*Bupleurum Chinense Dc.*	Chai-hu	柴胡 (柴胡)	Saikosapoins a-d, 2-methyl cyclopentaone	■	■	■	■		53.9%

**Unprepared Gypsum*	*Gypsum Fibrosum*	*Shi-gao*	石膏 (石膏)	*Calcium sulphate*	47.1%
Officinal Magnolia Bark	*Cortex Magnoliae Officinalis*	Hou-pu	厚朴 (厚朴)	Magnolol, honokiol	45.1%
Pilose Asiabell Root	*Radix Codonopsis*	*Dang-shen*	黨參 (党参)	*Methyl palmitate, octade-cane, nonadecane, heptadecane*	41.1%
Radix Asteris	*Aster Tataricus, L F.*	*Zi-yuan*	紫菀 (紫菀)	*Friedelin, shionone, shionoside A-C*	36.9%
Platycodon Root	*Radix Platycodonis*	*Jie-geng*	桔梗 (桔梗)		36.6%
Atractylodes Rhizome	*Rhizoma Atractylodis*	*Cang-zhu*	蒼朮 (苍朮)		35.4%
Rhizoma Zingiberis Officinalis	*Zingiber Officinale*	*Sheng-jiang*	生薑 (生姜)	*Zingiberol, zingiberene*	34.9%
Tsaoko Amomum Fruit	*Fructus Tsaoko*	*Cao-guo*	草果 (草果)	*1, 8-cineole, geraniol*	34.8%
Common Coltsfoot Flower	*Flos Farfarae*	*Dong-hua*	冬花 (冬花)	*Faradiol, butin, hyperin, chlorogenic acid, dicaffeoylquinic acid*	34.4%



[a]Frequency of use among all patients.

Notes: **Gypsum Fibrosum* is an antipyretic Chinese medicine mediates skin water content via Aquaporin-3. ***Rhizoma Pinelliae* requires processing before use. Three main categories of possible mechanism were identified: anti-infection (antiviral and antibacterial), immune-related (immunomodulating and anti-inflammatory) and symptomatic (anti-asthmatic) effect, as documented by previous *in vitro* and *in vivo* studies. Top five Chinese medicines used are highlighted and were predominantly immune-related medicines with anti-asthmatic effect.

Justification of Methodology

To encounter the non-randomized allocation of semi-individualized CM in this retrospective cohort, key known epidemiological (age, gender, history of diabetes, hypertension, coronary artery disease) and disease severity that were reported to correlate with prognosis were used to calculate the propensity score. Both inverse probability analysis and propensity score matching cohort analysis were presented. Since the strata of non-CM users were small, the matching on chronic kidney disease and biomarkers were unsatisfactory. Laboratory risk factors (C-reactive protein and lymphocyte count) and chronic kidney disease were therefore further adjusted in the multivariable Cox regression model as a secondary analysis, replacing disease severity. We further assessed the change of key biomarkers to explore the mechanism of effect and the potential adverse effects associated with the use of CM.

Underlying Reason, Handling and Outcome Assessment of the Small Unexposed Stratum

Due to the strong advocacy of using integrative medicine for COVID-19 management in China based on preliminary evidence (Chan *et al.*, 2020b), the strata of non-CM users were small. We believe that disease severity (16.8% vs. 34.0% severe/critical cases among CM-user vs. non-user group) and refusal to use CM as trial treatment in the earlier stage were the two main reasons of being non-CM users (Yang, 2020). To minimize the potential selection bias arise from the difference in severity, we stratified the analysis to assess the effect of CM among patients with different severity. After stratification, the demographics were well-balanced in both mild and severity/critical subgroups (Table S1). In addition, we matched disease severity in the propensity score matching cohort and adjusted demographics, comorbidities and biomarkers in the multivariable Cox regression model. Demographics were well-balanced in the matched cohort (Table 1, Fig. S3). Lastly, we performed a sensitivity analysis to increase the stratum size of the unexposed group for analysis. The result was robust.

External and Internal Validity

CM has been heavily used in China during the COVID-19 outbreak (Chan *et al.*, 2020b; National Health Comission *et al.*, 2020) as demonstrated by the utilization rate (94.7%) in our cohort. The overall mortality of our cohort was 4.5%, which was comparable to the reported national figure (GitHub, 2020). The high mortality (17.0%) of the non-CM users was mainly due to (1) the higher percentage of severe/critical cases among non-CM users (34.0%) and (2) overall high basal mortality in Wuhan as an epicentre early in the outbreak.

To counteract the effect of the difference in severity ratio, we stratified, weighted, matched and adjusted the disease severity in our analyses. In the stratified and matched analyses, the demographics between CM-user and non-user groups were comparable. For the high basal mortality, the mortality of the non-CM user group was comparable

to the reports from Wuhan during the early phase when medical resources were severely overloaded by sharp influx of symptomatic cases. Admission to the hospital was delayed, and CM was not fully utilized. The high mortality of the severe/critical non-CM users in our cohort (46.9%) was comparable with the recent findings from the RECOVERY trial (41.4%) (The RECOVERY Collaborative Group, 2020). The slightly higher rate of mortality in both mild and severe/critical cases for stratified analysis was likely due to the small size of strata. Therefore, we combined mild and severe/critical cases for the primary adjusted analysis and supplemented sensitivity analyses to further increase the stratum size for comparison. Although the case-fatality rate varied across different regions, partly related to the screening policy and capacity, the crude mortality of our cohort (4.5%) was substantially lower than majority of the regions (10.4–14.3%) with simultaneous outbreak where CM was not commonly used (Chan *et al.*, 2020b; GitHub, 2020).

From the prescription analysis, the prescription pattern reconciled with other reports from Wuhan (Luo *et al.*, 2020a; Wang *et al*., 2020a). The corresponding symptom-based indications included mild/no fever, dry cough or with little/yellowish/sticky sputum, malaise, chest tightness, dyspnea, poor appetite, abdominal distention, unsmooth defecation and loose stool, all of which were widely reported as the common presentations among COVID-19 patients (Chan *et al.*, 2020b; Mao *et al.*, 2020a, 2020b; Menni *et al.*, 2020; Wang *et al.*, 2020b). Therefore, evidence generated from this cohort has considerable generalizability to other settings.

Dose-Response Effectiveness and Minimal Potential Adverse Effect

From the primary analysis, the mortality rates and hazard ratios were significantly lower with add-on semi-individualized CM using multiple sensitivity analyses and different statistical methods adjusting key confounders. The effect of CM was more profound among severe/critical patients when compared to mild patients, likely due to the relatively low mortality in mild cases. Nevertheless. the response demonstrated a dose-dependent relationship pointing to causality between the use of semi-individualized CM and mortality reduction.

Further analysis on the key biomarkers showed that COVID-19 patients had a trend of slightly greater reduction in C-reactive protein and lactate dehydrogenase levels after receiving add-on semi-individualized CM, although not reaching statistical significance. This is consistent with the latest evidence from a case-series of critical patients receiving the Xuebijing injection, a key proprietary CM used in critical COVID-19 patients (Ma *et al.*, 2020), and gave rise to the hypothesis that these CMs are mild but multi-targeted and may act on multiple immunomodulating pathways to prevent cytokine storm (Zhong *et al.*, 2020). Although related biomarkers including TNF-α, IFNγ, MCP-1 and interleukins were unavailable as they were not routinely investigated for clinical purposes, we observed stabilized D-dimer levels in severe/critical cases which supported this hypothesis.

Our analysis also showed that the potential hepatotoxicity and nephrotoxicity were minimal, as the rate of elevated alanine aminotransferase, alkaline phosphatase and serum creatinine were lower than reports from other cohorts of COVID-19 patients (19–22.5%

with deranged liver function) (Mao *et al.*, 2020b; Yip *et al.*, 2020) and antiviral trials (17% with deranged liver function) (Hung *et al.*, 2020) related to the use of antivirals, interferons, corticosteroids and tocilizumab (Yip *et al.*, 2020).

Plausible Mechanisms and Related Report in SARS

From previous molecular docking and network pharmacology analyses, the affinity of the compounds from these CMs to ACE1 (with glyasperin F), ACE2 (with isorhamnetin, anemasaponin C and medicocarpin) and coronavirus 3CL hydrolase (with quercetin, luteolin, and naringenin) are strong. Pathway analyses showed that these CMs could act on key immunological (T cell receptor, Toll-like receptor) and inflammatory (TNF, PI3K-Akt) signaling pathways to prevent disease progression (Hong *et al.*, 2020; Ren *et al.*, 2020; Ruan *et al.*, 2020). On top of the shared anti-oxidant properties, three main categories of mechanism were identified: anti-infection (antiviral/antibacterial), immune-related (immunomodulating/anti-inflammatory) and symptomatic (anti-asthmatic) (Table 3). The top prescribed CMs, including *Rhizoma Pinelliae* (Wagner *et al.*, 2011), *Armeniacae Semen Amarum* (Do *et al.*, 2006) and *Poria* (Ríos, 2011; Sun, 2014), were immunomodulating drugs with an anti-asthmatic effect, followed by a batch of anti-infection CMs. Noteworthy, the broad and strong antiviral and antimicrobial effects of *Agastache Rugosa* (Zielińska *et al.*, 2014), *Radix Scutellariae* (Wang *et al.*, 2018), *Cortex Magnoliae Officinalis* (Amblard *et al.*, 2006) and *Fructus Tsaoko* (Dai *et al.*, 2016) were previously documented. This supported the use of multiple CMs with orchestrated effect as cocktail therapy.

During SARS outbreak in 2013, CMs was also used substantially in China. In a report of World Health Organisation, use of CM was associated with symptom alleviation, resolving lung inflammation, stabilizing blood oxygen level and reducing the use of steroid and antivirals (and the potential associated adverse events) in SARS management (World Health Organisation, 2004). Besides, similar formulations (*Herba Ephedrae*, *Armeniacae Semen Amarum*, *Gypsum Fibrosum and Licorice*) to the CMs used in COVID-19 had been shown to reduce fever duration in the previous H1N1 outbreak (Wang *et al.*, 2011) and were used as preventive strategy of SARS and H1N1 (Luo *et al.*, 2020b).

Implication to Research — Potential for Drug Repurposing

An important research area to follow up is the automation of clinical data collection to repurpose existing drugs for emerging infectious diseases (Pushpakom *et al.*, 2019). New drug development is almost impossible for a novel infectious disease due to the long research and development cycle. The vaccine would also take at least 12 months from research to marketing even with expedited process. The identification and evaluation of existing licensed medications for secondary application offer a more responsive strategy from a clinical perspective.

Parallel to the molecular approach adopted by the ReFRAME Collection (Riva *et al.*, 2020), we have previously established a platform for drug repurposing through a

phenotype-gene-drug network for CMs (https://www.symmap.org/) (Wu *et al.*, 2019). CMs have an advantage for drug repositioning screening, as their use is based on symptom-based diagnosis, requiring much less understanding on the virology and pathophysiology for molecular docking. This is possible, as symptoms reflect whole-system pathophysiological response and clusters of protein interaction (Zhou *et al.*, 2018, 2014). CM may not only target the pathogens but also modulate the whole-system innate immunity (Schijns and Lavelle, 2020), as reflected by the dominance of immune-related CMs used in our cohort. The same strategy with cocktail treatment composed of corticosteroids with anti-asthmatic effect and antivirals could be explored as potential intervention in clinical trials of conventional medicine for COVID-19.

Strengths and Limitations

This is a real-world study evaluating the effectiveness of add-on semi-individualized CM with a representative cohort. We demonstrated dose-response relationship of add-on CM by stratifying the *P*:*H* ratio among CM users as an assessment of causality. Besides, we performed multiple stratified, weighted, matched and adjusted analysis to ascertain the robustness of the result. We also analyzed the change of biomarkers and prescription content, and reviewed the biological plausibility of effect. Coherent findings using similar CMs on COVID-19 from RCTs of smaller scale were reported recently.

This study has several limitations. First, as an observational study with no randomization, unknown confounding factors that were not adjusted or matched may lead to bias in the study results. Also, we did not attempt to perform further analysis to single herb level, as CM is mainly used as formulations in practice. We hypothesized that a combination of these CMs concerted to target multiple pathways (Zhong *et al.*, 2020). Therefore, we adopted an efficacy-driven approach (Tang, 2006) in the analysis in view of the urgency, following an earlier detail review on possible mechanisms of these CMs (Zhong *et al.*, 2020). Further pharmacological research may identify a better optimized dosage. Lastly, since CM has been used extensively in China, the strata of unexposed group were small. Nevertheless, our results demonstrated a dose-dependent relationship between the use of CM and mortality in both the adjusted Cox regression model and propensity score matched cohort. The results were robust when tested with different definitions of semi-individualized CM exposure with increased size of the unexposed strata. Risk of bias from these limitations was minimized and is unlikely to change the conclusion seeing the magnitude of effect after a series of stratified, dose-response and sensitivity analyses.

Conclusion

Add-on semi-individualized Chinese medicine was associated with significant mortality reduction, in particular for severe/critical patients. Plausible mechanisms included the antiviral, anti-inflammatory, immunomodulating and anti-asthmatic effect previously documented. Chinese medicine could be considered as an add-on regimen for trial in view of the limited therapeutic options.

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Supplementary Figures

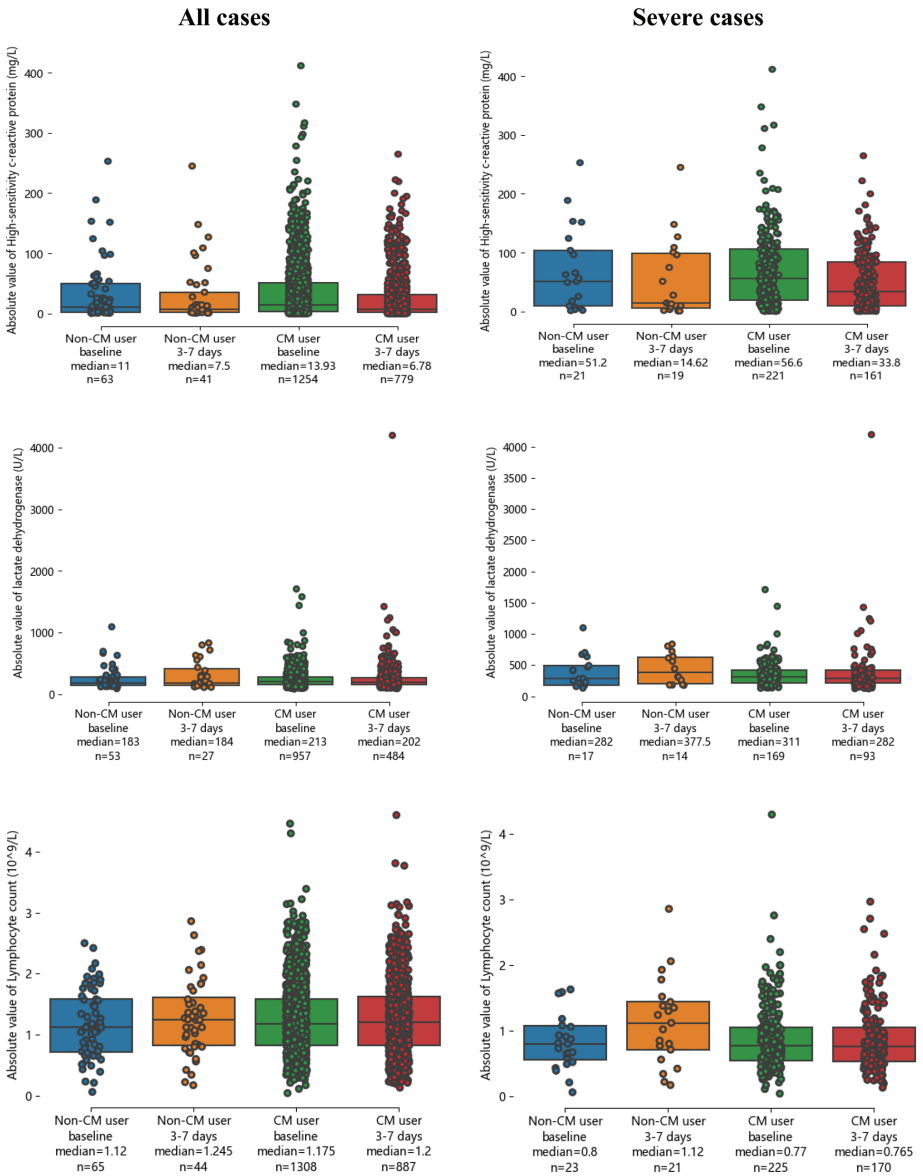

Figure S1. Change of key biomarkers in COVID-19 patients.

Notes: The change of key biomarkers after 3–7 days of hospitalization compared to baseline (0–2 days). The levels and changes of levels in key biomarkers are comparable between Chinese medicine users and non-users. COVID-19 patients had a slightly greater reduction in C-reactive protein and lactate dehydrogenase after receiving add-on semi-individualized Chinese medicine when compared to non-users. Patients also had comparable change of alkaline phosphatase, alanine transaminase and serum creatinine levels between groups and less increased d-dimer in severe/critical cases.

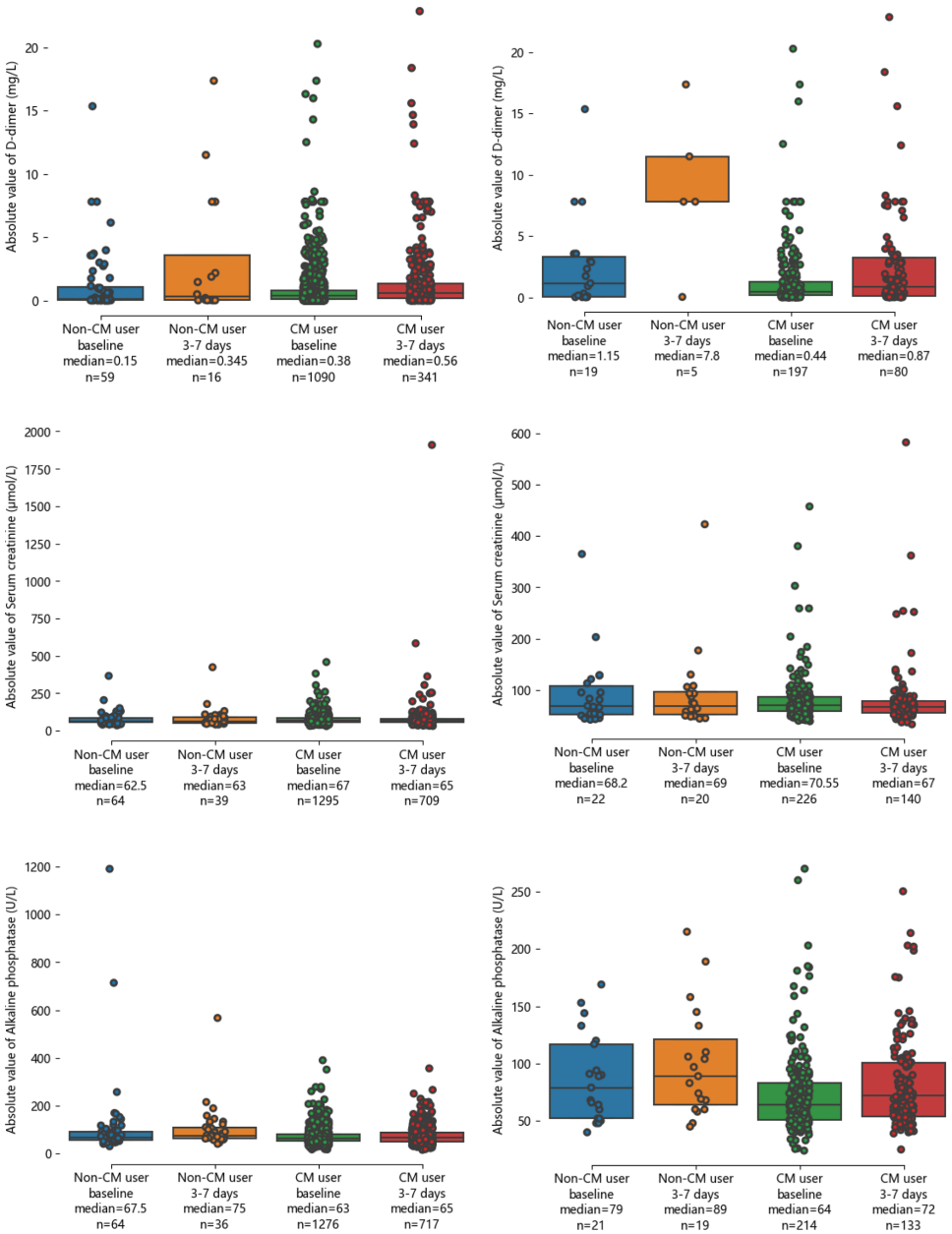

Figure S1. (*Continued*)

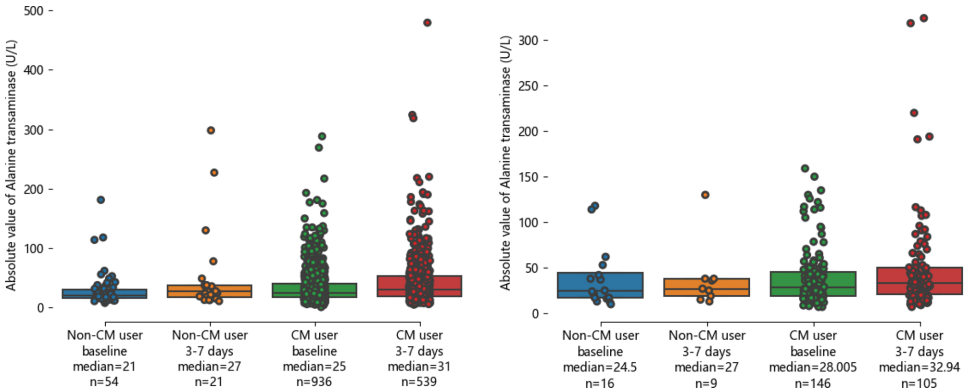

Figure S1. (*Continued*)

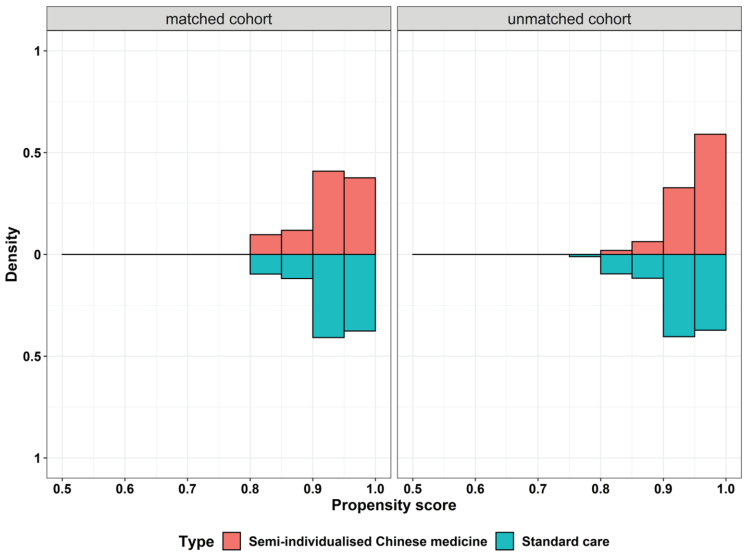

Figure S2. Distribution of propensity score for receiving semi-individualized Chinese medicine.

Notes: The distribution of propensity scores between semi-individualized Chinese medicine users and standard care control groups was balanced by matching. First set of imputation was used. 10 sets of imputation were generated, and the results were comparable.

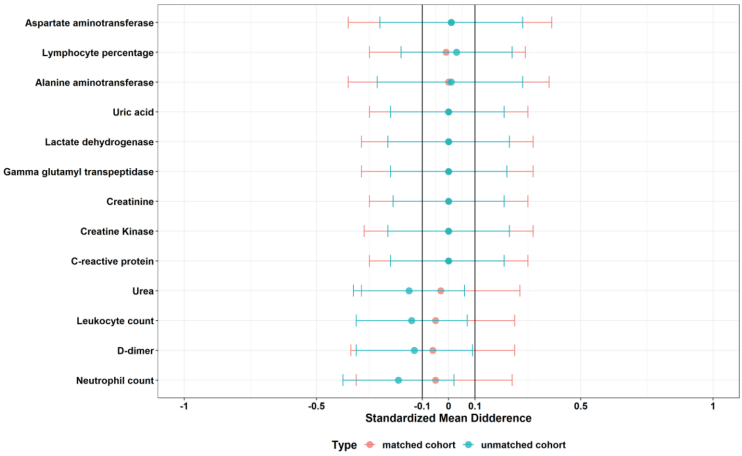

Figure S3. Standardized mean differences in risk factors between matched and unmatched sample.

Notes: Standardized mean difference of key biomarkers before and after propensity score matching. The standardized mean difference between add-on semi-individualized Chinese medicine (exposed) and standard care (unexposed) groups of all key biomarkers were adjusted to within 0.2 after propensity score matching.

Supplementary Tables

Table S1. Patient Characteristics by Severity

Characterwistics	Mild Cases				Severe Cases			
	Unmatched Cohort		Matched Cohort[a]		Unmatched Cohort		Matched Cohort[a]	
	Chinese Medicine + Standard Care (*n* = 1409)	Standard Care (*n* = 62)	Chinese Medicine + Standard Care (*n* = 62)	Standard Care (*n* = 62)	Chinese Medicine + Standard Care (*n* = 285)	Standard Care (*n* = 32)	Chinese Medicine + Standard Care (*n* = 31)	Standard Care (*n* = 31)
Age (yr) — median [IQR]	56.0 [45.0–66.0]	64.0 [52.8–70.8]**	63.5 [52.8–72.0]	64.0 [52.8–70.8]	65.0 [52.0–72.0]	67.5 [64.0–79.8]*	71.0 [62.0–83.0]	67.0 [64.0–78.5]
Female — *n* (%)	747 (53.0)	33 (53.2)	35 (56.5)	33 (53.2)	112 (39.3)	17 (53.1)	12 (38.7)	16 (51.6)
Comorbidities — *n* (%)								
Diabetes	179 (12.7)	12 (19.4)	10 (16.1)	12 (19.4)	56 (19.6)	5 (15.6)	3 (9.7)	5 (16.1)
Hypertension	372 (26.4)	22 (35.5)	20 (32.3)	22 (35.5)	109 (38.2)	11 (34.4)	11 (35.5)	11 (35.5)
[b]Chronic lung disease	40 (2.8)	3 (4.8)	2 (3.2)	3 (4.8)	30 (10.5)	1 (3.1)	3 (9.7)	1 (3.2)
Chronic kidney disease	28 (2.0)	3 (4.8)	2 (3.2)	3 (4.8)	9 (3.2)	1 (3.1)	0 (0)	1 (3.2)
Coronary heart disease	100 (7.1)	7 (11.3)	7 (11.3)	7 (11.3)	30 (10.5)	2 (6.2)	2 (6.5)	2 (6.5)
Cerebrovascular disease	46 (3.3)	2 (3.2)	5 (8.1)	2 (3.2)	27 (9.5)	1 (3.1)	3 (9.7)	1 (3.2)
Tumor	23 (1.6)	3 (4.8)	2 (3.2)	3 (4.8)	5 (1.8)	0 (0)	0 (0)	0 (0)
Time from symptom onset to admission (day) — median [IQR]	10.0 [7.0–15.0]	12.0 [7.0–15.0]	10.0 [6.2–15.0]	12.0 [7.0–15.0]	10.0 [7.0–15.0]	12.0 [7.0–15.0]	12.0 [7.5–15.0]	10.0 [7.0–12.5]
Prognosis — *n* (%)								
Deceased	12 (0.9)	1 (1.6)	0 (0.0)	1 (1.6)	52 (18.2)	15 (46.9)**	6 (19.4)	14 (45.2)*
Discharged	1397 (99.1)	61 (98.4)	62 (100.0)	61 (98.4)	233 (81.8)	17 (53.1)**	25 (80.6)	17 (54.8)*
Signs and Symptoms — *n* (%)								
Fever	1007 (71.5)	37 (59.7)*	43 (69.4)	37 (59.7)	215 (75.4)	17 (53.1)**	25 (80.6)	16 (51.6)*
Cough	779 (55.3)	34 (54.8)	30 (48.4)	34 (54.8)	167 (58.6)	20 (62.5)	18 (58.1)	20 (64.5)

Fatigue/malaise	125 (8.9)	5 (8.1)	11 (17.7)	5 (8.1)	24 (8.4)	2 (6.2)	5 (16.1)	2 (6.5)
Shortness of breath	115 (8.2)	7 (11.3)	7 (11.3)	7 (11.3)	53 (18.6)	8 (25.0)	4 (12.9)	8 (25.8)
Laboratory Investigations — Median [IQR]								
Lymphocytes (10^9/L)	1.3 [1.0–1.7]	1.4 [1.1–1.9]	1.3 [0.9–1.6]	1.4 [1.1–1.9]	0.8 [0.5–1.1]	0.8 [0.6–1.1]	0.8 [0.5–1.2]	0.8 [0.6–1.2]
D-dimer (mg/L)	0.4 [0.1–0.8]	0.2 [0.0–0.8]**	0.6 [0.3–0.9]	0.2 [0.0–0.8]**	0.5 [0.2–1.5]	1.7 [0.2–7.8]	0.9 [0.2–3.0]	2.0 [0.2–7.8]
Alanine aminotransferase (U/L)	25.0 [16.0–39.0]	20.0 [15.5–26.0]*	24.0 [15.5–37.5]	20.0 [15.5–26.0]	29.0 [19.0–45.0]	24.5 [16.8–44.8]	22.0 [17.0–39.0]	25.0 [17.0–47.5]
Alkaline phosphatase (U/L)	65.0 [52.0–83.0]	71.0 [58.8–93.8]*	63.0 [57.0–78.2]	71.0 [58.8–93.8]	65.0 [51.0–84.3]	84.0 [59.5–117.8]*	71.5 [53.2–105.8]	79.0 [59.0–111.5]
C-reactive protein (mg/L)	7.3 [3.1–32.5]	5.0 [3.1–13.0]	7.4 [3.1–40.1]	5.0 [3.1–13.0]	48.3 [13.3–97.2]	53.8 [7.6–119.2]	38.2 [7.1–120.0]	56.3 [9.3–124.3]
Lactate dehydrogenase (U/L)	199.0 [159.0–252.0]	167.0 [146.8–237.0]*	210.5 [167.2–254.8]	167.0 [146.8–237.0]*	294.0 [203.2–398.8]	314.0 [179.5–563.5]	289.5 [182.2–412.8]	314.0 [179.5–563.5]
Creatinine (μmol/L)	65.0 [55.0–79.2]	63.0 [54.0–77.0]	69.0 [54.0–83.2]	63.0 [54.0–77.0]	70.0 [58.0–86.0]	75.0 [54.0–104.8]	72.0 [59.0–94.5]	76.0 [54.0–108.0]
Serum albumin (g/L)	38.0 [35.5–40.7]	38.0 [35.1–39.2]	37.2 [34.8–40.0]	38.0 [35.1–39.2]	35.0 [32.0–37.9]	32.5 [31.0–34.9]*	32.9 [31.2–37.0]	32.3 [30.9–35.2]
Creatine kinase (U/L)	58.0 [41.0–87.7]	54.0 [44.0–79.5]	52.0 [38.0–91.0]	54.0 [44.0–79.5]	0.1 [0.1–0.3]	0.2 [0.1–0.5]	0.2 [0.1–0.3]	0.2 [0.1–0.5]
Radiological Investigations (Chest CT) — *n* (%)								
No identifiable abnormalities	99 (7.0)	2 (3.2)	6 (9.7)	2 (3.2)	35 (12.3)	4 (12.5)	3 (9.7)	4 (12.9)
Bilateral infiltrate	1177 (83.5)	57 (91.9)	54 (87.1)	57 (91.9)	241 (84.6)	27 (84.4)	27 (87.1)	26 (83.9)
Concurrent Treatment — *n* (%)								
ACE inhibitor/ARB	131 (9.3)	10 (16.1)	6 (9.7)	10 (16.1)	40 (14.0)	1 (3.1)	2 (6.5)	1 (3.2)
Antivirals	1336 (94.8)	54 (87.1)**	59 (95.2)	54 (87.1)	273 (95.8)	30 (93.8)	29 (93.5)	29 (93.5)
Antibiotics	943 (66.9)	31 (50.0)**	45 (72.6)	31 (50.0)**	250 (87.7)	28 (87.5)	28 (90.3)	27 (87.1)
Glucocorticoids	307 (21.8)	11 (17.7)	17 (27.4)	11 (17.7)	174 (61.1)	21 (65.6)	17 (54.8)	21 (67.7)
IV immunoglobin	178 (12.6)	6 (9.7)	9 (14.5)	6 (9.7)	105 (36.8)	11 (34.4)	14 (45.2)	11 (35.5)

[a]Matched by gender, age, hypertension, diabetes, coronary artery disease.

[b]Including chronic obstructive pulmonary disease, asthma and chronic bronchitis.

Notes: *$p < 0.05$, **$p < 0.01$ between add-on semi-individualized Chinese medicine user and non-user.

Table S2. Hazard Ratios of Variables Included in the Multivariable Cox Regression Model

	All Cases *n* = 1788 Hazard Ratio	**Mild Cases *n* = 1471 Hazard Ratio**	**Severe/Critical Cases *n* = 317 Hazard Ratio**
Age (year)	1.06 (1.04 to 1.08) $p < 0.001$	1.04 (0.99 to 1.08) $p = 0.13$	1.05 (1.03 to 1.08) $p < 0.001$
Gender (male)	0.95 (0.57 to 1.58) $p = 0.85$	0.66 (0.20 to 2.11) $p = 0.48$	1.04 (0.59 to 1.84) $p = 0.89$
Past Medical History			
Hypertension	0.98 (0.62 to 1.56) $p = 0.94$	0.60 (0.16 to 2.23) $p = 0.45$	1.24 (0.75 to 2.05) $p = 0.39$
Diabetes	1.32 (0.77 to 2.23) $p = 0.30$	0.42 (0.05 to 3.37) $p = 0.41$	1.51 (0.87 to 2.64) $p = 0.14$
Coronary artery disease	0.98 (0.52 to 1.86) $p = 0.96$	2.61 (0.64 to 10.69) $p = 0.18$	0.95 (0.46 to 1.95) $p = 0.88$
Chronic kidney disease	1.16 (0.42 to 3.25) $p = 0.77$	2.26 (0.25 to 20.13) $p = 0.47$	0.81 (0.24 to 2.69) $p = 0.73$
Laboratory Investigation			
C-reactive protein	1.008 (1.005 to 1.010) $p < 0.001$	1.01 (1.00 to 1.02) $p = 0.27$	1.006 (1.003 to 1.009) $p < 0.001$
Lymphocyte count	0.22 (0.11 to 0.42) $p < 0.001$	0.76 (0.23 to 2.48) $p = 0.65$	0.52 (0.25 to 1.09) $p = 0.08$

Notes: Multivariable Cox regression model adjusted for age, gender, C-reactive protein, lymphocyte count, history of diabetes, hypertension, coronary artery disease, chronic kidney diseases. Severe cases were defined as respiratory rate >30 breaths/min, oxygen saturation = < 93% or PaO2/FiO2 ratio = < 300 mmHg. Critical cases were defined as including > = 1 of the following criteria: shock; respiratory failure requiring mechanical ventilation; combination with other organ failures; and admission to intensive care unit.

Table S3. Odds Ratios of Receiving Semi-Individualized Treatment for Categorical Variables Included in the Propensity Score Model

	***n* = 1788 Odds Ratio (95% CI)**
Age	
<40 yr	1.55 (0.79 to 3.03)
40–59 yr	2.67 (1.60 to 4.46)
60–79yr	0.55 (0.36 to 0.84)
> = 80 yr	0.30 (0.17 to 0.55)
Gender (male)	1.10 (0.73 to 1.67)
Past Medical History	
Hypertension	0.73 (0.47 to 1.13)
Diabetes	0.73 (0.42 to 1.26)
Coronary artery disease	0.79 (0.39 to 1.60)

Table S4. Hazard Ratios of Variables Included in the Multivariable Cox Regression Model with Inverse Probability Weighting by the Propensity Score (Primary Analysis)

	All Cases (n = 1788) Hazard Ratio	**Mild Cases (n = 1471) Hazard Ratio**	**Severe/Critical Cases (n = 317) Hazard Ratio**
Age (year)	1.07 (1.04 to 1.10) $p < 0.001$	1.00 (0.95 to 1.04) $p = 0.74$	1.07 (1.04 to 1.10) $p < 0.001$
Gender (male)	0.68 (0.35 to 1.29) $p = 0.23$	0.22 (0.07 to 0.69) $p = 0.01$	0.81 (0.42 to 1.56) $p = 0.52$
Past Medical History			
Hypertension	0.84 (0.47 to 1.51) $p = 0.56$	0.35 (0.10 to 1.29) $p = 0.12$	1.06 (0.60 to 1.87) $p = 0.93$
Diabetes	1.18 (0.56 to 2.48) $p = 0.67$	0.20 (0.02 to 2.09) $p = 0.18$	1.45 (0.66 to 3.18) $p = 0.35$
Coronary artery disease	0.49 (0.25 to 0.96) $p = 0.04$	1.82 (0.43 to 7.64) $p = 0.41$	0.58 (0.30 to 1.12) $p = 0.10$
Chronic kidney disease	0.71 (0.14 to 3.49) $p = 0.67$	0.03 (0.0005 to 1.50) $p = 0.08$	1.08 (0.38 to 3.07) $p = 0.89$
Laboratory Investigation			
C-reactive protein	1.009 (1.004 to 1.014) $p < 0.001$	1.00 (0.99 to 1.01) $p = 0.94$	1.007 (1.002 to 1.012) $p = 0.002$
Lymphocyte count	0.33 (0.14 to 0.73) $p = 0.007$	0.13 (0.02 to 0.94) $p = 0.04$	0.58 (0.26 to 1.29) $p = 0.18$

Notes: Multivariable Cox regression model weighted by inverse probability and the propensity score adjusted for age, gender, history of diabetes, hypertension, coronary heart disease and disease severity.

Table S5. Sensitivity Analysis on Hazard Ratios Using Different Definitions of Semi-Individualized Chinese Medicine Exposure

Analysis on Mortality on All Cases (n = 1788)	**At Least 1 Prescription During Hospitalization**	**At Least 30% of Hospitalization Period with Prescription**	**At Least 60% of Hospitalization Period with Prescription**
Mortality/Patient at Risk (%)			
Semi-individualized Chinese medicine	64/1694 (3.8)	54/1594 (3.4)	35/1376 (2.5)
Non-semi-individualized Chinese medicine	16/94 (17.0)	26/194 (13.4)	45/412 (10.9)
Crude Hazard Ratio (Unadjusted Cox Regression) of Unmatched Cohort	0.19 (0.11 to 0.33) $p < 0.001$	0.24 (0.15 to 0.38) $p < 0.001$	0.23 (0.15 to 0.36) $p < 0.001$
Adjusted Hazard Ratio (Multivariable Cox Regression) of Unmatched Cohort[a]	0.27 (0.15 to 0.48) $p < 0.001$	0.28 (0.17 to 0.47) $p < 0.001$	0.32 (0.20 to 0.52) $p < 0.001$
Propensity Score Matched Hazard Ratio[b]			
By inverse probability weighting (all users vs. non-users)	0.42 (0.23 to 0.77) $p = 0.005$	0.40 (0.24 to 0.65) $p < 0.001$	0.41 (0.25 to 0.66) $p < 0.001$
By propensity score matching	0.23 (0.06 to 0.68) $p = 0.013$	0.45 (0.21 to 0.90) $p = 0.028$	0.40 (0.22 to 0.71) $p = 0.002$

[a]Adjusted for age, gender, C-reactive protein, lymphocyte count, history of diabetes, hypertension, coronary artery disease, chronic kidney diseases, and disease severity.

[b]Matched by age, gender, history of diabetes, hypertension, coronary heart disease and disease severity.

Table S6. Summary of the Chinese National Guideline on COVID-19 Management

Severity	Key Presentations	Recommended Formulation (with Herbal Equivalent Dosage in Gram)
Mild Case:		
Subtype 1	Fever, malaise, myalgia, cough with sputum, poor appetite, anorexia, vomiting, sticky and greasy stool with unsmooth defecation	Ma-huang 6g, shi-gao 15g, xing-ren 9g, qiang-huo 15g, ting-li-zi 15g, guan-zhong 9g, di-long 15g, xu-chang-qing 15g, huo-xiang 15g, pei-lan 9g, cang-zhu 15g, fu-ling 45g, bai-zhu 30g, shan-zha 9g, 9g, mai-ya 9g, hou-pu 15g, bin-lang 9g, cao-guo 9g, sheng-jiang 15g
Subtype 2	Mild/no fever, chilly, malaise, myalgia, dry cough or with little sputum, sore throat	Bin-lang 10g, cao-guo 10g, hou-pu 10g, zhi-mu 10g, huang-qin 10g, chai-hu 10g, chi-shao 10g, lian-qiao 15g, qing-hao 10g, cang-zhu 10g, da-qing-ye 10g, gan-cao 5g
Subtype 3	Fever, dry cough or cough with little/yellowish sputum, **chest tightness, shortness of breath, abdominal distention, constipation**	Ma-huang 6g, xing-ren 15g, shi-gao 30g, yi-yi-ren 30g, cang-zhu 10g, huo-xiang 15g, qing-hao 12g, hu-zhang 20g, ma-bian-cao 30g, lu-gen 30g, ting-li-zi 15g, ju-hong 15g, gan-cao 10g
Subtype 4	Mild/no fever, dry cough or little sputum, malaise, chest tightness, abdominal distention, **loose stool**	Cang-zhu 15g, chen-pi 10g, hou-pu 10g, huo-xiang 10g, cao-guo 6g, ma-huang 6g, qiang-huo 10g, sheng-jiang 10g, bin-lang 10g
Severe Case:		
Subtype 5	Fever, malaise, cough with little yellowish and sticky sputum or hemoptysis, **dyspnea**, anorexia, poor appetite, unsmooth defecation	Ma-huang 6g, xing-ren 9g, shi-gao 15g, gan-cao 3g, huo-xiang 10g, hou-pu 10g, cang-zhu 15g, cao-guo 10g, ban-xia 9g, fu-ling 15g, da-huang 5g, huang-qi 10g, ting-li-zi 10g, chi-shao 10g
Subtype 6	High fever, thirsty, dyspnea, **confusion, agitation**, and may accompany with purpura/rash/hematemesis/nasal bleeding	Shi-gao 30–60g, zhi-mu 30g, di-huang 30–60g, shui-niu-jiao 30g, chi-shao 10g, xuan-shen 30g, lian-qiao 15g, mu-dan-pi 15g, huang-lian 6g, zhu-ye 12g, ting-li-zi 10g, gan-cao 6g
Critical Case:		
Subtype 7	Dyspnea or on mechanical ventilation, confusion, agitation, **spontaneous sweating with cold extremities**	Ren-shen 15g, fu-zi 10g, shan-zhu-yu 15g with An-gong-niu-huang pill or Su-he-xiang pill