



Review Article

Randomized controlled trials of traditional, complementary, and integrative medicine-based interventions for coronavirus disease 2019 (COVID-19): A bibliometric analysis and review of study designs



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ABSTRACT

Background: To date, the coronavirus disease 2019 (COVID-19) pandemic remains ongoing and continues to affect millions of people worldwide. In the effort of fighting this pandemic, there has been an increasing interest in the potential of traditional, complementary, and integrative medicines (TCIMs) in engaging COVID-19. This study presents a bibliometric analysis of the research trends of TCIMs for COVID-19.

Methods: Six databases were searched on July 15, 2021, to retrieve all the citations on TCIM-focused randomized controlled trials (RCTs) available on COVID-19. Only RCTs that mentioned at least one TCIMs for the treatment and/or management of COVID-19 were eligible. Data such as number and countries of trials conducted, publication journal, research focus, study design, and sample size were extracted for analysis.

Results: The resulting 56 articles were authored by 553 unique authors, and included 28 English articles, 19 Chinese articles with English abstracts, and 9 Chinese articles without English abstract. Analyses had shown that China was the dominant country with TCIM related RCT publications, followed by India and the United States. The included articles were published across 24 English journals and 22 Chinese journals with a wide range of impact factors from 0.220 to 56.272. The most commonly studied TCIM modalities included Chinese herbal decoction (n=12) and Chinese patent medicine (n=16). In terms of study designs, TCIM interventions were integrated with standard medicine across the trials with most trials having a small to medium sample size and open-labeled.

Conclusion: This bibliometric analysis of RCTs demonstrated the research trends and characteristics of TCIM utilized in COVID-19 research. Although there are still many research gaps and limitations for pandemic research, the publication of TCIM-focused RCTs is anticipated to show a continuously increasing trend.

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1. Introduction

As of August 3, 2021, coronavirus disease 2019 (COVID-19) has affected more than 198 million people worldwide.¹ While appropriate precautions such as social distancing, staying home, wearing a mask, and frequent handwashing are continuously taken, the world remains fully engaged and continues its effort to tackle the ongoing pandemic. Being part of the effort, there has been a growth in the interest to include traditional, complementary, and

integrative medicines (TCIMs) in treating or preventing COVID-19. TCIM includes traditional medicine indigenous to different amorphous rationalities, traditions, and cultures, as well as a broad range of health care practices and supplements that are yet to be integrated into the dominant health care system. Existing systematic reviews and meta-analyses with a focus on TCIMs for COVID-19 have shown positive effects on improving clinical symptoms and complementing standard medications.²⁻⁴ Additional evidence has also shown that TCIMs may strengthen physical and psychological resilience which is worth to be studied further.^{5, 6}

Despite the considerable number of TCIM-related studies published on COVID-19, there have been fairly few efforts taken to systematically analyze and describe the trends of these researches.

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The assessment of publication trends is necessary to understand the quantity and quality of these TCIM-focused COVID-19 studies while identifying their research gaps and avenue for future research. A bibliometric approach is useful in quantitatively analyzing literature characteristics and publication trends, where its findings can be used to identify strengths and limitations in the field of research.

This bibliometric study aimed to analyze the publication trends in TCIM randomized controlled trials (RCTs) since the outbreak of this ongoing pandemic, including (1) quantity of RCT publications, (2) most productive countries based on where the trials were conducted, (3) most common journals with their subject categories and recent impact factors, (4) most cited articles, (5) most commonly used TCIM modalities, and (6) characteristics of study designs.

2. Methods

2.1. Search strategies

Six bibliographic databases including PubMed, Embase, Allied and Complementary Medicine Database (AMED), China National Knowledge Infrastructure (CNKI), Wanfang, Chinese Science and Technology Periodical Database (VIP) were searched for publications related to TCIM approach for COVID-19. PubMed is the key database among health science researchers as it comprises extensive citations for biomedical literature with free access and user-friendliness. As PubMed alone does not cover all relevant literature, Embase is used as a supplement to identify studies that are not indexed in PubMed. AMED, on the other hand, is a specialized database designed on alternative and allied therapies-related subjects. Being the country that first considered TCIM approach for COVID-19 and issued relevant national guidelines, China has widely studied TCIM for its effectiveness in the treatment and prevention of COVID-19.⁷ Therefore, 3 major Chinese databases were also included in the literature search. CNKI is the largest Chinese journal database with constant updates and free access to wide-ranging coverage of citations in various fields. As a supplement to CNKI, Wanfang which is currently indexed in EBSCO Information Services (EBSCO), and VIP which has the highest indexing of Chinese journals, are both preferred leading Chinese databases for the literature search of clinical researches.

The literature search was performed on July 15, 2021. The authors used Medical Subject Heading (MeSH) terms, title/abstract words, and author keywords in PubMed, and equivalent indexed subject headings and terms were used in the other databases. The list of TCIM therapies provided by the World Health Organization⁸ and National Center for Complementary and Integrative Health⁹ were also referred to extend the search coverage. The complement search strategies are provided in the supplement. In addition to the comprehensive database search, relevant systematic reviews with or without meta-analysis were manually screened for additional eligible RCTs.

2.2. Selection of studies

2.2.1. Eligibility criteria

Only randomized controlled trials (RCTs) relating to TCIM for the management and/or treatment of COVID-19 were included in this bibliometric analysis. RCTs mentioning COVID-19 but not TCIM, or vice versa, were excluded. Other clinical studies such as case-controlled trials, observational studies, and case series/reports were also excluded. Research protocols, methodological studies, reviews, dissertations, conference proceedings, and abstracts were not eligible. As the COVID-19 is an emergency in public health,

preprints indexed in the aforementioned electronic databases were considered for inclusion.

2.2.2. Screening and selection process

Titles and abstracts screening were performed by one author using reference manager software, Endnote 20.1. The full text of the potentially eligible RCTs were retrieved and assessed for inclusion by one author. All the screening and selection were verified by a second author and any disagreement was resolved by consensus with an arbiter.

2.2.3. Data retrieval, processing, and extraction

Bibliometric data were retrieved using export function of the electronic databases and were manually extracted for the following information: title, authors' names, affiliations and affiliated countries, DOI, language of publication, publication type, publication month and year (issue online), publication journal, research focus, trial design, country of the trial conducted, sample sizes, TCIM modalities, intervention and comparison regimes, outcome measured, and trial registry number. All results were verified by a second author. The raw data were exported on the same day of the literature search to avoid discrepancies between the database's daily updates.

2.3. Bibliometric approach

Bibliometrics is the use of data from citation indexes to analyze, monitor, and visualize study publication trends, impacts, and research gaps. Specifically, the publications and citations, journal performance, and other information of interest such as types of TCIM modalities and outcome measures were analyzed in this study. This bibliometric analysis did not involve human research or protocol that require ethical approval from the relevant review board or committee.

2.4. Data analyses

Data were summarized using frequencies with percentages. For the analysis of study characteristics, the number of citations was retrieved from Clarivate Analytics' Web of Science (WoS) database for all studies regardless of their indexing in English or Chinese databases. To describe the journal's performance and whether the journal is TCIM-focused journal, the authors used Journal Citation Reports (JCR) impact factor and journal category for English articles, and CNKI reports for Chinese articles. Both JCR and CNKI defined the journal impact factor as the ratio between the number of all citations in a given year and the number of citable articles published during the previous 2 years. The research and publication trends associated with the eligible RCTs were also identified and presented. Visualization of the research trend using word clouds was created with wordart.com.

3. Results

3.1. Quantity of publication

Results revealed 90 eligible publications on TCIM-focused RCTs. Among them, 56 (63%) were published as original full-length research articles and 34 (37%) were published as protocols that reported the study design and rationale. As the consistency of protocols with the final study report might not be definite, protocol publications were excluded in the final analysis. Therefore, only a total of 56 articles were included and reviewed in the bibliometric analysis. All the 56 RCTs mentioned at least one TCIM for the management and treatment of COVID-19. A flowchart on the study selection process is provided in Fig. 1.

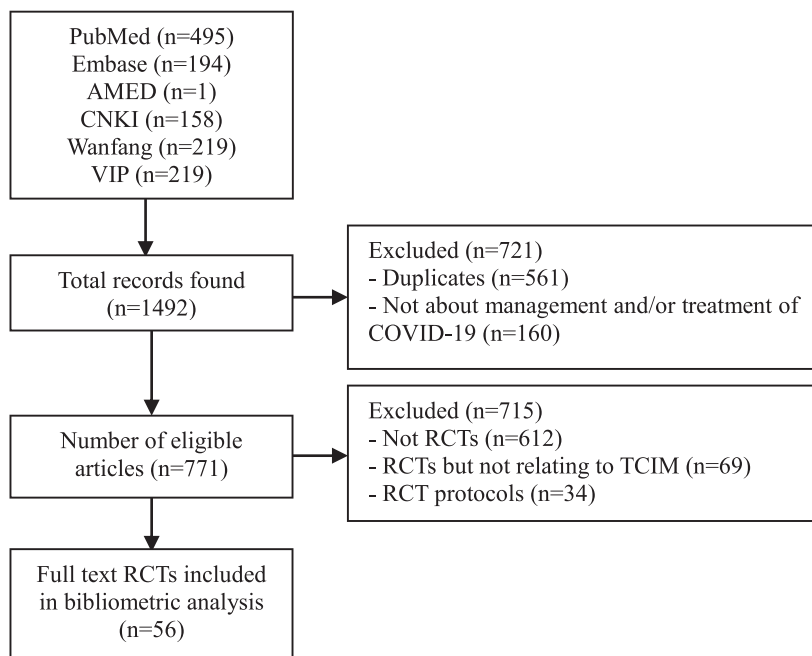


Fig. 1. Study selection and analysis flowchart.

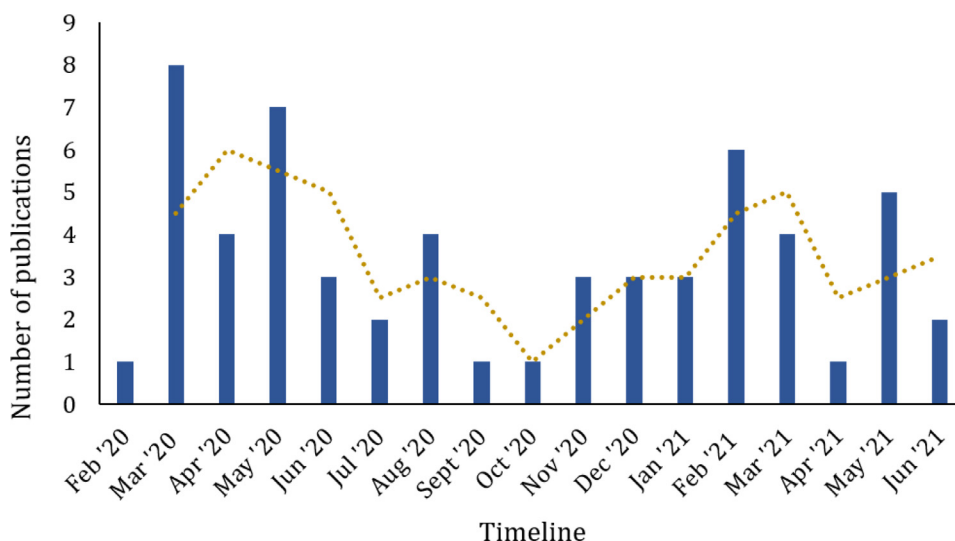


Fig. 2. Trends of TCIM focused randomized control trial research since COVID-19 outbreak.

Across 574 authors of the included publications, 553 authors were unique and the number of publication per author ranged from 1 to 4 (1 article (n=537); 2 articles (n=12); 3 articles (n=3); and 4 articles (n=1)). In terms of language, 28 articles (50%) were published in English and 28 articles (50%) were published in Chinese of which English titles and abstracts were provided for 19 articles. The number of TCIM focused publications (Fig. 2) showed a fluctuation seesaw over the pandemic.

3.2. Countries with high publications

Throughout the pandemic, China was the leading country with TCIM related RCT publications, followed by India, United States, and Iran. Publications were affiliated from the following 13 countries: China (n=41), India (n=5), United States (n=4), Iran (n=4), Belgium (n=2), Brazil (n=2), Australia (n=1), Canada (n=1), Germany (n=1), Pakistan (n=1), Saudi Arabia (n=1), Spain (n=1), and

Turkey (n=1). The number of countries affiliated per publication only involved 1 (n=51) to 2 (n=7) countries.

3.3. Journal analysis

Most of the journals that published TCIM RCTs were from the field of general medicine, health care sciences, pharmacology, and integrative medicine. In total, 56 articles were published in 46 journals, of which 24 were English journals and 22 were Chinese journals. Only 5 journals (21%) were identified as TCIM-focused English journals and 12 journals (55%) as TCIM-focused Chinese journals. The impact factor of these journals ranged widely from 0.220 to 56.272. The number of articles published per journal ranged from 1 to 3. The articles that had been cited at least 5 times in Web of Science database, as of the search date, are provided in Table 1 and the details of the journals are provided in Table 2. The analysis of the terminology used for the article title showed the

Table 2
Journals that published TCIM-focused randomized controlled trials for COVID-19

Journals	No. of articles	TCIM journal	2020 Impact factor*
<i>English</i>			
Phytomedicine	3	Yes	5.340
Biomedicine & Pharmacotherapy	2	No	6.529
Complementary Therapies in Clinical Practice	2	Yes	2.446
JAMA	1	No	56.272
JAMA Network Open	1	No	8.483
Pharmacological Research	1	No	7.658
Annals of Intensive Care	1	No	6.925
Phytotherapy Research	1	No	5.878
Frontiers in Pharmacology	1	No	5.810
Nutrients	1	No	5.717
Journal of Translational Medicine	1	No	5.531
Frontiers in Medicine	1	No	5.091
International Immunopharmacology	1	No	4.932
Frontiers of medicine	1	No	4.592
Scientific Reports	1	No	4.379
Journal of Steroid Biochemistry and Molecular Biology	1	No	4.292
Annals of Palliative Medicine	1	No	2.595
Postgraduate Medical Journal	1	No	2.401
Integrative Medicine Research	1	Yes	2.368
Journal of medical virology	1	No	2.327
European Journal of Medical Research	1	No	2.175
Chinese Journal of Integrative Medicine	1	Yes	1.978
Journal of Complementary and Integrative Medicine	1	Yes	NA
Cureus	1	No	NA
<i>Chinese</i>			
International Infectious Diseases	2	No	0.047
Hebei Journal of Traditional Chinese Medicine	2	Yes	0.731
Chinese Journal of Experimental Traditional Medical Formulae	2	Yes	2.327
Chinese Acupuncture and Moxibustion	2	Yes	1.597
Journal of Emergency in Traditional Chinese Medicine	2	Yes	0.991
Pharmacology and Clinics of Chinese Materia Medica	2	Yes	1.079
Chinese Critical Care Medicine	1	No	1.820
Journal of Traditional Chinese Medicine	1	Yes	1.555
Traditional Chinese Drug Research and Clinical Pharmacology	1	Yes	1.277
Chinese Pharmaceutical Journal	1	No	1.141
China Tropical Medicine	1	No	1.122
Journal of Xi'an Jiaotong University (Medical Sciences)	1	No	1.071
Journal of Hunan University of Chinese Medicine	1	Yes	1.059
Guangdong Medical Journal	1	No	1.021
Herald of Medicine	1	No	0.954
Modernization of Traditional Chinese Medicine and Materia Medica-World Science and Technology	1	Yes	0.761
Chinese Journal of Virology	1	No	0.753
Jiangsu Journal of Traditional Chinese Medicine	1	Yes	0.742
China Pharmaceuticals	1	No	0.689
Zhejiang Journal of Integrated Traditional Chinese and Western Medicine	1	Yes	0.457
Guangming Journal of Chinese Medicine	1	Yes	0.328
Medical Journal of Communications	1	No	0.220

*Latest impact factor as reported by Journal Citation Report (JCR) for English journals and by China National Knowledge Infrastructure (CNKI) for Chinese journals. The journals are listed in descending order of article number; for those with the same number of article(s), the order is by the impact factor.

few studies including larger sample size of more than 200 study participants (Fig 4).

3.6. Main research outcomes of TCIM related RCTs

Over the studied population, 5,169 (87%) participants were positive cases, 343 (6%) were suspected or positive cases, and 148 (2%) were suspected cases of COVID-19. The severity of the diseases ranged from mild to critical to recovery. After standardizing and merging similar outcomes, there were 33 outcomes reported in the included RCTs, including admission to intensive care unit, adverse events, acute physiology and chronic health evaluation (APACHE) II score, arterial blood gas parameters, changes in oxygenation index, chest X-ray or computed tomography (CT) findings, clinical symptoms score, duration of hospital admission, frequency and duration of mechanical ventilator assistance, Glasgow coma scale, health-

related laboratory markers, hospitalization rate, incidents of acute respiratory distress syndrome (ARDS) development, inflammatory markers, medication status, mortality, need for vasoactive drugs, organ functions, overall improvement rate, overall rate of clinical cure, peak expiratory flow rate, prevalence of antibiotic, quality of life, rate and time to negative conversion of viral tests, rate of advancing to critical, rate of clinical deterioration, remission rate and time of clinical symptoms, retest of viral tests, severe adverse events, survival rate, traditional Chinese medicine (TCM) syndrome score, TCM tongue and pulse diagnosis score, and time to disease recovery. Details of the outcomes measured according to the severity of disease are provided in Table 5.

The full information of all RCTs containing all of the aforementioned characteristics is available in the supplement for the convenience of clinical researchers who are interested in pursuing the original publication or foster further researches.

Table 3
Types of TCIM modalities used in the trials for COVID-19 patients

Type of TCIM	Modalities	No. of trials
Chinese medicine (n=37)	Chinese herbal decoction	12
	Chinese patent medicine	16
	Chinese herbal injection	3
	Moxibustion	1
	Combined interventions	5
	Chinese herbal decoction and moxibustion	1
	Auricular acupuncture and Qigong	1
	Chinese medicine music therapy and Qigong	1
	Chinese herbal decoction and fumigation	1
	Chinese patent medicine and Qigong	1
	Health supplements (n=15)	Vitamin D
Vitamin C		3
Herbs		3
Zinc		1
Propolis		1
Omega-3 fatty acid		1
Zinc and Ascorbic Acid		1
Others (n=4)		Ayurvedic medicine
	Guided imagery	1
	Progressive muscle relaxation	1
	Ozone therapy	1

Table 4
Details of the type of TCIM intervention used.

Intervention category	Interventions used
Chinese herbal decoction	Jiawei Dayuan decoction, Moxing Xuanfei Jiedu decoction, Qingfei Paidu decoction, Qingfei Touxie Fuzheng prescription, Xuanfei Baidu decoction, Xuanfei Qingre decoction, Yidu-toxicity blocking lung decoction, Xiao Chaihu decoction with Maxingshigan or Sanren decoction, Herbal decoction by pattern identification, Self-prescribed decoction
Chinese patent medicine	Feiyan Yihao granules, Gegen Qinlian pill, Huoxiang Zhengqi drop pills, Jinhua Qinggan granules, Jinyinhua Oral Liquid, Keguan-1 powder, Lianhua qingwen granules, Qingre Kang oral liquid, Shenhuang Granule, Shenling Baizhu San, Shuanghuanglian oral liquids, Shufeng Jiedu Capsule, Toujie Quwen granules, Xianglan Jiedu, Yiqi Huoxue San, Yiqi Yangyin granules
Chinese herbal injections	Reduning injection, Xiyanning injection, Xuebijing injection
Other traditional Chinese medicine intervention	Taiji Liu Qigong, Baduanjin, TCM five elements music therapy, Liu Zhi Jue
Ayurvedic medicine	Giloy Ghanvati, Swasari Ras, Ashwagandha, Tulsi Ghanvati, Anu Taila
Health supplements	Ascorbic acid, Zinc gluconate, Calcifediol, Curcumin and piperine formulation, Diammonium Glycyrrhizinate enteric capsules, Intravenous vitamin C, Intravenous zinc, Omega-3 fatty acids fortified formula, Oral vitamin D3, Standardized Brazilian green propolis extract, Zingiber officinale and Echinacea
Others	Progressive muscle relaxation (PMR), Guided imagery, Ozone therapy (Ozonized rectal insufflation with minor auto haemotherapy)

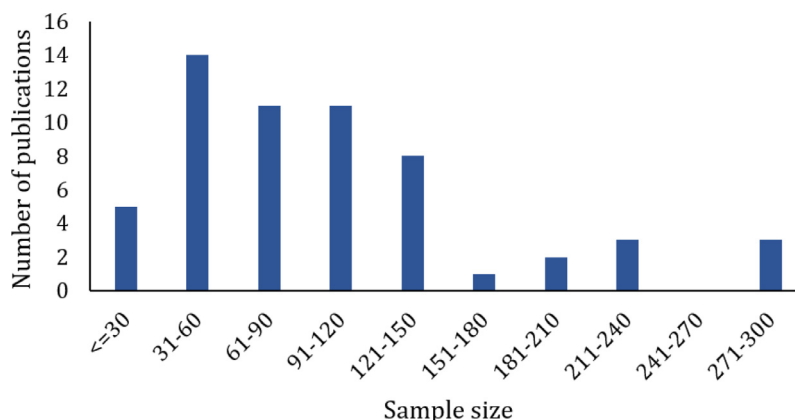


Fig. 4. Sample size of included COVID-19 randomized controlled trials relating to TCIM intervention.

4. Discussion

This study quantitatively explored the current publication trends of TCIM-focused RCTs, as of July 2021. The 56 publications retrieved from 6 databases demonstrated the efforts taken to investigate the potential of TCIM in treating and/or managing COVID-19. The publications during the past 18 months suggest that TCIM

RCT publication fluctuates and is yet to be leveled off, having possibilities of continued growth of publication in the near future. The country with the highest productivity is dominated by China, given that TCIM approach is initiated by China through the usage of traditional Chinese medicine in the management of COVID-19. Globally, the number of distributing countries remains limited and scattered. Although TCIM-focused RCTs are partially pub-

Table 5
Outcomes measured in the TCIM-focused randomized controlled trials for COVID-19

Population studied	Severity of COVID-19	Outcomes measured
Positive cases (n=5169)	Mild	Remission rate and time of clinical symptoms Inflammatory markers Hospitalization rate Chest CT findings Overall rate of clinical cure Adverse events
	Mild or asymptomatic	Health-related laboratory markers Inflammatory markers Rate and time to negative conversion of viral tests Adverse events
	Moderate	Remission rate and time of clinical symptoms Health-related laboratory markers Inflammatory markers Duration of hospital admission Chest CT findings TCM syndrome score Time to negative conversion of viral tests Rate of clinical deterioration Overall rate of clinical cure Adverse events
	Severe	Remission rate and time of clinical symptoms Inflammatory markers Duration of hospital admission APACHE II score Prevalence of antibiotic Chest X-ray and CT findings Frequency of mechanical ventilator assistance Mortality Time to negative conversion of viral tests Rate of clinical deterioration Overall rate of clinical cure Adverse events
	Critical	Health-related laboratory markers Duration of hospital admission Admission to intensive care unit Duration of mechanical ventilator assistance Changes in oxygenation index Arterial blood gas parameters Glasgow coma scale Organ functions Survival rate Mortality Severe adverse events
	Recovery	Remission rate of clinical symptoms Inflammatory markers Peak expiratory flow rate TCM syndrome score Quality of life Chest CT findings Retest of viral tests Overall rate of clinical cure Adverse events
	Mild to moderate	Remission rate and time of clinical symptoms Health-related laboratory markers Inflammatory markers Duration of hospital admission Admission to intensive care unit Changes in oxygenation index Chest CT findings TCM syndrome score Time to negative conversion of viral tests Rate of clinical deterioration Overall rate of clinical cure Adverse events

(continued on next page)

Table 5 (continued)

Population studied	Severity of COVID-19	Outcomes measured
	Mild to severe	Remission rate and time of clinical symptoms Health-related laboratory markers Inflammatory markers Duration of hospital admission Admission to intensive care unit Changes in oxygenation index Chest X-ray or CT findings Frequency and duration of mechanical ventilator assistance Mortality TCM syndrome score TCM tongue and pulse diagnosis score Time to negative conversion of viral tests Rate of clinical deterioration Overall rate of clinical cure Adverse events
	Moderate to severe	Health-related laboratory markers Inflammatory markers Duration of hospital admission Admission to intensive care unit Frequency and duration of mechanical ventilator assistance Clinical symptoms score Mortality Adverse events
	Mild to critical	Remission rate and time of clinical symptoms Health-related laboratory markers Inflammatory markers Changes in oxygenation index Chest CT findings Organ functions Time to disease recovery Rate and time to negative conversion of viral tests Adverse events
	Severe to critical	Inflammatory markers Frequency and duration of mechanical ventilator assistance Rate of advancing to critical Mortality Organ functions Overall improvement rate Adverse events
	Not specified	Remission rate and time of clinical symptoms Inflammatory markers Duration of hospital admission Admission to intensive care unit Frequency and duration of mechanical ventilator assistance Need for vasoactive drugs TCM syndrome score Chest CT findings Organ functions Rate of clinical deterioration Mortality Medication status Overall improvement rate Overall rate of clinical cure Time to negative conversion of viral tests Adverse events
Suspected cases (n=148)	Ambulatory	Remission rate and time of clinical symptoms Incidents of ARDS development Hospitalization rate Admission to intensive care unit Frequency and duration of mechanical ventilator assistance Chest CT findings Mortality Time to negative conversion of viral tests Adverse events

APACHE, acute physiology and chronic health evaluation; ARDS, acute respiratory distress syndrome; CT, computed tomography; TCM, traditional Chinese medicine.

Inflammatory markers, including levels of cluster of differentiation (CD) 3+, CD4+, CD4+/CD8+, CD45+, CD8+, creatinine, C-reactive protein (CRP), D-Dimer, erythrocyte sedimentation rate (ESR), ferritin, fibrinogen, high-sensitivity-CRP, interferon gamma (IFN- γ), interleukin-2 receptor (IL-2R), interleukin(IL)-4, IL-6, IL-8, lactate dehydrogenase (LDH), partial pressure of carbon dioxide (PCO₂), partial pressure of oxygen (PO₂), procalcitonin (PCT), tumor necrosis factor alpha (TNF- α), 25-hydroxy-cholecalciferol [25(OH)D]; lymphocyte (LYM) cell counts, LYM%, neutrophils (NEU), NEU%, neutrophil-to-lymphocyte (N/L) ratio, and white blood cell (WBC) counts.

Organ functions, including myocardial, liver, kidney, and Sequential Organ Failure Assessment (SOFA) score.

Medication status, including Chinese medicine, antibiotics, anti-viral drug, anti-inflammatory drug etc.

Emotional wellbeing and quality of life outcomes including 12-Item Short Form Survey (SF-12), Burnout Scale, Hamilton Anxiety Rating Scale (HAM-A), Hamilton Depression Rating Scale (HDRS), Pittsburgh Sleep Quality Index (PSQI), Self-Rating Depression (SDS), Sleep State Self-Rating Scale (SRSS), Spielberger State-Trait Anxiety Inventory (STAI), Pain quality (Short-Form McGill Pain Questionnaire (SF-MPQ), Pain intensity (Visual Analogue Scale), Subjective Units of Distress Scale (SUDs), Zung Self-Rating Anxiety Scale (SAS).

lished in Chinese, most studies are open access with English titles and abstracts, provided by CNKI for non-Chinese readers. Notably, CNKI has developed an open-access specialized platform in English that currently indexed more than 7,500 COVID-19 related studies from 2,000 Chinese and non-Chinese journals to disseminate research findings.¹⁰ The included RCTs were found to be published in biomedical journals in a wide range of fields, with only a little more than one-third of the articles being published in TCIM-focused journals. On the other hand, a little less than half of the articles were published in journals indexed in Science Citation Index Expanded (SCIE) which raises potential questions on the credibility and quality of the studies.

This analysis found that the TCIM modalities mentioned in the included articles are highly disproportionate. It is foreseeable that a vast majority of TCIMs mentioned are related to traditional Chinese medicine as a high proportion of these trials were conducted in China and published by Chinese researchers. However, TCIMs mentioned in articles that are published in high impact factors journals or have a high number of citations are mostly on health supplements such as vitamin C, vitamin D, and zinc. This indicates that health supplements, with a relatively smaller proportion of studies published, gain more attention and recognition among researchers and journals. In the meantime, much fewer studies focused on TCIM modalities such as Ayurveda and mind-body practices, and there are yet to have any studies published on other modalities, showing the potential avenue for future research.

Looking at the analysis of the retrieved data, 2-armed parallel RCTs were highly dominant, suggesting that study investigators were conducting comparison studies where the related clinical question was focused on the effectiveness of the treatment arm (i.e. comparing the effectiveness of TCIM interventions with established interventions for the treatment and/or management of COVID-19). Meanwhile, reporting on the masking (also known as blinding) of the RCTs is a huge issue that should not be ignored. Blinding is an important methodologic component of RCTs to reduce bias and increase the validity of the results, and is equally important to the randomization method. However, a high proportion of the studies did not mention blinding, causing their study findings to be questionable. It is also found that too many trials were open and too few were double-blinded, which is generally considered more common in trials related to COVID-19. This bibliometric analysis also observed that small to medium-sized studies were dominant, which is a common limitation that leads to a certain degree of bias in study findings. In terms of outcome measures, it is seen that the outcomes measured varied across the trials with many of less critical outcomes in each intended population. Implications of such heterogeneity should not be ignored in future studies, and researchers should consider selecting their outcomes by referring to the core outcome set developed by Core Outcome Measures in Effectiveness Trials (COMET) Initiative.¹¹ There is also a lack of consistency in the terminology for the study design in the title, indicating lack of proper reporting as suggested by CONSolidated Standards Of Reporting Trials (CONSORT) guidelines to include identification of a randomized trial in the title.

In current situation, there is no doubt that clinical research on COVID-19 faces many ethical challenges due to the complexity of the disease. Yet, well-designed trials are immensely necessary as badly-designed trials are likely to produce potentially misleading or exaggerated information; in the meantime, exposing trial participants to a higher risk of harm. Given the urgency of COVID-19 situation, the perception that core methodological components of high-quality RCTs, such as adequate sample size, proper randomization or blinding, and validated outcome measures, are expendable is highly inappropriate. Several rapidly published research trials with suboptimal designs have faced retraction, but they are not free from affecting clinical practice to face the consequences

risen from the results of such studies. As exemplified by hydroxychloroquine, its usage had increased after the rapid publication of an open-label, non-randomized, small-sampled trial claiming its effectiveness and was later shown to be no different from placebo and revoked in a well-designed RCT with a large sample size.^{12, 13} Therefore, RCTs with suboptimal designs will not help either patients or clinicians, and may result in significant ethical lapse. Instead of allowing exceptionalism, researchers should coordinate their studies to uphold the gold standard of RCT to contribute to the advancement of clinical evidence base for COVID-19.¹⁴

To the authors' knowledge, this study is the first bibliometric analysis of TCIM-focused RCTs. In contrast to a number of COVID-19 bibliometric analyses published over the past year, the authors centered their study to RCTs only, and manually screened and extracted all the data to provide a comprehensive review on the state of TCIM clinical research. Particularly, a bibliometric analysis on the global trends of overall TCIM research providing a larger view of the publication landscape¹⁵ and a bibliometric analysis focusing on traditional Chinese medicine¹⁶ have been published in recent months. It is worth mentioning that several general comparisons can be drawn to the findings of this study in comparison with these bibliometric analyses. One study¹⁵ identified that the vast majority proportion of publications included traditional Chinese medicine and vitamin D supplementation, whereas the other study¹⁶ found that research direction is highly concentrated in the clinical researches focusing on traditional Chinese medicine in the treatment of COVID-19. These findings are highly in line with our findings where traditional Chinese medicine has the greatest proportion in TCIM-focused RCTs publications, followed by vitamin D supplementation.

Nevertheless, there are limitations of this study. First, the authors did not include explicit search terms related to each TCIM modalities such as specific herb/product names or technique used (e.g. curcumin, calcifediol, Baduanjin); however, these interventions were included if they were described as TCIM modalities. Therefore, there may be other RCTs on these TCIM interventions that were missed out. Second, a number of non-English or non-Chinese journals may not be indexed in the aforementioned databases; hence, it is possible that TCIM-focused RCTs that were published in their native language or local journals may have been neglected. Regrettably, such articles are often hard to capture as their accessibility is highly limited to authors, and there could be other forms of less known TCIM modalities that were overlooked in this analysis.

In conclusion, this bibliometric analysis of RCTs demonstrated the research trends of TCIMs mentioned in COVID-19 research. There are still many research gaps in the pandemic research of TCIMs which requires evaluation of study designs for more rigorous research from various countries. The burgeoning literature on TCIM-focused clinical trials for COVID-19 in the future is highly anticipated.

Author contributions

Conceptualization: MSL. Methodology: LA, ES. Software: LA. Validation: MSL. Formal analysis: LA, ES. Investigation: MSL. Data curation: LA. Writing – Original Draft: LA. Writing – Review & Editing: MSL, ES. Visualization: MSL. Supervision: MSL. Project administration: MSL. Funding acquisition: MSL.

Conflict of interests

LA, ES, and MSL are editors of IMR but their status had no bearing on editorial consideration. This article was externally peer-reviewed. There is no other conflict of interests.

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Ethical statement

Not applicable.

Data availability

The data that support the findings of this study are available as supplementary material.

References

- World Health Organization (WHO). WHO Coronavirus (COVID-19) Dashboard, <<https://covid19.who.int/table>>; Published 2020.
- Ang L, Song E, Lee HW, Lee MS. Herbal medicine for the treatment of Coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis of randomized controlled trials. *J Clin Med*. 2020;9(5). doi:10.3390/jcm9051583.
- Zhou LP, Wang J, Xie RH, Pakhale S, Krewski D, Cameron DW, et al. The effects of traditional Chinese medicine as an auxiliary treatment for COVID-19: a systematic review and meta-analysis. *J Altern Complement Med*. 2021;27(3):225–237. doi:10.1089/acm.2020.0310.
- Liang S-B, Fang M, Liang C-H, Lan H-D, Shen C, Yan L-J, et al. Therapeutic effects and safety of oral Chinese patent medicine for COVID-19: A rapid systematic review and meta-analysis of randomized controlled trials. *Complem Ther Med*. 2021;60. doi:10.1016/j.ctim.2021.102744.
- Seifert G, Jeitler M, Stange R, Michalsen A, Cramer H, Brinkhaus B, et al. The relevance of complementary and integrative medicine in the COVID-19 pandemic: a qualitative review of the literature. *Front Med*. 2020;7(946). doi:10.3389/fmed.2020.587749.
- Tillu G, Chaturvedi S, Chopra A, Patwardhan B. Public health approach of Ayurveda and Yoga for COVID-19 prophylaxis. *J Altern Complement Med*. 2020;26(5):360–364. doi:10.1089/acm.2020.0129.
- Ang L, Lee HW, Choi JY, Zhang J, Soo Lee M. Herbal medicine and pattern identification for treating COVID-19: a rapid review of guidelines. *Integr Med Res*. 2020;9(2). doi:10.1016/j.imr.2020.100407.
- World Health Organization (WHO). Health topic: Traditional, complementary and integrative medicine, <https://www.who.int/health-topics/traditional-complementary-and-integrative-medicine#tab=tab_1>; Published 2021 Accessed July 10.
- National Center for Complementary and Integrative Health. Health Topics A–Z, <<https://www.nccih.nih.gov/health/atoz>>; Published 2021 Accessed July 10.
- China National Knowledge Infrastructure (CNKI). Open access (OA) Online-first publishing of research papers on COVID-19, <<https://xgbteng.oversea.cnki.net/xgbt/en>>; Published 2021 Accessed August 1.
- Core Outcome Measures in Effectiveness Trials (COMET) Initiative. Core outcome set developers' response to COVID-19, <<https://www.comet-initiative.org/studies/details/1538>>; Published 2021 Accessed August 1.
- The RECOVERY Collaborative Group Effect of Hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med*. 2020;383(21):2030–2040. doi:10.1056/NEJMoa2022926.
- Saag MS. Misguided use of Hydroxychloroquine for COVID-19: The infusion of politics into science. *JAMA*. 2020;324(21):2161–2162. doi:10.1001/jama.2020.22389.
- London AJ, Kimmelman J. Against pandemic research exceptionalism. *Science*. 2020;368(6490):476–477. doi:10.1126/science.abc1731.
- Ng JY. Global research trends at the intersection of coronavirus disease 2019 (COVID-19) and traditional, integrative, and complementary and alternative medicine: a bibliometric analysis. *BMC Complem Med Therapies*. 2020;20(1):353. doi:10.1186/s12906-020-03151-8.
- Yang K-L, Jin X-Y, Gao Y, Xie J, Liu M, Zhang J-H, et al. Bibliometric analysis of researches on traditional Chinese medicine for coronavirus disease 2019 (COVID-19). *Integr Med Res*. 2020;9(3). doi:10.1016/j.imr.2020.100490.