Effects of (Combined) Chinese Medicine on the Risk of Death From COVID-19: A Retrospective Data Analysis Based on 4567 Patients

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Research

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Abstract

Background

The coronavirus disease 2019 (COVID-19) epidemic is still ongoing, but the optimal treatment remains unclear. China adopted a series of measures, including widespread screening, strict quarantine and early treatment, combining western medicine with Chinese medicine, leading to rapid control of its spread. Nevertheless, the effects of (combined) Chinese medicine in reducing the toll of COVID-19 lack proof from statistics.

Objective

We conducted a retrospective data analysis to determine whether (combined) Chinese medicine is able to affect patient outcomes and to decrease the risk of death in COVID-19 patients.

Methods

The data were acquired by outputting the formatting information from the HIS system and then extracting and recording it in the database for complete cases. The demographics, disease onset, treatment, survival/death and all of the clinical classifications, groups and definitions were verified by specialists in the clinic, along with the research methodology and statistics, before conducting the statistical analysis. The characteristics of the cohort and the clinical symptoms and signs, prescriptions and outcomes were described and analyzed by the mean ± SD, median, interquartile range and composition ratio. Analysis of variance was used for comparisons between the measurement data sets; otherwise, the rank sum test was used. Counting data were compared between groups using the chi square test and Fisher's exact test. Tendency matching was adopted to make the general data balance between groups. A Cox proportional hazard model was used to compare the risk of death among the different groups.

Results

Four centers were included in our study, and a total of 6,076 patients' clinical records were obtained after combining the data. We included 4567 cases for the descriptive statistics, and the crude case fatality rate was 3.0%. Compared with using only western medicine, (combined) Chinese medicine reduced the risk of death from COVID-19 after adjusting for other prognostic risk factors (HR = 0.135, 95% CI (0.088, 0.208)). Multivariate Cox regression also indicated that when applying the clinical classification of severe/critical, age ≥ 65 years old, coronary heart disease or chronic kidney disease and a time from onset to hospital admission of fewer than 14 days, all of these factors increased the risk of death.

Conclusion

(Combined) Chinese medicine can significantly reduce the risk of death from COVID-19, but the specific strategy/solution, effects and amount need further exploration in future studies.

Introduction

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, has led to a pandemic of more than 40 million infected individuals and 1.11 million deaths[1]. The COVID-19 pandemic not only poses a massive challenge to the global health system but also has handicapped economic development and social stability worldwide. Thus far, the efficacy and the safety of drugs and vaccines needs to be proven, and the best methods to control the pandemic are still early detection and quarantine, with the proper treatment approach being unclear.

China insisted upon early diagnosis, quarantine and treatment using western medicine along with Chinese medicine, and it quickly controlled the disease. In the fight against COVID-19, China also went from panic and disorder to calm and order. Treatment protocols for COVID-19 matured in clinical practice as well. Since the fifth version of the protocol published on February 4, 2020, the Chinese government has alleviated Wuhan City's pandemic pressure from the aspects of necessary items, equipment, personnel and a shortage of sickbeds. Based on the experience of using Chinese medicine in the early stages, the National Health Commission and the State Administration of Traditional Chinese Medicine promoted and comprehensively strengthened the use of Chinese medicine in the COVID-19 epidemic. According to the incomplete statistics, the utilization rate of Chinese medicine in the treatment of COVID-19 in all provinces in China is approximately 90%.

Albeit, currently, clinical trials of Chinese medicine are mostly observational, there is no denying that Chinese medicine plays an important role in relieving symptoms and preventing the progression of the disease. A newly published systematic review and meta-analysis of 1474 patients with COVID-19 treated with a combination of western and Chinese medicine showed that, in the combined Chinese medicine group, the overall clinical response rate (OR=2.67, 95% CI 1.83–3.89, I^2=0%), CT scan improvement (OR=2.43, 95% CI 1.80–3.29, I^2=0%), percentage of severe/critical cases (OR=0.40, 95% CI 24–0.67, I^2=17.1%) , negative rate of reverse transcription polymerase chain reaction (RT-PCR) (OR=2.55, 95% CI 1.06–6.17, I^2=56.4%), and symptom disappearance rate (fever, cough and fatigue) were better than in the control group [4]. However, there is still a lack of research evidence supporting the treatment effect of combined Chinese medicine in reducing death and critical illness.

Therefore, based on Wuhan's large-scale introduction of Chinese medicine treatment for COVID-19, the related data were retrospectively analyzed, and further study of traditional Chinese medicine combined with western medicine for COVID-19 is very important. Reducing mortality is the key to clinical treatment, and whether (combined) Chinese medicine can affect COVID-19 clinical outcomes needs further study.

Our study is a retrospective analysis, and the application for an exemption from informed consent was approved by the Ethics Committee of the Guangdong Hospital of Traditional Chinese Medicine (batch number: ZE2020-049-01).

Research objective

Data source: COVID-19 inpatients in four designated hospitals (the following are the four centers) in Wuhan City from February 4, 2020, to April 30, 2020. The diagnostic criteria refer to the protocol published by the National Health Committee. A positive laboratory test was defined as a confirmed case.

Inclusion criteria: Laboratory-confirmed cases

Exclusion criteria: Time of admission was missing or was prior to February 4, 2020; the discharge status was missing; and a lack of information about medication.

Methods

Supervision:

This study was funded by the National Administration of Traditional Chinese Medicine and was designed by the researchers. The data were analyzed and interpreted by the authors. All of the authors reviewed the manuscript and ensured the accuracy and completeness of the data.

Information extraction:

In this study, COVID-19 medical records from Centers 1 and 4 were directly exported as formatted information by the HIS system and then checked and classified by professionals engaged in data management. COVID-19 medical records from Centers 2 and 3 were extracted and entered into the database from the original medical records after authorization, and then were exported as a formatted database. During the data extraction, the information generated or required to be clinically judged by professionals was calculated and discussed by clinical experts, clinical research methodology experts, statistical experts and other experts, and then clearly defined. The extracted information included 1) demographic information, such as sex, age and basic diseases; 2) case information, such as the time of onset, time of admission, and clinical classification of vital signs; 3) treatment information, including whether antiviral drugs, antibiotics, hormone immunotherapy, Traditional Chinese medicine decoction granules, etc., were used; and 4) prognostic information, including survival/death.

Definition of different clinical types:

According to the diagnosis and treatment protocol of COVID-19, patients were clinically classified as: 1) mild: clinical symptoms were mild, and no manifestations of pneumonia were observed on imaging; 2) common: with symptoms such as fever and respiratory tract symptoms, with imaging findings of pneumonia; 3) severe: met any of the following criteria: RR 30 times/min with shortness of breath; at rest,

oxygen saturation was 93%; arterial partial pressure of oxygen ($Pa0_2$)/oxygen concentration ($Fi0_2$) 300 mg, 1 mmHg= 0.1 Pa; and 4) critical: respiratory failure and needing mechanical ventilation or going into shock, combined with other organ failure, requires care in the ICU.

Definition of different groups:

1. Intervention measures included basic treatment (oxygen therapy, liquid therapy, etc.), antivirals, antibiotics, hormones or immune support, identified as the western medicine group.
2. On the basis of the abovementioned western medicine group, those who used Chinese patent medicine or Chinese medicine decoctions or Chinese medicine granules for COVID-19 treatment at the same time were identified as the Chinese Medicine/Chinese Medicine combined group.

Statistical analysis methods:

The clinical outcomes, the disease population characteristics, the clinical symptoms and signs, etc., were calculated based on the medication group. A descriptive analysis of the mean ± SD median (interquartile interval), composition ratio and rate was performed for the comparison between the data groups. The counting data were compared between groups using the chi-square test, Fisher's exact probability method, etc., and propensity matching was adopted so that the general data between the groups was balanced. A Cox proportional hazard model was used to correct for factors such as demographic admission classification, and the death risk of the different groups was investigated. The Schoenfeld residual test was used to check the proportionality assumption of the Cox regression.

Results

Generation conditions:

In this study, the clinical medical records of 2554 patients from center 1 (Wuhan Huoshenshan Hospital), center 2 (Hubei Province Hospital of Integrated Traditional Chinese and Western Medicine), center 3 (Wuhan Raytheon Hospital), and center 4 (Wuhan Hankou Hospital) were obtained. The clinical medical records of 6076 patients were obtained by combining the data from the 4 hospitals. A total of 13 patients were excluded due to not having COVID-19, 180 patients were excluded due to a lack of admission time data, 803 patients were excluded because their hospital admission was before February 4, 2020, 449 patients were excluded due to missing treatment data, and 645 patients were excluded due to missing hospital discharge status data. Finally, 4,567 patients were included in the descriptive analysis (Figure 1, Table 1). Among them, there were 2,250 males (49.3%) and 2,529 females (50.7%). The oldest was 100 years old and the youngest was 2 years old, averaging 58.3 and 14.8 years old, respectively. The most common clinical type of the hospitalized patients was the common type (3285 patients, accounting for 71.9%), followed by the severe type (1034 patients, accounting for 22.6%), and there were fewer mild and critical cases. A total of 139 patients died in the hospital, and the calculated crude case fatality rate was 3.0%

Table 1 Descriptive analysis

Item	Available sample size	n (%)
Sex	4567	
Male		2250 (49.3)
Female		2317 (50.7)
Age, M (SD)	4566	58.5 (14.7)
Age		
< 65 years		2841 (62.2)
65 years ~		1725 (37.8)
Underlying disease, n (%)	4567	
Cardiovascular and cerebrovascular diseases		1574 (34.5)
Diabetes		619 (13.6)
Chronic liver disease		234 (5.1)
Chronic respiratory disease		348 (7.6)
Chronic renal disease		160 (3.5)
Tumor		91 (2.0)
Days from onset to admission, M (SD)	4448	26.5 (15.4)
Days from onset to admission		
<14 days		969 (21.8)
14 days		1290 (29.0)
28 days		2189 (49.2)
Clinical classification of admission, N (%)	4566	
Mild		157 (3.4)
Common		3285 (71.9)
Severe		1034 (22.6)
Critical		90 (2.0)
Hospital stay, M (SD)	4567	15.9 (9.6)
Discharge status		
Death		139 (3.0)
Survival (recovery, improvement, stability or otherwise)		4428 (97.0)

Comparison of general conditions between the different intervention groups:

A total of 4,567 COVID-19 patients were divided into the western medicine group and the traditional Chinese medicine/combined traditional Chinese medicine and western medicine group for general situational comparisons according to whether traditional Chinese medicine, decoctions or granules for COVID-19 treatment were used together in the intervention measures (Table 2). In addition to sex and combining with tumor-based diseases, there were statistically significant differences between the two groups in age, clinical classification, onset to admission time, chronic liver disease, chronic respiratory system disease, and chronic kidney disease ($P<0.05$), with imbalances between the groups. Therefore, only the prognosis (crude case fatality rate) of different clinical types between the two groups was described (Table 3). Among the 4,567 patients in this group, the crude case fatality rate was 18.5% in the western medicine group and 2.2% in the Chinese medicine/Combined Chinese medicine group.

Table 2 Comparison of general conditions between different intervention groups

Item	Available sample size	Western medicine (n=243)	Chinese Medicine/Combined Chinese Medicine Group (n=4324)	*P*
Sex n(%)	4567	243	4324	0.005
Male		141 (58.0)	2109 (48.8)	
Female		102 (42.0)	2215 (51.2)	
Age, M (SD)	4566	62.6 (16.3)	58.3 (14.6)	<0.001
Age n (%)		243	4323	<0.001
< 65 years		122 (50.2)	2719 (62.9)	
65 years +		121 (49.8)	1604 (37.1)	
Clinical classification at admission, N (%)	4566	243	4323	<0.001
Mild		1 (0.4)	156 (3.6)	
Common		144 (59.3)	3141 (72.6)	
Severe		83 (34.2)	951 (22.0)	
Critical		15 (6.2)	75 (1.7)	
Days from onset to admission, M (SD)	4448	19.0 (14.8)	27.0 (15.3)	<0.001
Days from onset to admission N (%)		239	4209	<0.001
< 14		110 (46.0)	859 (20.4)	
14 -		57 (23.8)	1233 (29.3)	
≥ 28		72 (30.1)	2117 (50.3)	
Associated underlying disease n (%)	4567			
Cardiovascular and cerebrovascular disease		92 (37.9)	1482 (34.3)	0.252

Diabetes	33 (13.6)	586 (13.6)	0.990
Chronic liver disease	23 (9.5)	211 (4.9)	0.002
Chronic respiratory disease	42 (17.3)	306 (7.1)	<0.001
Chronic renal disease	44 (18.1)	116 (2.7)	<0.001
Tumor	5 (2.1)	86 (2.0)	0.815*

*Fisher's exact test

Table 3 Crude case fatality rates among the different intervention groups

	n	outcome	Western medicine (n=243)	Chinese medicine/combined Chinese medicine (n=4324)
Total sample	4567	death	45 (18.5)	94 (2.2)
		survival	198 (81.5)	4230 (97.8)
Mild	157	death	0 (0.0)	0 (0.0)
		survival	1 (100.0)	156 (100.0)
Common	3285	death	8 (5.6)	14 (0.4)
		survival	136 (94.4)	3127 (99.6)
Severe	1034	death	25 (30.1)	38 (4.0)
		survival	58 (69.9)	913 (96.0)
Critical	90	death	12 (80.0)	42 (56.0)
		survival	3 (20.0)	33 (44.0)

Comparison of general conditions and prognosis between groups after propensity matching:

To ensure balance for comparability between groups, propensity matching was adopted. With age, sex, the onset of admission type and the number of days after admission combined with basic diseases (cardiovascular and cerebrovascular disease, diabetes, liver disease, chronic respiratory disease, renal disease and tumor) as matching variables, the western medicine group and combined Chinese medicine group were matched at a 1:2 ratio, the tolerance of matching was 0.01, and data for 243 patients in the western medicine group and 486 patients in the (combined) Chinese medicine group were obtained. The results showed that after matching, there were no statistically significant differences between the two groups regarding sex, age, clinical classification of admission, diabetes, liver disease, chronic lung

disease, kidney disease, tumors and cardiovascular and cerebrovascular diseases (P≤0.05), except for the time from onset to admission, which was comparable between the groups (Table 4).

Table 4 Comparison of general conditions between the different intervention groups after propensity matching (n=729)

item	Western medicine (n=239)	Chinese medicine/combined Chinese medicine (n=478)	*P*
Sex n (%)			0.874
Male	141 (58.0)	279 (57.4)	
Female	102 (42.0)	207 (42.6)	
Age, M (SD)	62.6 (16.3)	61.7 (14.5)	0.439
Age n (%)			0.373
< 65 years	122 (50.2)	261 (53.7)	
≥65 years	121 (49.8)	225 (46.3)	
Clinical classification of admission, n (%)			0.150*
Mild	1 (0.4)	9 (1.9)	
Common	144 (59.3)	281 (57.8)	
Severe	83 (34.2)	179 (36.8)	
Critical	15 (6.2)	17 (3.5)	
Days from onset to admission, M (SD)	19.0 (14.8)	22.4 (15.8)	**0.006**
Days from onset to admission n (%)			0.060
<14	110 (46.0)	176 (37.2)	
14-	57 (23.8)	120 (25.4)	
≥28	72 (30.1)	177 (37.4)	
Associated underlying diseases n (%)			
Cardiovascular and cerebrovascular disease	92 (37.9)	201 (41.4)	0.364
Diabetes	33 (13.6)	83 (17.1)	0.224
Chronic liver disease	23 (9.5)	49 (10.1)	0.792
Chronic respiratory disease	42 (17.3)	85 (17.5)	0.945
Chronic renal disease	44 (18.1)	78 (16.0)	0.483
Tumor	5 (2.1)	20 (4.1)	0.150

*Fisher's exact test

Case fatality rate comparison between groups after propensity matching:

The fatality rates of the different intervention groups were compared among the data sets after bias matching (Table 5). Among the 243 patients in the western medicine group, 45 died, with a fatality rate of 18.5%. Among the 486 patients in the (combined) Chinese medicine group, 39 patients died, with a fatality rate of 8.0%. The difference in fatality rates between the two groups was statistically significant ($P \leq 0.05$). Furthermore, the case fatality rate of the common type of COVID-19 in the western medicine group was higher than that in the (combined) Chinese medicine group (8/144, 5.6% vs 2/281, 0.7%), and the difference was statistically significant ($P<0.05$). The case fatality rate of severe COVID-19 in the western medicine group was also higher than that in the (combined) Chinese medicine group (25/83, 30.1% vs 25/179, 14.0%), and the difference between the two groups was statistically significant ($P<0.05$), suggesting that (combined) Chinese medicine treatment may affect the prognosis of common and severe COVID-19.

Table 5 Fatality rate comparison between the different intervention groups after propensity matching

	Outcome	Western medicine (n=243)	Chinese medicine/combined Chinese medicine (n=486) (n=486)	*P*
Total sample	Death	45 (18.5)	39 (8.0)	<0.001
	Survival	198 (81.5)	447 (92.0)	
Mild	Death	0	0	-
	Survival	1	9	
Common	Death	8 (5.6)	2 (0.7)	0.003*
	Survival	136 (94.4)	279 (99.3)	
Severe	Death	25 (30.1)	25 (14.0)	0.002
	Survival	58 (69.9)	154 (86.0)	
Critical	Death	12 (80.0)	12 (70.6)	0.691*
	Survival	3 (20.0)	5 (29.4)	

*Fisher's exact test

Multivariate Cox regression analysis of the prognostic factors:

The chi-square test, CMH test and Cox regression analysis showed that there was no center effect; that is, the data from the four centers could be combined for analysis. To further investigate the prognostic effect of the (combined) Chinese medicine treatment on COVID-19 and to correct for the influence of factors such as general admission classification combined with underlying diseases, a Cox proportional hazard regression model was used for the analysis, with outcome variable Y=1 indicating death and Y=0 indicating survival. Sex, age stratification (<65 years old, ≥65 years old), type of admission (mild + normal, severe and critical), onset to days of admission (<14 days, 14–28 days, ≥28 days), groups (western medicine and (combined) Chinese medicine) and basic diseases (cardiovascular and cerebrovascular diseases, diabetes, liver diseases, chronic lung diseases, kidney diseases, tumors) were screened by the Forward Wald method. The results showed that after adjusting for other factors, combined Chinese medicine still reduced the risk of death from COVID-19 compared with western medicine alone (HR=0.135, 95% CI 0.088, 0.208). The risk of death was 6.991 times higher for the severe type and 67.338 times higher for the critical type than for the mild/normal type. Compared with onset to days of admission>28 days, the risk death of <14 days was 4.688 times higher, and the risk of death at 14–28 days was 1.965 times higher. The risk of death in patients >65 years old was 2.557 times that in ≤65-year-old patients; the risk of death in those with CKD was 1.705 times higher than that in those without CKD (Table 6, Figure 2).

Table 6 Multivariate Cox regression analysis of the prognostic factors for propensity matching

Characteristic		HR (95% CI)	
		Multivariable	*P*
Group	Western medicine	1 (reference)	<0.001
	(Combined) Chinese medicine	0.135 (0.088,0.208)	
Admission classification	Mild+common	1 (reference)	
	Severe	**6.991 (4.274,11.436)**	<0.001
	Critical	**67.338 (40.022,113.299)**	<0.001
Days of onset to admission	<14 days	**4.688 (2.904,7.569)**	<0.001
	14 days-	**1.965 (1.196,3.229)**	0.003
	≥28 days	1 (reference)	
Age	<65 years	1 (reference)	
	≥65 years	**2.557 (1.681,3.889)**	<0.001
Chronic kidney disease	Yes	**1.705 (1.070,2.717)**	0.025
	No	1 (reference)	

Discussion

Around the world, epidemiologists are setting short and long-term projections of COVID-19 as a way to mitigate the spread and impact of SARS-CoV-2. Although their forecasts and timetables vary, they all agree that COVID-19 is still present and the future depends on many unknown factors [5]. Therefore, the prevention and treatment of COVID-19, the expansion of intensive care capacity, the detection of effective treatments, and the reduction of mortality from COVID-19 remain long-term clinical and public health issues.

According to the current global COVID-19 data report, the crude case fatality rate is approximately 2.9% (1,060786/36 4440433) [1]. In this study, in order to avoid any influence of the early confusion, shortages, and the COVID-19 case fatality rate, we eliminated all patients admitted before February 4, 2020. At the same time, to eliminate other important causes of missing data, we included a descriptive analysis of 4567 cases, and the crude mortality was 3.0%, in line with the global outbreak data.

Importantly, in this study, we found that, after adjusting for other prognostic risk factors, the risk of death from COVID-19 was reduced by (combined) Chinese medicine compared with western medicine alone,

while any bias caused by a shortage of medical supplies was avoided as much as possible. However, in this set of data, there may be some defects in our definition of a (combined) Chinese medicine intervention. First, due to the incomplete information about the original medical advice, it was not possible to define the timing of the Chinese medicine intervention and to discuss the dose-time effect. Interestingly, we analyzed the data with detailed medication information from Center 1 and found that there was a certain correlation between the time of using Chinese medicine and the prognosis. Second, there may be differences in the clinical effects of Chinese medicine decoctions, granules and proprietary Chinese medicine. Due to the limited number of cases and the incomplete original medical advice information, this study failed to further stratify the (combined) Chinese medicine treatment scheme and evaluated only the impact of (combined) Chinese medicine treatment on the prognosis at the overall level. An in-depth analysis and discussion is needed to further clarify which programs, drugs or prescriptions are effective. Third, in this study, the Chinese medicine diagnosis and treatment schemes, drugs and prescriptions adopted by the different centers may be different, and the diagnosis and treatment levels in different centers may also be different. However, in the Cox risk regression analysis, we did not find any influence of a center effect, which may be related to the early formation of a unified treatment scheme in China.

Multivariate Cox regression also showed that being clinically categorized as severe/critical, ≥65 years of age, and complicated with chronic kidney disease all increased the risk of death in COVID-19 patients, which is basically consistent with the current reports on the prognostic factors of COVID-19 at home and abroad [6-7]. However, due to the lack of laboratory examination results and dynamic monitoring data, indicators such as the D2-cluster level, IL-6, SOFA score, total bilirubin, myocardial markers, platelets and so on were not included in the analysis of prognostic factors of COVID-19 in this study. In addition, this study found that a time from onset to admission to the hospital <14 days or 14–28 days increased the risk of death from COVID-19. When analyzing the reasons for this finding, even if we excluded patients admitted before February 4th, during the period of resource shortages, we note that resources after that time were still limited, and the Chinese government, based on humanitarian needs, used a priority strategy for severe patients. As a result, patients admitted in the early stage might have a higher risk of death. Therefore, we further analyzed and compared the time of onset to admission of patients among the different clinical types (enclosure Table 3), and we found that the clinical type of admission in the severe group and the proportion of patients with onset to admission days <14 days had the highest rate of death. The admission classification of the critical type group and the proportion of days from onset to admission was higher, indicating that the number of days from onset to admission was indeed correlated with the clinical classification of disease admission, which also reasonably explained the results of the multivariate Cox regression.

In addition, the cases in this study were all from Wuhan. Due to the influence of hospitalization, diagnosis and treatment strategy and other factors, the number of cases treated by pure western medicine was relatively small, so the number of cases that could be included in the propensity matching was limited.

Patients in different centers may be transferred to another hospital, but according to the medical records of this group, no such cases have been found, and no double-counting of cases has occurred.

Conclusion

In summary, (combined) Chinese medicine treatment can significantly reduce the risk of death from COVID-19, but specific (combined) Chinese medicine treatment strategies, schemes, specific effects, and dose-response relationships still need to be further explored in carefully designed trials.

Abbreviations

Not applicabal

Declarations

Ethics approval and consent to participate

Not applicabal

Consent to publish

Not applicabal

Availability of data and materials

Not applicabal

Authors' Contributions

Not applicabal

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Statement and Competing interests

There is no conflict of interest in this paper. All authors were involved in the research and are responsible for the contents of this paper.

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Figures

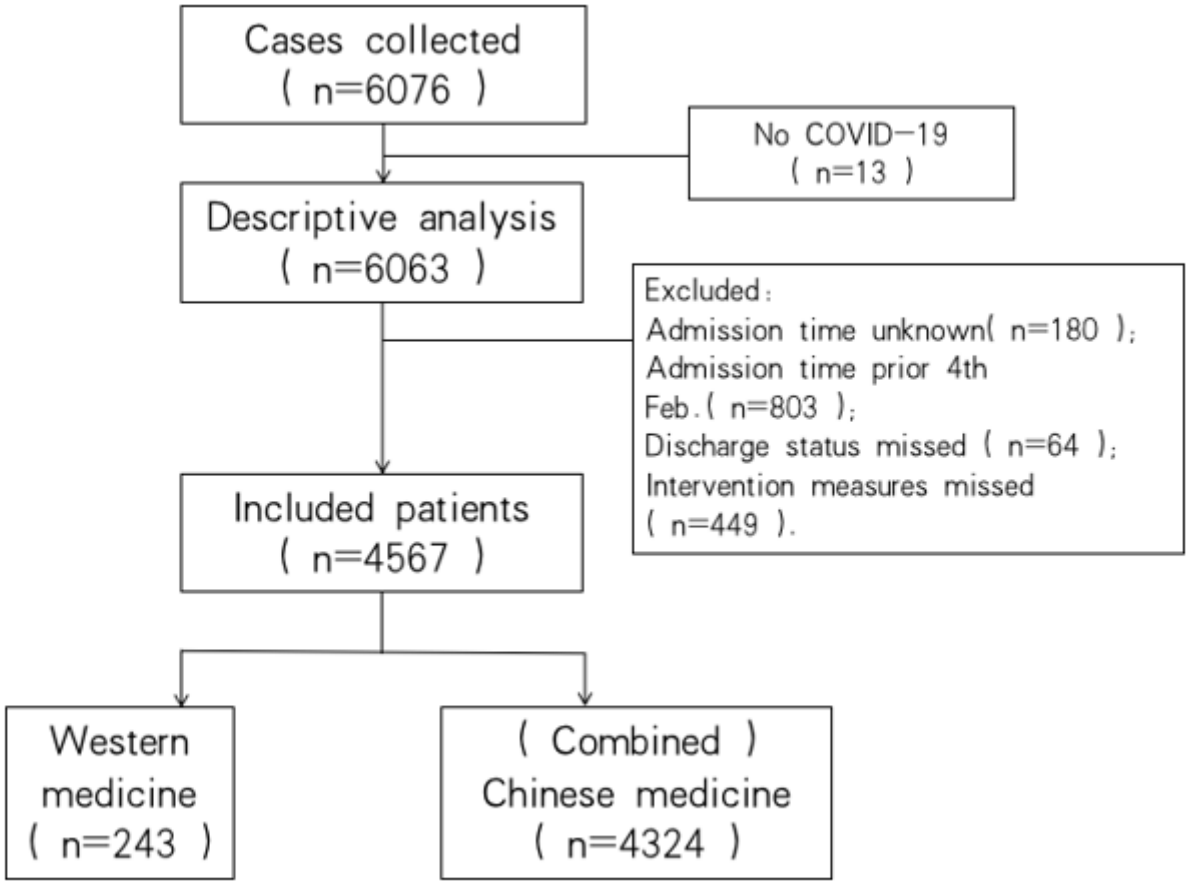

Figure 1

Flowchart

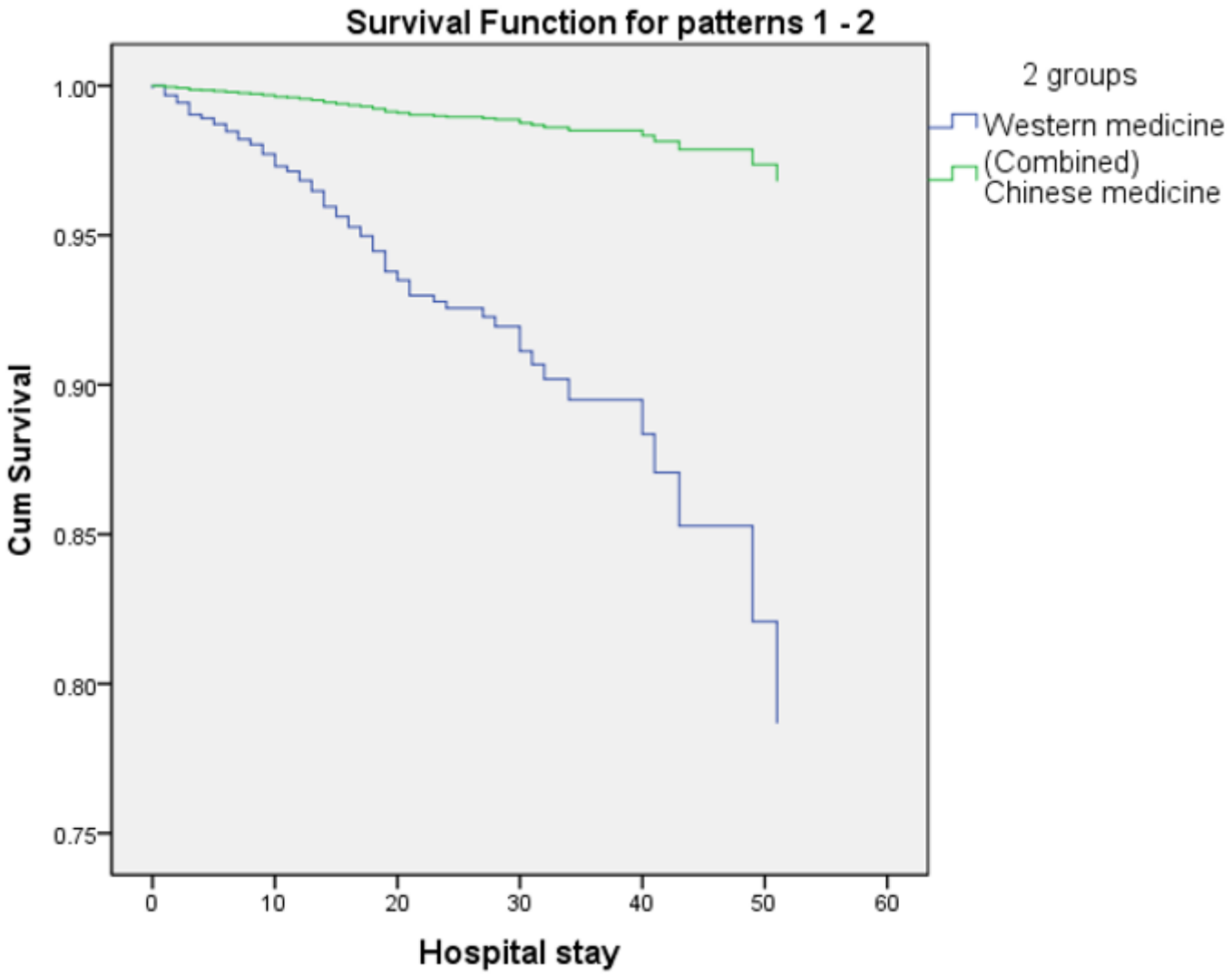

Figure 2

Cox regression model for the risk of death in the different groups

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