Effects of traditional Chinese medicine on treatment outcomes of severe COVID-19 patients: A single-centre study.

Kun Xiao (xiaok301@foxmail.com)
Chinese People's Liberation Army

Yongjiu Xiao
The 940 th Hospital of Joint Logistics Support Force of Chinese People's Liberation Army

Binbin Li
Sun Yat-sen University

Chang Liu
Nankai university

Xiuyu Huang
Sun Yat-sen University

Ling Ma
The 940 th Hospital of Joint Logistics Support Force of Chinese People's Liberation Army

Zhi Rong Qian
Sun Yat-sen University

Xiaopeng Zhang
The 940 th Hospital of Joint Logistics Support Force of Chinese People's Liberation Army

Qian Zhang
the Seventh Medical Center of Chinese PLA General Hospital

Dunqing Li
Muskingum University

Xiaoqing Cai
The 940 th Hospital of Joint Logistics Support Force of Chinese People's Liberation Army

Xiangyong Yan
The 940 th Hospital of Joint Logistics Support Force of Chinese People's Liberation Army

Shuping Luo
Laboratory of Vaccine and Antibody Engineering, Beijing Institute of Biotechnology

Dawei Xiang
The 940 th Hospital of Joint Logistics Support Force of Chinese People's Liberation Army

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Effects of traditional Chinese medicine on treatment outcomes of severe COVID-19 patients: A single-centre study

Yongjiu Xiao [a*], M.D., Binbin Li [b*], Ph.D., Chang Liu [c,k*], Ph.D. Xiuyu Huang [b*], M.S., Ling Ma [d*], M.D., Zhi Rong Qian [b,e], M.D., Xiaopeng Zhang [f], M.D., Qian Zhang [g], M.D., Dunqing Li [h], B.A., Xiaoqing Cai [d], M.D., Xiangyong Yan [f], M.D., Shuping Luo [i], M.D., Dawei Xiang [j#], M.D., Kun Xiao [k#] M.D.,

[a] Emergency Department, The 940th Hospital of Jiont Logistics Support Force of Chinese People's Liberation Army, 33rd Nanbinhe Rd., Lanzhou, Gansu Province, 730050, China

[b] Scientific Research Center, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, Guangdong, 518000, China

[c] School of medicine, Nankai university, Tianjin, 300000, China

[d] Department of Cardiology, The 940th Hospital of Joint Logistics Support Force of Chinese People's Liberation Army, No. 333, Nanbinhe Road., Lanzhou, Gansu Province, 730050, China

[e] Department of Radiation Oncology, Fujian Medical University Union Hospital, Fuzhou, 350000, China

[f] Department of Traditional Chinese Medicine, The 940th Hospital of Joint Logistics Support Force of Chinese People's Liberation Army, No. 333, Nanbinhe Road, Lanzhou, Gansu Province, 730050, China

[g] Department of Geriatric Diseases, the Seventh Medical Center of Chinese PLA General Hospital, Beijing 100700, China

[h] Health and sport administration, Muskingum University, Ohioan, the United States.

[i] Laboratory of Vaccine and Antibody Engineering, Beijing Institute of Biotechnology, Beijing, China, 20 Dongdajie, Fengtai, Beijing 100071, China

[j] The 940th Hospital of Joint Logistics Support Force of Chinese People's Liberation Army, No. 333, Nanbinhe Road., Lanzhou, Gansu Province, 730050, China

[k] Center of Pulmonary & Critical Care Medicine, Chinese People's Liberation Army (PLA) General Hospital, Beijing, 100853, China

* Yongjiu Xiao, Binbin Li, Chang Liu, Xiuyu Huang, Ling Ma contributed equally to this manuscript.

[#] Corresponding author: Kun Xiao, E-mail: xiaok301@foxmail.com; tel:15321215699

Dawei Xiang, E-mail: xiangdawei2020@163.com; tel: 13716608331

Alternate author: Zhi Rong Qian, Email: zrqian@hotmail.com; tel: 13049649955

Take-home message: COVID-19 remains a worldwide epidemic that is out of control. In China's fight against the disease, traditional Chinese medicine (TCM) treatment may accelerate recovery and largely improve the outcomes of critically ill COVID-19 patient

Abstract

No specific effective therapeutic drugs have been identified for COVID-19. Critically ill COVID-19 patients in the ICU experience high mortality. This project aims to study the effects of traditional Chinese medicine (TCM) treatment on deadly outcomes caused by COVID-19. A total of 123 critically ill COVID-19 patients who received close monitoring at the ICU of Vulcan Hill Hospital between February 2, 2020, and April 15, 2020 (Wuhan, China) participated in this observational study. All these ICU patients received supportive management. Eighty-one patients were given additional TCM treatment. Clinical characteristics during the treatment period (up to 39 days) and the clinical outcome of each patient were closely monitored and analysed. We observed that patients treated with TCM had lower mortality than the non-TCM treatment group (16 of 81 vs. 31 of 42; 0.3 person/month vs. 2.9

person/month). In the adjusted Cox proportional hazards models, TCM treatment was associated with improved survival [multivariate HR, 0.13; 95% confidence interval (CI), 0.06–0.24; $P < 0.001$]. Furthermore, we found that TCM treatment could partially improve the inflammation status by reducing the levels of proinflammatory cytokines and recovering multiple organic functions. TCM treatment may decrease inflammation status by reducing the level of proinflammatory cytokines and allowing the recovery of multiple organic functions, which could improve the survival rate of critically ill COVID-19 patients.

Keywords

COVID-19; Critically ill; Traditional Chinese medicine; Clinical outcome

1. Introduction

A new viral pneumonia associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was termed coronavirus disease 2019 (COVID-19) and declared a Public Health Emergency of International Concern by the World Health Organization (WHO) on January 30, 2020. When COVID-19 broke out, tens of thousands of Chinese people were infected, particularly in Wuhan[1]. Since the outbreak of COVID-19 in early 2020, several mutant strains have been of particular concern. The most notable strains include Alpha, first appearing in the UK, Beta in South Africa, Gamma in Brazil, and Delta in India. B.1.617.2 (Delta) is the most ferocious novel coronavirus strain in the world. According to research data, its infection ability is 60% higher than that of the Alpha novel coronavirus strain found in the UK last year, and the transmission capacity is twice that of the original novel coronavirus. Thus, Delta is already the world's leading pandemic strain[2, 3].

COVID-19 patients have some common symptoms of upper respiratory infections, including fever, dry cough, and shortness of breath. Lymphopenia and elevated lactate dehydrogenase are nonspecific symptoms[1]. At present, the treatment methods include anti-infection, supportive treatment and antiviral therapy. However, no specific therapies have yet been proven effective for the treatment of COVID-19 patients. Thus, supplemental oxygen therapy, supportive management of acute hypoxic respiratory failure and ARDS remain common treatment methods[4-6]. Finding more effective strategies to treat and reverse the course of severe COVID-19 is an important challenge. Previously, the prescription "Shenhuang Granule", self-developed by the team of Longhua Hospital affiliated with the Shanghai University of Traditional Chinese Medicine, has been shown to effectively prevent the disease progression of patients with severe COVID-19 and significantly reduce the mortality rate of patients with severe COVID-19[7]. In addition, teams from Dongzhimen Hospital of Beijing University of Chinese Medicine found that the proportion of severe patients who used traditional Chinese medicine (TCM) and then developed mild and moderate symptoms was slightly higher than that of patients who did not use TCM, and there were no deaths[8]. In some cases, short-term neuromuscular blockade with cisatracurium or other muscle relaxants can also help improve patient oxygenation[9]. Previous studies reported that the plasma of patients with severe COVID-19 contains high concentrations of cytokines, including GCSF, IP10, MCP1, MIP1A, and TNFα, indicating that there is an association between cytokine storm and disease severity[10].

Many efforts have been invested in the development of antiviral vaccines and screening of existing antiviral molecules. There is still no effective treatment for COVID-19. According to current data, compared with conventional treatment, dexamethasone therapy showed a similar effectiveness as supplemental oxygen and improved the survival rate of patients[11]. In addition, several small molecule antiviral medicines (remdesivir, favipiravir, lopinavir, etc.) have been reported to be effective; among them, remdesivir shortened the recovery time from 15 to 11 days according to U.S. clinical trial data[12, 13]. Thus, remdesivir was approved by the U.S. Food and Drug Administration (FDA) for COVID-19 treatment on October 22, 2020. However, a global study sponsored by the World Health Organization (WHO) showed that remdesivir has little benefit to patient survival and treatment duration. Additionally, small molecule antiviral agents may cause serious adverse events, including vomiting, low blood pressure and abnormal liver and kidney function. Although other antiviral therapies, immunomodulators, and anticoagulants are under clinical research, there is an urgent need to develop safer and more potent drugs.

Lianhuaqingwen (LHQW), a classical Chinese medical preparation, is composed of two classical TCM formulae, Yinqiao San and Maxing Shigan Tang. Historically, LHQW has been used to treat influenza-like illness[14]. Previous data have indicated that LHQW had a better effect on viral clearance and performed better in symptom relief[15]. Notably, Li and colleagues' evidence demonstrated that LHQW, which mainly affects antiviral activity and the inflammatory response, could prevent COVID-19[16]. A study of subjects who had close contact with confirmed COVID-19 patients found that treatment with LHQW capsules for 14 days during quarantine medical observation resulted in a significant reduction in positive nucleic acid testing from nasal and pharyngeal swabs and was effective in preventing SARS-CoV-2 infection[17]. Lastly, Hu et al. found that treatment with LH capsules for 14 days significantly improved the recovery rate of clinical symptoms such as fever, fatigue and cough in COVID19 patients, shortened the duration of symptoms, improved pulmonary imaging lesions, and increased the clinical cure rate compared with the usual treatment group[18].

The aim of this study, which was based on the medical records of 123 critically ill COVID-19 patients hospitalized in the ICU of Vulcan Hill Hospital between February 2, 2020, and April 15, 2020 (Wuhan, China), was to perform a detailed analysis of cytokine changes during the inflammation process and to evaluate the effect of TCM treatment on the survival rate.

1. Methods

1.1. Study Design

This study was conducted at the ICU of Vulcan Hill Hospital between February 2, 2020, and April 15, 2020 (Wuhan, China). The follow-up of patients was conducted until date. This study was approved by the ethics committees of Vulcan Hill Hospital, and each patient was fully informed about the study content. All patients enrolled in this study who underwent a real-time reverse-transcriptase polymerase chain reaction (RT–PCR) assay of nasal and pharyngeal swab specimens and had CT image features of pneumonia were diagnosed with COVID-19 according to the diagnostic criteria of the guidelines. According to the fifth edition of the COVID-19 diagnosis and treatment guidelines, critically ill COVID-19 was defined as follows: a. respiratory distress, respiratory rate ≥30 times/minute; b. oxygen

saturation ≤93%; c. arterial oxygen partial pressure/inspired oxygen partial pressure ≤300 mmHg [17]. Patients with one of the following conditions were excluded: 1) patients who were transferred to the hospital with critical underlying diseases; 2) patients with severe underlying disease who died within 48 h after admission; and 3) patients who lacked important data. Finally, 123 patients met the inclusion criteria and were enrolled in this study.

2.2. Traditional Chinese medicine treatment

The two types of prescriptions commonly used in clinical treatment are shown in Supplementary data Table 2. These medicinal herbs were boiled in 1000 ml of pure water for approximately 30 minutes to obtain a tincture of approximately 600 ml. Each tincture was divided into three doses of 200 ml each and administered orally three times daily.

2.3. Data collection and procedures

The medical records of COVID-19 patients were reviewed, and demographic, clinical laboratory, treatment, and outcome data were extracted from the electronic medical records. The physicians (Dr. XY and Dr. XK) checked all the data.

Based on the therapeutic drugs administered, the patients were divided into the TCM treatment group and the non-TCM treatment group. Both groups included critically ill COVID-19 patients.

2.4. Statistical analysis

Baseline characteristics were summarized using means and standard deviations or medians and interquartile ranges for skewed variables and the frequency (percentages) for continuous and categorical variables. Group comparisons were made using Wilcoxon rank-sum tests and Pearson's chi-squared test, as appropriate. Laboratory and other clinical parameters were analysed using a mixed-effects repeated measures model with random effects, which included change from baseline as an outcome variable with the corresponding baseline value as a continuous covariate. The baseline value, hospitalization days and treatment were also included in the model. The primary comparison was the difference in the least-squares (LS) mean among the groups. To assess the association between TCM treatment and death due to COVID-19, a multivariable Cox proportional hazard regression model was used to estimate the hazard ratios (HRs) and 95% confidence intervals for the time to the occurrence of death. A P value < 0.05 was considered statistically significant. All analyses were performed using Stata, version 16.0 (Stata Corp., College Station, TX, USA).

2. Results

3.1. Comparison of TCM treatment and non-TCM treatment among all 123 critically ill COVID-19 patients

A total of 123 eligible critically ill COVID-19 patients hospitalized in the ICU of Vulcan Hill Hospital were diagnosed using RT–PCR (GeneoDX Co., Ltd). The detailed analysis of the demographic and clinical characteristics and the medication history of all enrolled patients is summarized in Table 1. All the patients were critically ill and given supportive treatment. Specifically, 123 patients were divided into two groups: 81 patients were treated with TCM, including 13 patients treated with TCM + convalescent plasma therapy, and 42 patients were in the non-TCM group. The

patient age ranged from 59 to 82 years. A total of 50.6% of patients had hypertension in the TCM group and 54.8% had hypertension in the non-TCM group. Furthermore, 3 (9.5%) and 4 (3.7%) patients in the TCM and non-TCM groups had coronary heart disease, respectively, and 16% in the TCM group and 26.2% in the non-TCM group had diabetes, respectively. Additionally, 13.6% and 7.1% of the patients had a medical history of pulmonary diseases in the TCM group and the non-TCM cohort, respectively. The above preclinical conditions did not differ significantly between the groups ($P > 0.05$). Notably, patients with immunosuppression, fatty liver and liver cirrhosis were enrolled in the TCM group.

A detailed analysis of the baseline laboratory data of all enrolled patients is summarized in Table 2. Several laboratory factors differed significantly between the TCM treatment and non-TCM treatment groups. In the non-TCM group, the levels of creatinine, AST, DBIL, CK, PT, serum phosphorus and serum chlorine were significantly higher than those in the TCM group ($P < 0.05$). Meanwhile, the levels of LDH, serum calcium and total carbon dioxide were markedly higher in the TCM group than in the non-TCM group ($P < 0.05$). Although the number of white blood cells, LYM%, NEUT%, PLT, globulin, ALT, and D-dimer tended to be higher in the TCM group, there were no significant differences ($P > 0.05$). Additionally, the levels of IBIL, blood sugar, TT, serum potassium, serum sodium, and serum magnesium were comparable between the TCM group and the non-TCM group. However, these differences were not independent factors associated with mortality in critically ill COVID-19 patients (data not shown).

3.2. Efficacy of TCM treatment in critically ill COVID-19 patients

To evaluate the effect of TCM treatment, we assessed whether TCM treatment was related to the survival rate in the overall cohort. Of the 123 critically ill COVID-19 cases evaluated, 47 died, and the follow-up time was 39 days. TCM treatment was associated with improved survival [multivariate HR, 0.13; 95% confidence interval (CI), 0.06 to 0.24; $P < 0.001$; log-rank $P < 0.001$] (Table 3, Figure 1). Furthermore, the TCM treatment group had lower mortality than the non-TCM treatment group (16 of 81 vs. 31 of 42; 0.3 person/month vs. 2.9 person/month) (Table 4). Other baseline clinical characteristics, laboratory data and medication history were not independently associated with mortality in critically ill COVID-19 patients (data not shown).

Further, we explored whether convalescent plasma therapy could enhance patient immunity against the SARS-CoV-2 virus in the TCM group. Unfortunately, 13 patients' clinical status seemed to be comparable with those who had not accepted convalescent plasma therapy (data not shown). Additionally, we further evaluated the effect of TCM plus convalescent plasma combination therapy on improved survival. Similarly, the survival data displayed no difference [multivariate HR, 0.11; 95% confidence interval (CI), 0.03 to 0.37; $P < 0.001$; log-rank $P < 0.001$] (Supplementary data Table 1, Supplementary data Figure 1), demonstrating that convalescent plasma therapy did not affect the clinical status or survival of patients with severe COVID-19.

3.3. Treatment effect in relation to other features in critically ill COVID-19 patients

To reveal the molecular mechanism underlying the improved survival rate as a result of TCM, we

summarized the patient clinical changes throughout the treatment (Table 4). Notably, the level of neutrophilic granulocytes, as an indicator of the inflammation state of the patient (NEUT%), was significantly lower in the TCM group compared to prior treatment (P = 0.01), suggesting an attenuated degree of peripheral inflammation (Table 4). Additionally, nearly half of the patients had a higher level of lactic dehydrogenase (LDH), indicating multiple organic dysfunctions in severe COVID-19 cases before treatment (Table 1), which was robustly reduced in the TCM group compared with the non-TCM group (P < 0.001). From the start of treatment, patient thrombin time (TT), which reflects liver and renal function, was also significantly shortened after TCM treatment (-1.27 s, P = 0.04). Compared with the non-TCM group, creatine kinase (CK) was largely decreased with TCM treatment (-75.52 U/L, P = 0.007), suggesting that TCM improved patient cardiac function. Synchronously, the high-level state of D-dimer before treatment was also improved in the TCM treatment group (-1.27 μg/L, P = 0.03). Together, these results demonstrated that TCM treatment improved the survival rate of patients with severe COVID-19 by facilitating the recovery of body system function.

3. Discussion

LHQW has broad-spectrum antiviral, anti-infection, and immunomodulatory effects. Meanwhile, it can alleviate the clinical symptoms of patients and interrupt the process of virus transformation in the human body. Previous studies have implied that the early combination of LHQW arbidol may shorten the recovery time and improve the prognosis of patients with COVID-19[16]. At present, the mechanism of new coronary pneumonia is not sufficiently clear.

In our present study, we found that high levels of cytokines involved in inflammation were largely decreased after TCM treatment. Li and colleagues reported that LHQW capsules significantly inhibited SARS-CoV-2 replication in Vero E6 cells and reduced proinflammatory cytokine production at the mRNA level[19]. The latest research has confirmed that LHQW has an inhibitory effect on the in vitro proliferation of a variety of different strains of influenza viruses and can block the early stage of viral infection. Mechanistically, LHQW suppresses A/PR/8/34 virus-induced p65 phosphorylation. The NF-κB signalling pathway is mainly involved in viral replication and can regulate the production of cytokines and chemokines during severe influenza infections. The phosphorylation of NF-κB inhibits the output of viral RNA and virus transmission and reduces virus-induced interleukin (IL-6, IL-8) and tumour necrosis factor (TNF-α) levels. The gene expression of interferon-inducible protein (IP-10) and monocyte chemotactic protein (MCP-1) has a regulatory effect on the immune response to viral infection[20]. Other studies have confirmed that LHQW can reduce the expression of IL-8, TNF-α, IL-17 and IL-23 in serum IL-8 and IL-17 and in the sputum of AECOPD patients. Additionally, it can reduce the level of serum Th17 cytokines (IL-17, IL-6) in patients with COPD, increase the level of Treg cytokines (IL-10, TGF-β), and improve the lungs of patients by regulating the balance of Th17/Treg cytokines in the body features. When used in children with mycoplasma pneumoniae pneumonia (MPP) with atelectasis, it can upregulate CD3+ and CD4+ and downregulate the expression of CD8+ in T lymphocyte subsets; reduce serum CRP, IL-6, and PCT levels; and adjust the imbalance of T lymphocyte subsets to inhibit inflammation[21].

In conclusion, this observational, retrospective study demonstrated that TCM treatment has largely improved the survival rate of critically ill COVID-19 patients. Therefore, we recommend using TCM treatment to accelerate recovery and improve the prognosis of critically ill COVID-19 patients. Multiple-centre studies and large samples are still necessary for further verification.

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Conflict of interest.

The authors declared that they have no conflicts of interest to this work. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

Guarantor

All authors had full access to the full data in the study and accept responsibility to submit for publication.

Author contributions

Zhi Rong Qian, Dawei Xiang, and Kun Xiao contributed the central idea; the remaining authors contributed to data curation; Yongjiu Xiao, Binbin Li, Zhi Rong Qian and Kun Xiao analysed most of the formal data. Yongjiu Xiao, Binbin Li, Chang Liu, Ling Ma, Zhi Rong Qian, Dawei Xiang and Kun Xiao contributed to the investigation and methodology; all authors discussed the results and revised the manuscript.

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Ethics approval and consent

The study was approved by The 940th Hospital of Jion Logistics Support Force of Chinese People's Liberation Army. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. The registration no. of the study/trial: No. 2022KYLL157. Animal studies: Not applicable.

Abbreviations

COVID-19, coronavirus disease 2019

CI, confidence interval

CK, creatine kinase

FDA, Food and Drug Administration

HR, hazard ratios

IL, interleukins

IP, interferon-inducible protein

LHQW, Lianhuaqingwen

LS, least-squares

LDH, lactic dehydrogenase

MCP, monocyte chemotactic protein

MPP, mycoplasma pneumoniae pneumonia

QPD, qingfei paidu decoction

RT–PCR, real-time reverse-transcriptase polymerase chain reaction

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

TCM, traditional Chinese medicine

TNF, tumour necrosis factor

WHO, World Health Organization

References

1. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC: **Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review**. *Jama* 2020, **324**(8):782-793.
2. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S *et al*: **Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant**. *N Engl J Med* 2021, **385**(7):585-594.
3. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM *et al*: **Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization**. *Nature* 2021, **596**(7871):276-280.
4. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E *et al*: **Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)**. *Crit Care Med* 2020, **48**(6):e440-e469.
5. Wilson K, Chotirmall S, Bai C, Rello J: **COVID-19: interim guidance on management pending empirical evidence**. *From an American thoracic society-led international task force* 2020, **12**.
6. National Institutes of Health (US): **Coronavirus disease 2019 (COVID-19) treatment guidelines**. In.; 2020.
7. Zhou S, Feng J, Xie Q, Huang T, Xu X, Zhou D *et al*: **Traditional Chinese medicine shenhuang granule in patients with severe/critical COVID-19: A randomized controlled multicenter trial**. *Phytomedicine* 2021, **89**:153612.
8. Ye YA: **Guideline-Based Chinese Herbal Medicine Treatment Plus Standard Care for Severe Coronavirus Disease 2019 (G-CHAMPS): Evidence From China**. *Front Med (Lausanne)* 2020, **7**:256.
9. Marini JJ, Gattinoni L: **Management of COVID-19 Respiratory Distress**. *Jama* 2020, **323**(22):2329-2330.
10. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y *et al*: **Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China**. *Lancet* 2020, **395**(10223):497-506.
11. Horby P, Lim W, Emberson J, Mafham M, Bell J, Linsell L: **Effect of dexamethasone in hospitalized patients withcovid-19: preliminary report**. *N Engl J Med* 2020, **383**(2):1.
12. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB: **Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review**. *Jama* 2020, **323**(18):1824-1836.
13. Beigel JH, Tomashek KM, Dodd LE: **Remdesivir for the Treatment of Covid-19 - Preliminary Report. Reply**. *N Engl J Med* 2020, **383**(10):994.
14. Ge H, Wang YF, Xu J, Gu Q, Liu HB, Xiao PG *et al*: **Anti-influenza agents from**

Traditional Chinese Medicine. *Nat Prod Rep* 2010, **27**(12):1758-1780.

15. Duan ZP, Jia ZH, Zhang J, Liu S, Chen Y, Liang LC *et al*: **Natural herbal medicine Lianhuaqingwen capsule anti-influenza A (H1N1) trial: a randomized, double blind, positive controlled clinical trial**. *Chin Med J (Engl)* 2011, **124**(18):2925-2933.
16. Li LC, Zhang ZH, Zhou WC, Chen J, Jin HQ, Fang HM *et al*: **Lianhua Qingwen prescription for Coronavirus disease 2019 (COVID-19) treatment: Advances and prospects**. *Biomed Pharmacother* 2020, **130**:110641.
17. Gong X, Yuan B, Yuan Y, Li F: **Efficacy and Safety of Lianhuaqingwen Capsules for the Prevention of Coronavirus Disease 2019: A Prospective Open-Label Controlled Trial**. *Evid Based Complement Alternat Med* 2021, **2021**:7962630.
18. Hu K, Guan WJ, Bi Y, Zhang W, Li L, Zhang B *et al*: **Efficacy and safety of Lianhuaqingwen capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: A multicenter, prospective, randomized controlled trial**. *Phytomedicine* 2021, **85**:153242.
19. Runfeng L, Yunlong H, Jicheng H, Weiqi P, Qinhai M, Yongxia S *et al*: **Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2)**. *Pharmacol Res* 2020, **156**:104761.
20. Li JH, Wang RQ, Guo WJ, Li JS: **Efficacy and safety of traditional Chinese medicine for the treatment of influenza A (H1N1): A meta-analysis**. *J Chin Med Assoc* 2016, **79**(5):281-291.
21. Dong L, Xia JW, Gong Y, Chen Z, Yang HH, Zhang J *et al*: **Effect of lianhuaqingwen capsules on airway inflammation in patients with acute exacerbation of chronic obstructive pulmonary disease**. *Evid Based Complement Alternat Med* 2014, **2014**:637969.

Figures

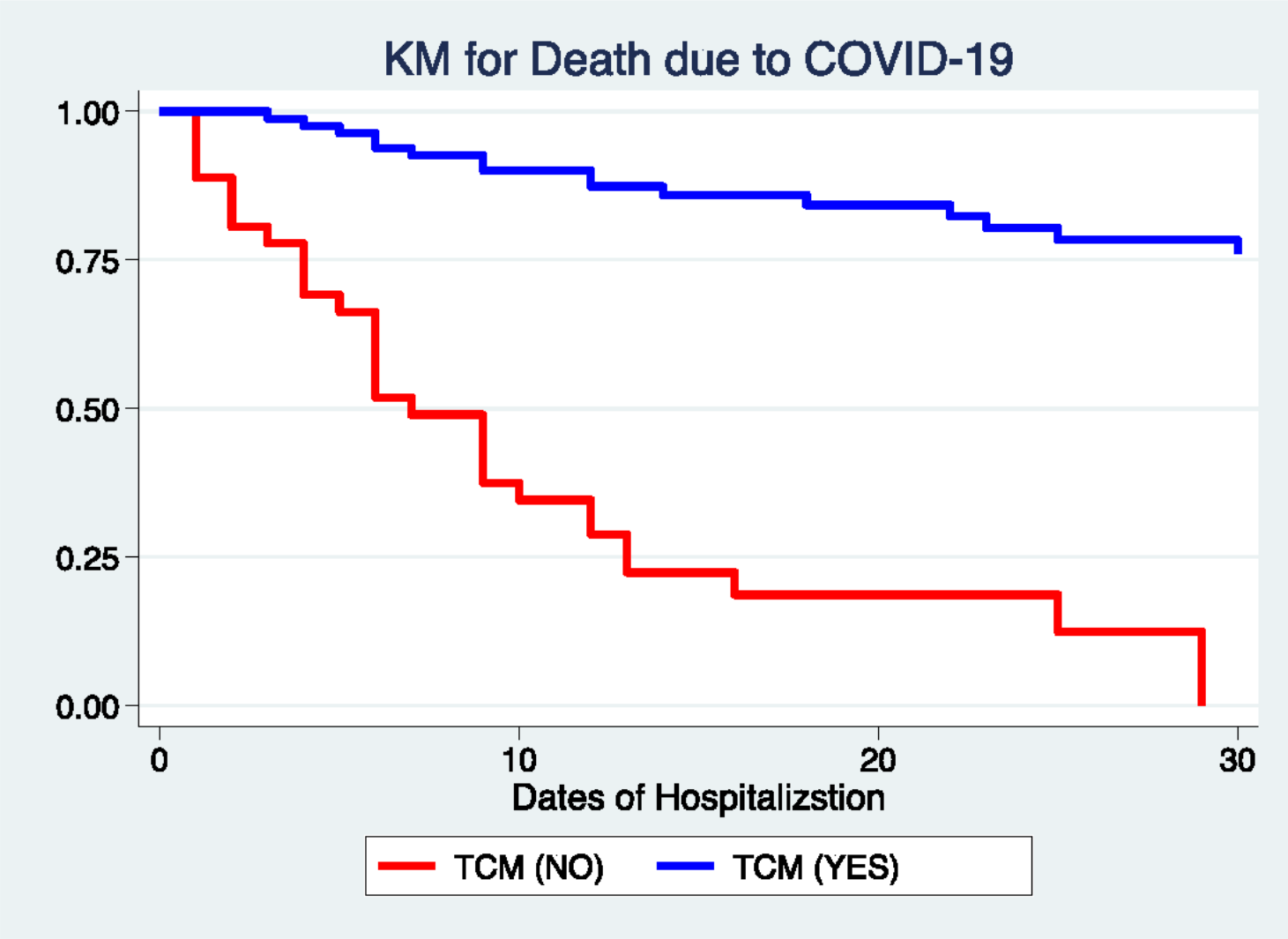

Figure 1

Kaplan–Meier analysis of 123 COVID-19 patients according to whether they received TCM treatment. (Log-rank P < 0.001)

Supplementary Files

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