新型冠状病毒肺炎的中医药临床研究: 基于文献计量学分析的解读与思考

李逸雯^{1,2†}, 刘玥^{1,2†}, 吕诚³, 杨洪军⁴, 陈可冀^{1*}, 黄璐琦^{2,4*}

1. 中国中医科学院西苑医院, 国家中医心血管病临床医学研究中心, 北京 100091;

2. 中国中医科学院中国中医药循证医学中心, 北京 100700;

3. 中国中医科学院中医临床基础医学研究所, 北京 100700;

4. 中国中医科学院, 北京 100700

† 同等贡献

* 联系人, E-mail: kjchenvip@163.com; huangluqi01@126.com

2021-03-11 收稿, 2021-04-15 修回, 2021-04-22 接受, 2021-04-23 网络版发表

国家重点研发计划(2020YFC0841500)和中国中医药循证医学中心“业务研究室主任专项”(2020YJSZX-4)资助

摘要 新型冠状病毒肺炎(COVID-19, 简称“新冠肺炎”)疫情在全球范围内蔓延, 对人类健康造成巨大威胁. 目前已有疫苗问世, 但仍没有可靠的治愈办法. 中医药的临床应用在国内疫情防控中发挥了重要作用, 并已涌现出若干临床研究, 其中中医药治疗新冠肺炎的临床研究文献信息、治疗现状及规律值得系统归纳与解读, 为未来的临床与科研提供基础. 检索2020年1月1日至2021年3月1日期间PubMed、Embase、Web of Science、medRxiv、中国知网、万方数据库及中国生物医学文献数据库, 纳入中医药治疗COVID-19的临床研究文献, 获取文献的基本信息及治疗内容信息, 评价文献质量, 进行文献计量学分析. 共纳入47篇文献, 绝大多数以中文发表(42篇, 占全部文献的89.36%); 从临床试验注册的文献量(12篇)、被引量(单篇最高被引62次)及相关质量评价量表(改良Chalmers评分平均61.40分)的结果来看, 整体研究质量仍有待提高. 共涉及中药复方66个, 其中苦杏仁、甘草、石膏、麻黄、茯苓、藿香等中药使用频次较高. 结局指标中临床症状(发热、咳嗽、乏力等)缓解率、普通型转为重型率, 实验室指标中的白细胞总数、淋巴细胞总数及C反应蛋白、肺CT影像学变化及不良反应受到关注. 目前中医药治疗新冠肺炎的临床研究质量亟待提高, 未来需进一步规范中医药临床循证研究的设计与实施. 中医药主流治法为清热解表化湿, 麻杏石甘汤为最常用的经典祖方, “三药三方”在临床得到广泛应用. 经中医药治疗后临床症状显著缓解, 常见实验室指标、肺部影像学改善明显, 安全性良好. 中医药通过多机制、多途径防治COVID-19, 其规律值得进一步探讨.

关键词 新冠肺炎, 中医药, 临床研究, 文献计量学

自2019年12月至今, 新型冠状病毒肺炎(COVID-19, 简称“新冠肺炎”)疫情对全球的卫生健康造成了极大的危害^[1]. 目前我国疫情控制稳定, 在抗击疫情的过程中, 中医药及中西医结合在临床救治中应用率达到80%以上^[2], 对疫情的迅速控制起到了不可忽视的作

用. 国家卫生健康委员会办公厅先后共发布了8版《新型冠状病毒肺炎诊疗方案》(http://www.gov.cn/jzhengce/jzhengceku/2020-08/19/content_5535757.htm), 各地区也相继发布了新冠肺炎中医药诊治方案^[3]. 经临床使用经验重点筛选出“三药三方”(金花清感颗粒、连

引用格式: 李逸雯, 刘玥, 吕诚, 等. 新型冠状病毒肺炎的中医药临床研究: 基于文献计量学分析的解读与思考. 科学通报, 2021, 66: 3385–3394

Li Y W, Liu Y, Lü C, et al. Clinical trials for Traditional Chinese Medicine against coronavirus disease 2019 (COVID-19): Interpretation based on bibliometric analysis (in Chinese). Chin Sci Bull, 2021, 66: 3385–3394, doi: [10.1360/TB-2021-0125](https://doi.org/10.1360/TB-2021-0125)

花清瘟胶囊、血必净注射液和清肺排毒汤、化湿败毒方、宣肺败毒方^[4]广泛应用于新冠肺炎的防治,同时在全国范围内开展了很多以中医药为干预手段的临床研究,积累了诸多应用经验。

本研究通过文献计量学的方法,筛选自2020年1月至2021年3月已发表的中医药干预新冠肺炎的临床研究文献,通过不同维度的系统整理,对其整体情况、实施内容及对新冠肺炎的治疗效果进行分析,同时进行解读与思考,以期对中医药防治新冠肺炎乃至其他急性传染性疾病的临床研究提供参考。

1 方法

(i) 检索策略. 计算机检索Web of Science、Embase、PubMed、中国知网(CNKI)、万方医学(WanFang Database)、中国生物医学文献服务系统(SinoMed). 检索起止时间为2020年1月1日至2021年3月1日. 英文检索词为: Chinese medicine、herbal medicine、herb、acupuncture、alternative medicine、complementary therapy、formula、decoction、capsule、granules、COVID-19、coronavirus、SARS-CoV-2. 中文检索词为: 中医、中药、中西医结合、针灸、汤、方、颗粒、新冠肺炎、新型冠状病毒肺炎. 检索式根据不同数据库适当调整。

(ii) 纳入标准. (1) 研究内容与COVID-19治疗或康复相关; (2) 研究类型为临床对照研究, 包括干预性研究或观察性研究; (3) 研究干预措施为各种剂型的口服中药(汤剂、颗粒剂、片剂、胶囊、冲剂、口服液等)、中药注射液、针灸; (4) 发表语言为中文或英文。

(iii) 排除标准. (1) 系统综述、meta分析或重复发表的或仅有摘要而无法获得全文的文献; (2) 中医证候调查研究; (3) 已被撤稿或被严重质疑的论文。

(iv) 文献计量学分析. 纳入统计的文献计量学信息包括发表语言、临床试验注册信息、收稿日期、作者所在单位信息以及作者数量、文章被引量、临床研究类型(随机对照研究、非随机对照研究)、COVID-19的临床分型(轻型/普通型/重型/危重型/恢复期^[3])、样本量、受试者收治机构及所在地区、受试者的平均年龄/年龄范围、使用的中医药手段、药物组成及使用方法、干预时间、观察结局指标及不良反应. 被引量于2021年1月26日使用Google Scholar检索。

对临床对照研究进行质量评价, 由于多数研究设计目的与方法与随机对照研究相似, 均旨在评价干预

药物的近期临床疗效及不良反应等, 因此对纳入所有研究进行统一的评价. 综合随机对照试验(randomized controlled trial, RCT)与非随机对照试验的质量评价要求, 予以改良的Chalmers量表评分, 对6个方面共10项细则进行评价: (1) 研究对象(样本量计算、纳入排除标准的规定、基线情况); (2) 随机过程(试验中的随机); (3) 盲法与分配隐藏的应用; (4) 干预措施的定义; (5) 统计分析是否合理; (6) 随访及结果(随访失访的说明、研究的起止时间、主要结局的表达). 每个条目计0~10分, 共计100分(具体量见表S1)。

对文献计量学分析及质量评价结果作平均数、中位数、比例、排名或其他适当的描述性统计。

(v) 数据汇总和可视化展示. 采用Endnote X9软件对文献进行管理. 采用预先制订的资料采集表提取资料, 应用epidata 3.1软件进行录入, 并应用Excel2010进行数据汇总. 采用Edrawsoft 9.4绘制描述性图例(图1和2)、采用Citespace V5.5.2绘制发表单位的共线图(图3)、采用SPSS Modeler 18绘制中药的关联规则网络(图4(a))。

2 结果

2.1 一般信息

本研究共检索到47篇中医药治疗新冠肺炎的临床对照研究, 检索流程见图1. 其中英文15篇(占全部文献的31.91%), 中文32篇(68.09%). 全部研究实施分配隐藏以及盲法均受限, 仅以随机化方法作为分类依据, 随机对照研究共19篇(40.43%), 非随机对照研究共28篇(59.57%). 前瞻性研究共25篇(53.19%), 回顾性研究共22篇(46.81%). 共有12项研究具有临床试验预注册信息, 其中英文文献11篇, 中文文献1篇。

本研究纳入的47篇临床研究文献共6565例新冠肺炎患者被纳入统计分析, 单篇的平均样本量为139.7例. 中医药治疗COVID-19的临床对照研究中, 纳入患者的疾病分型最多者为轻型-普通型, 具体纳入的分型情况见图2。

湖北省为主要的实施地区, 总计纳入约4693例新冠肺炎患者, 剩余纳入人群来自全国其他14个省份(多中心研究按各试验中心所在地区计算实施地区). 研究的收稿日期集中于2020年3月(13篇, 27.67%). 以上研究对象主要为武汉疫情集中暴发期间的COVID-19患者群体。

对照研究中全部作者共来自135家单位(二级单位/

图 1 (网络版彩色)文献检索流程图
Figure 1 (Color online) Flowchart of the literature search

学科不进行划分, 大学及其附属医院计为不同单位), 其中31家(占全部单位的22.96%)位于湖北. 有国际合作的研究共2篇^[5,6]. 具体共现情况见图3.

2.2 研究的质量评价

文献被引量普遍较低, 仅2篇文献的被引量 ≥ 10 ^[7,8]. 单篇文献最高被引62次, 该篇被国外学者引用4次. 整体上, 引用以上文献的多数仍为中国学者.

全部试验的改良Chalmers量表平均得分为61.40分, 其中6项平均得分分别为: 研究对象6.87分、随机过程1.85分、盲法与分配隐藏的应用0分、干预措施的定义8.53分、统计分析是否合理9分、随访及结果7.14分. 引起研究报告质量下降的主要原因为随机化不合理、未实现盲法及分配隐藏、样本量不足等. 总分 ≥ 70 分

的共6篇(10.34%), 总分 ≥ 70 分的具体文献情况见表1.

2.3 中医药使用情况及结局

纳入临床研究的患者平均年龄为50.26岁. 发表研究最多的中医药种类为连花清瘟胶囊/颗粒^[8,10,14~16](5篇, 10.64%).

涉及的中药复方共66个, 其中已上市中成药12种(颗粒剂、胶囊、口服液等剂型), 分别为藿香正气胶囊、金花清感颗粒、金叶败毒颗粒、金银花口服液、兰香解毒口服液、连花清咳颗粒、连花清瘟胶囊/颗粒、清热抗毒口服液、疏风解毒胶囊、双黄连口服液、痰热清胶囊、玉屏风颗粒; 中药注射液1种, 为血必净注射液. 共涉及中药药物134味(根据《中国药典2020年版》^[17]纳入), 其中苦杏仁、甘草、石膏、麻黄

图2 中医药防治COVID-19临床试验纳入患者分型及样本量分布图。研究的纳入标准可包含多个分期,绿色系列柱形为纳入患者疾病分期低于重型者;黄色系列柱形为纳入患者疾病分期低于危重型者;红色系列柱形为纳入患者疾病分期包含危重型者;蓝色系列柱形为纳入患者疾病分期包含康复后(恢复期)者。有1篇(样本量75人)未报告纳入的疾病分期

Figure 2 Classification and sample size of distribution patients included in the clinical trials. Inclusion criteria include multiple types of COVID-19. The green series of columns are those with milder stages than severe type. The yellow series of columns are those with milder stages than critical type. The red series of columns are those with critical type; the blue series of columns are those with stages including convalescence. One study (sample size 75) did not report the type of COVID-19

图3 各研究单位共现图。以“机构”为网络节点,生成135个节点,378条连线构成的研究机构合作共现图。图中点表示不同机构,连线表示机构间合作情况,连线越粗表示机构间合作密切程度越高

Figure 3 Co-occurrence of affiliations. Nodes represent affiliations, and lines represent cooperative relationships. The thicker the lines, the closer the cooperation between the affiliations. The cooperative co-occurrence of affiliations consisting of 135 nodes and 378 lines

等药物出现频次较高,将前20味高频出现的中药进行归纳,具体频次分布见图4。结合文献质量评价结果,质

量较高的6篇文献共涉及中药药物39味,高质量文献中的高频用药与全部文献结果相似(图4),主要包含苦杏

图 4 高频中药频次及关联规则网络示意图。(a) 高频出现的中药关联规则。点表示中药, 连线表示中药共同出现于一个复方, 连线越粗表示药物之间的关联越强。(b) 全部文献中高频出现的中药(排名前20)。(c) 高质量文献中高频出现的中药(排名前11)。(b), (c)中相同颜色对应的中药相同

Figure 4 High-frequency herbs and network association. (a) Association rules of herbs appear frequently. The nodes denote herbs, and lines denote the co-occurrence of herbs in a compound. The thicker the lines, the stronger the association between the herbs. (b) Herbs frequently appeared in all studies (top 20). (c) Herbs frequently appeared in high-quality studies (top 11). In (b) and (c), the herbs corresponding to the colors is the same

表 1 中医药干预COVID-19临床研究一览表^{a)}

Table 1 List of clinical trials of COVID-19 with Traditional Chinese Medicine (TCM)

文献	药物名称	临床研究注册号	随机化	基线资料情况	平均年龄(岁)	药物组成	服用方法	干预时间(d)	样本量(人)	不良反应	被引量(次)	文献质量评分
[9]	化湿败毒颗粒	ChiMCT-R2000002-940	随机对照(随机数表)	轻型-重型	56.00	麻黄、赤芍、石膏、苦杏仁、大黄、厚朴、黄芪、苍术、藿香、草果、茯苓、半夏、甘草、葶苈子	口服200 mL/次 bid	14	195	(-)	0	85
[8]	连花清瘟胶囊	CTRTR-C2000029-434	随机对照(随机数表)	普通型-重型	51.1	连翘、金银花、炙麻黄、苦杏仁、石膏、板蓝根、绵马贯众、鱼腥草、广藿香、大黄、红景天、薄荷脑、甘草	口服4粒/次 tid	14	284	(-)	62	84
[10]	藿香正气滴丸及连花清瘟颗粒	ChiCT-R2000029-601	随机对照(随机数表)	轻型-危重型	54.06	连花清瘟颗粒(见左)+苍术、陈皮、厚朴、白芷、茯苓、大腹皮、生半夏、紫苏叶油	藿香正气滴丸: 口服1袋/次 bid 连花清瘟颗粒: 口服1袋/次 tid	14	283	不详	5	80
[11]	克冠1号方	NC-T04251871	随机对照(随机数表)	普通型-重型	49.05	金银花、连翘、桑叶、菊花、薏苡仁、浙贝母、苦杏仁	口服200 mL/次 bid	14	47	(-)	2	74
[12]	宣肺败毒汤	ChiCT-R2000034-795	随机对照(根据住院次数及抛硬币随机化)	轻型-重型	59.62	麻黄、苦杏仁、石膏、苍术、薏苡仁、藿香、虎杖、葶苈子、马鞭草、芦根、青蒿、橘红、甘草	口服19.4 g/次 bid	7	42	(-)	3	74
[13]	寒湿疫方颗粒	ChiCT-R2000029-601	前瞻性非随机对照	轻型-普通型	48.39	麻黄、石膏、苦杏仁、羌活、葶苈子、贯众、地龙、徐长卿、藿香、佩兰、苍术、茯苓、白术、山楂、麦芽、厚朴、槟榔、草果、生姜	口服	>2	296	不详	2	70

a) 此表仅列改良Chalmers评分大于70分的临床研究; (-)为对照组与试验组(中医药干预组)不良反应无统计学意义; 服用方式中bid为每日2次, tid为每日3次样本量(人)指用于统计分析的病例数

仁、藿香、麻黄、石膏、甘草、苍术等药物。与中药关联规则网络图的提示意义一致(图4),该高频药物组合类似传统方剂麻杏石甘汤。中医药的临床研究在中药辨证用药选择上存在较高一致性。

轻型/普通型患者的用药与重型/危重型患者的中药用药方案无明显差异,但恢复期与患病期的中药用药方案存在差异。患病期的临床分型与中医辨证治疗无明显相关性,是否处于疾病恢复期与中医辨证治疗具有一定的相关性。

在观察结局指标的选择上,受到关注的结局(图5)依次为:主症(包括发热、干咳、乏力)的改善情况(27篇, 57.45%)、其他症状(包括咳嗽、胸闷、腹泻等)的改善情况(18篇, 38.30%)、普通型进展为重型率(18篇, 38.30%)、病毒核酸检测转阴率(10篇, 21.28%)。辅助检查中受关注的为:胸部CT的影像学改善情况(22篇, 46.81%),实验室指标中的白细胞总数变化(17篇, 36.17%)、淋巴细胞总数变化(16篇, 34.04%)、超敏C反应蛋白降低情况(15篇, 31.91%),部分文章也对照了凝血相关指标(D-dimer、PT、APTT等)、免疫相关指标(IL-6、IL-8、CD4⁺、CD8⁺等)及肝肾功能等。辅助检查中,白细胞总数变化虽最受关注,但其中10篇提示,中医药组较对照组白细胞总数的变化无统计学差异。21项研究(44.68%)关注了不良反应发生率,其中20篇显示中药组不良反应与对照组无统计学差异,中医药的

安全性良好。以“三方三药”为干预方式的研究共14篇,结局及不良反应情况可见图5。

3 讨论

本研究通过文献计量方法,分析了已发表的中医药防治新冠肺炎临床研究证据的现状。所纳入文献的收稿时间集中于2020年3月,集中报告了湖北新冠肺炎疫情暴发期间的中医药治疗效果^[18]。文献发表较为及时,为之后的新冠肺炎中西医结合临床防治提供了循证依据。

纳入的研究中随机对照试验数量接近半数,反映出中医药临床研究人员对随机对照试验重要性的重视,但结合疫情复杂的临床救治情况及规范盲法、安慰剂的实施困难,研究者在涉及研究及报告过程可能过度追求循证证据级别而忽略了研究方案的规范实施^[19]。不合理的随机化、盲法与分配隐藏的缺失会增加偏倚,同时实施干预、获取结局指标及统计学处理的合理性应受到重视。本次改良Chalmers评分结果显示,部分研究未进行样本量估算或纳入样本量过小,纳入标准对受试者年龄范围、合并症等定义不清,未实施分配隐藏与盲法、未对基线情况进行全面的统计学比较等问题仍存在。非随机对照研究中,回顾性研究数量多于前瞻性研究,可能造成部分临床数据的缺失及回忆偏倚^[20]。全部已发表的临床研究文献中有12篇标有注册

图5 中医药临床研究中受关注的结局及不良反应示意图。(a)以“三方三药”为干预中药的研究中对各结局的报告频次;(b)全部临床对照研究中对各结局的报告频次

Figure 5 Outcomes and adverse reactions of concern in clinical trials with TCM. (a) Frequency of outcomes in studies involving “three drugs and three perceptions” as intervention; (b) frequency of outcomes in all clinical studies

信息,多数临床研究的预注册意识不足,提示中医药临床研究实施的规范性有待提高。多数文献被引量低,特别是外国学者引用方面,提示国外对于中医药干预COVID-19临床疗效的认可度有待提高。高质量研究、经注册的临床研究与整体研究的中医药治疗内容相似,提示中医药治疗原则存在一致性。中医药的人用经验^[21]可为中医药循证医学提供证据或导向。

中医药被广泛应用于各临床分型及严重程度的COVID-19,多数用于轻型及普通型患者,其治疗优势群体值得进一步研究。高频的观察结局中普通型转为重型率、病毒核酸转阴率、临床症状的缓解率、实验室指标及CT的影像学改变等项目可量化,造成偏倚的可能性较小,在一定程度反映了中医药的临床治疗效果^[22]。值得关注的是,多项临床研究发现,中医药对于临床症状的缓解率较对照组显著提高。在新冠肺炎疫情巨大压力下,发热、咳嗽、乏力等新冠肺炎患者常见临床症状较快的缓解对于减轻医疗工作者和患者的压力具有重要的意义。以上试验表明,中医药具有良好安全性。

观察结果的选择有助于探索潜在的药理机制,实验室指标中最受关注的为白细胞总数、淋巴细胞总数、C反应蛋白的变化^[7,12,23-25]。细胞因子及凝血相关指标在本次纳入的文献中报道较少,但有研究提示,中医药组在降低TNF- α 、IL-6、CD4⁺等水平上具有统计学意义^[6,26]。目前已上市的抗病毒药物对COVID-19未加快临床恢复速度、降低病死率^[27],而麻杏石甘汤、连花清瘟胶囊等中药在COVID-19的治疗及其他流行性感胃中对临床症状改善作用明确,其机制是多途径的。目前细胞因子风暴被证实与COVID-19的严重程度相关^[28],以上中药复方网络药理学提示,参与氧化还原酶活性、脂质代谢过程、脂质结合过程、小分子代谢过程、动态平衡过程、多个炎症相关通路^[29-31],参与白细胞介导的免疫途径、干扰素 γ 介导的信号传导途径、免疫应答调节信号传导途径、白介素介导的信号传导途径和Fc γ 受体介导的吞噬作用,以上富集的通路均与细胞因子风暴^[32]密切相关。“三方三药”作为重点方药,存在可能的特异性靶标超过250个,有效活性化

合物超过150个,活性化合物槲皮素、山奈酚等最受关注^[29,30,33],二者均广泛存在于多种植物如麻黄、甘草等中。另一方面,D-dimer作为预测COVID-19的风险因素^[34],中医药干预后下降水平具有统计学意义^[35,36]。中医药干预后多种细胞因子及D-dimer的变化,提示中医药在多种途径上改善COVID-19的结局。

中医药干预组共计出现66个不同的中药复方,其中多数复方主要功效均为解表,出自中医经典名方(如麻杏石甘汤、藿朴夏苓汤、藿香正气散等)或已上市的中成药(金花清感颗粒、连花清瘟胶囊等)。传统中医理论对疫病(传染性疾病)有系统论述,本次疫情同样以“疫戾之气”为害。病毒在肺、消化道、皮肤组织上的高表达^[37],印证了“肺与大肠相表里”、“肺主皮毛”等理论。温病多自口鼻而入,症状变化迅速,外感温邪,肺宣降失调致气机郁结化热、水液盈虚失度,出现发热咳嗽、痰涎壅盛等症。疫情中方剂多具有清热解表、化湿祛痰(消除致病因素)、宣肺理气(调理脏腑功能)等作用。高频中药的四气五味不尽相同,麻黄、杏仁、藿香等药性为温性,仍广泛用于清热解表类方剂,提示中医“解表”理论具有独立于寒温的内涵,同时中药通过配伍发挥更大作用,如麻杏石甘汤中石膏与麻黄配伍可提升脏腑郁热的功效,另一方面减轻麻黄发汗的作用。连花清瘟胶囊/颗粒的研究数量最多,可能的原因为该药上市时间较久,便于短期内大量投入临床使用及组织开展临床研究。研究结果提示,该药在改善COVID-19的各项结局上临床效果较稳定^[8]。

中国政府对于新冠肺炎疫情的防治取得了积极成效,中西医结合在其中扮演了重要的角色。但多地区、多单位、中西医合作研究成果的不足提示,未来应从长远规划,加强中医药防治传染病人才队伍建设,培养高水平复合型中医药防治传染病人才,强化中西医优势合作,根据各地实际情况加强传染病医院、生物安全防护三级实验室(P3实验室)等防治机构的中医药平台搭建。进一步规范中医药临床循证研究的实施,对于提升中医药防治急性、突发传染病的临床与循证研究水平,具有重要的现实意义。

参考文献

- Gillespie T R, Leendertz F H. COVID-19: Protect great apes during human pandemics. *Nature*, 2020, 579: 497
- COVID-19 Collaborating Group, Institute of Clinical Basic Medicine of Traditional Chinese Medicine, China Academy of Chinese Medical Sciences. Evidence-based Traditional Chinese Medicine treatment recommendations for COVID-19 (in Chinese). *Chin Med J*, 2020, 21: 1611-1616
[中国中医科学院中医临床基础医学研究所新型冠状病毒肺炎协作组. 基于循证的新型冠状病毒肺炎中医治疗建议. 中华医学杂志, 2020,

- 21: 1611–1616]
- 3 Yu M K, Chai Q Y, Liang C H, et al. Summary analysis of TCM prevention and treatment plan of COVID-19 (in Chinese). *J Trad Chin Med*, 2020, 5: 383–387 [于明坤, 柴倩云, 梁昌昊, 等. 新型冠状病毒肺炎中医预防及诊疗方案汇总分析. *中医杂志*, 2020, 5: 383–387]
 - 4 Guo P F, Zhang Y B, Xu L J, et al. Integrated network pharmacology and molecular docking techniques to explore the molecular mechanism of “Three Drugs Three Prescriptions of Traditional Chinese Medicine” core drug group against COVID-19 (in Chinese). *World J Tradit Chin Med* (serial online), 2021, <http://kns-cnki-net-https.cnki.gzzyy.qfcl.com:2222/kcms/detail/11.5529.R.20201019.1640.002.html> [郭鹏飞, 张永斌, 许律捷, 等. 整合网络药理学和分子对接技术探讨“三药三方”核心药组防治COVID-19的分子机制研究. *世界中医药*, 2021, <http://kns-cnki-net-https.cnki.gzzyy.qfcl.com:2222/kcms/detail/11.5529.R.20201019.1640.002.html>]
 - 5 Chen J, Lin S, Niu C, et al. Clinical evaluation of Shufeng Jiedu Capsules combined with umifenovir (Arbidol) in the treatment of common-type COVID-19: A retrospective study. *Expert Rev Respir Med*, 2021, 15: 257–265
 - 6 Zhao J, Yang X, Wang C, et al. Yidu-toxicity blocking lung decoction ameliorates inflammation in severe pneumonia of SARS-COV-2 patients with Yidu-toxicity blocking lung syndrome by eliminating IL-6 and TNF- α . *Biomed Pharmacother*, 2020, 129: 110436
 - 7 Xin S, Cheng X, Zhu B, et al. Clinical retrospective study on the efficacy of Qingfei Paidu decoction combined with Western medicine for COVID-19 treatment. *Biomed Pharmacother*, 2020, 129: 110500
 - 8 Hu K, Guan W J, Bi Y, 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
 - 9 Liu J, Yang W, Liu Y, et al. Combination of Hua Shi Bai Du Granule (Q-14) and Standard Care in the Treatment of Patients with Coronavirus Disease 2019 (COVID-19): A Single-center, Open-label, Randomized Controlled Trial. *Phytomedicine*, 2021, <https://doi.org/10.1016/j.phymed.2021.153671>
 - 10 Xiao M, Tian J, Zhou Y, et al. Efficacy of Huoxiang Zhengqi dropping pills and Lianhua Qingwen granules in treatment of COVID-19: A randomized controlled trial. *Pharmacol Res*, 2020, 161: 105126
 - 11 Wang J B, Wang Z X, Jing J, et al. Exploring an integrative therapy for treating COVID-19: A randomized controlled trial. *Chin J Integr Med*, 2020, 26: 648–655
 - 12 Xiong W Z, Wang G, Du J, et al. Efficacy of herbal medicine (Xuanfei Baidu decoction) combined with conventional drug in treating COVID-19: A pilot randomized clinical trial. *Integr Med Res*, 2020, 9: 100489
 - 13 Tian J, Yan S, Wang H, et al. Hanshiyi Formula, a medicine for SARS-CoV2 infection in China, reduced the proportion of mild and moderate COVID-19 patients turning to severe status: A cohort study. *Pharmacol Res*, 2020, 161: 105127
 - 14 Yu P, Li Y Z, Wan S B, et al. Efficacy observation of Lianhua Qingwen granules combined with Abidol in the treatment of mild COVID-19 (in Chinese). *Chin Pharm J*, 2020, 55: 1042–1045 [余平, 李叶子, 万少兵, 等. 连花清瘟颗粒联合阿比多尔治疗轻度新型冠状病毒肺炎的疗效观察. *中国药理学杂志*, 2020, 55: 1042–1045]
 - 15 Cheng D Z, Wang W J, Li Y, et al. Effect analysis of Lianhua Qingwen Capsules in 51 patients with COVID-19: A multi-center retrospective study (in Chinese). *Tianjin J Trad Chin Med*, 2010, 37: 509–516 [程德忠, 王文菊, 李毅, 等. 51例新型冠状病毒肺炎患者应用中药连花清瘟胶囊疗效分析: 多中心回顾性研究. *天津中医药*, 2010, 37: 509–516]
 - 16 Liu L L, Yuan L F, Feng Y, et al. Clinical observation of Abidol combined with Lianhua Qingwen Capsule in the treatment of COVID-19 (in Chinese). *Tianjin J Trad Chin Med*, 2010, 41: 1207–1210 [柳丽丽, 袁连方, 冯毅, 等. 阿比多尔联合连花清瘟胶囊治疗新型冠状病毒肺炎的临床观察. *天津中医药*, 2010, 41: 1207–1210]
 - 17 Pharmacopoeia Commission of the People’s Republic of China. *Pharmacopoeia of the People’s Republic of China* (in Chinese). Volume 1. Beijing: China Medical Science Press, 2020. 3–259 [国家药典委员会. *中华人民共和国药典*. 一部. 北京: 中国医药科技出版社, 2020. 3–259]
 - 18 Yang Z, Zeng Z, Wang K, et al. Modified SEIR and AI prediction of the epidemics trend of COVID-19 in China under public health interventions. *J Thorac Dis*, 2020, 12: 165–174
 - 19 Chinese Medical Doctor Association Integrated Chinese and Western Medicine Physicians Branch, Chinese Association of Integrated Chinese and Western Medicine Evidence-based Medicine Professional Committee. Guidelines for clinical research methods of TCM and integrated Traditional Chinese and western medicine (in Chinese). *Chin J Integr Trad West Med*, 2015, 35: 901–932 [中国医师协会中西医结合医师分会, 中国中西医结合学会循证医学专业委员会. *中医药与中西医结合临床研究指南*. *中国中西医结合杂志*, 2015, 35: 901–932]
 - 20 Blome C, Augustin M. Measuring change in quality of life: Bias in prospective and retrospective evaluation. *Value Health*, 2015, 18: 110–115
 - 21 Chen X, Shen L, Bai D. Key issues and reflections of medical institution preparation in the research and development of empirical Traditional Chinese Medicine for human use (in Chinese). *Chin J New Drugs*, 2020, 29: 1830–1835 [陈旭, 申琳, 柏冬. 医疗机构制剂在人用经验中药创新药研发的关键问题与思考. *中国新药杂志*, 2020, 29: 1830–1835]
 - 22 Luo X, Ni X, Lin J, et al. The add-on effect of Chinese herbal medicine on COVID-19: A systematic review and meta-analysis. *Phytomedicine*, 2021, 85: 153282
 - 23 Shi N, Guo L, Liu B, et al. Efficacy and safety of Chinese herbal medicine versus Lopinavir-Ritonavir in adult patients with coronavirus disease

- 2019: A non-randomized controlled trial. *Phytomedicine*, 2021, 81: 153367
- 24 Wen L, Zhou Z G, Jiang D X, et al. Observation of inflammatory markers and outcome in patients with severe COVID-19 using the Xuebijing injection (in Chinese). *Chin Crit Care Med*, 2020, 32: 426–429 [文隆, 周志国, 姜迪譔, 等. 血必净注射液对重型新型冠状病毒肺炎患者炎症指标及病情转归的疗效观察. *中华危重病急救医学*, 2020, 32: 426–429]
- 25 Fan A Y, Gu S, Alemi S F. Chinese herbal medicine for COVID-19: Current evidence with systematic review and meta-analysis. *J Integr Med*, 2020, 18: 385–394
- 26 Fu X X, Lin L P, Tan X H. Clinical study of 37 cases using integrated Traditional Chinese and western medicine for COVID-19 (in Chinese). *Trad Chin Drug Res Clin Pharm*, 2020, 31: 600–604 [傅晓霞, 林路平, 谭行华. 中西医结合治疗新型冠状病毒肺炎37例临床研究. *中药新药与临床药理*, 2020, 31: 600–604]
- 27 Gao W J, Wang B, Lü Y, et al. Current prevalence of COVID-19 and development of countermeasures (in Chinese). *Chin J Epidemiol*, 2021, 42: 22–27 [高文静, 王波, 吕筠, 等. 新型冠状病毒肺炎流行现状及应对策略进展. *中华流行病学杂志*, 2021, 42: 22–27]
- 28 Tang Y, Liu J, Zhang D, et al. Cytokine storm in COVID-19: The current evidence and treatment strategies. *Front Immunol*, 2020, 11, <https://doi.org/10.3389/fimmu.2020.01708>
- 29 Tao Q, Du J, Li X, et al. Network pharmacology and molecular docking analysis on molecular targets and mechanisms of Huashi Baidu formula in the treatment of COVID-19. *Drug Dev Ind Pharm*, 2020, 46: 1345–1353
- 30 Xia Q D, Xun Y, Lu J L, et al. Network pharmacology and molecular docking analyses on Lianhua Qingwen capsule indicate Akt1 is a potential target to treat and prevent COVID-19. *Cell Prolif*, 2020, 53: e12949
- 31 Chen J, Wang Y K, Gao Y, et al. Protection against COVID-19 injury by Qingfei Paidu decoction via anti-viral, anti-inflammatory activity and metabolic programming. *Biomed Pharmacother*, 2020, 129: 110281
- 32 Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Resp Med*, 2020, 8: 420–422
- 33 Yu S, Wang J, Shen H. Network pharmacology-based analysis of the role of Traditional Chinese herbal medicines in the treatment of COVID-19. *Ann Palliat Med*, 2020, 9: 437–446
- 34 Li Y, Zhao K, Wei H, et al. Dynamic relationship between D-dimer and COVID-19 severity. *Br J Haematol*, 2020, 190: e24–e27
- 35 Ai X Y, Luo C, Lin L P, et al. Efficacy of integrated Traditional Chinese and western medicine for COVID-19 in Guangzhou (in Chinese). *Chin J Trop Med*, 2020, 20: 746–750 [艾香英, 罗纯, 林路平, 等. 广州市新型冠状病毒肺炎中西医结合治疗疗效. *中国热带医学*, 2020, 20: 746–750]
- 36 Lian J, Zhang S J, Li G L, et al. Retrospective analysis of 1938 cases of COVID-treated by integrated Traditional Chinese and western medicine (in Chinese). *J Trad Chin Med*, 2020, 61: 2126–2130 [连捷, 张树军, 李国林, 等. 中西医结合治疗新型冠状病毒肺炎38例回顾性分析. *中医杂志*, 2020, 61: 2126–2130]
- 37 Ding Y Q, Bian X W. An analysis of some problems of novel coronavirus disease 2019 (COVID-19) based on the results of SARS autopsy (in Chinese). *Chin J Pathol*, 2020, 49: 291–293 [丁彦青, 卞修武. 从SARS尸体解剖发现, 浅析新型冠状病毒感染疾病(COVID-19)的若干问题. *中华病理学杂志*, 2020, 49: 291–293]

补充材料

表S1 改良的Chalmers量表

本文以上补充材料见网络版csb.scichina.com. 补充材料为作者提供的原始数据, 作者对其学术质量和内容负责.

Summary for “新型冠状病毒肺炎的中医药临床研究: 基于文献计量学分析的解读与思考”

Clinical trials for Traditional Chinese Medicine against coronavirus disease 2019 (COVID-19): Interpretation based on bibliometric analysis

Yiwen Li^{1,2†}, Yue Liu^{1,2†}, Cheng Lü³, Hongjun Yang⁴, Keji Chen^{1*} & Luqi Huang^{2,4*}

¹ National Clinical Research Center for Cardiovascular Diseases of Traditional Chinese Medicine, Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing 100091, China;

² China Center for Evidence-based Medicine of Traditional Chinese Medicine, China Academy of Chinese Medical Sciences, Beijing 100700, China;

³ Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing 100700, China;

⁴ China Academy of Chinese Medical Sciences, Beijing 100700, China

† Equally contributed to this work

* Corresponding authors, E-mail: kjchenvip@163.com; huangluqi01@126.com

The coronavirus disease 2019 (COVID-19) has been spreading worldwide, posing a significant threat to human health. Currently, vaccines are available, but there is still no reliable cure for this disease. Traditional Chinese Medicine (TCM) has played an important role in addressing this epidemic, and several clinical studies have emerged regarding treatments for COVID-19 by TCM; status of those treatments, and patterns regarding these are worth summarizing and interpreting systematically. A comprehensive search of clinical trials was performed in various platforms, including PubMed, Embase, Web of Science, medRxiv, China National Knowledge Infrastructure, WanFang Data, and SinoMed, from January 1, 2020 to March 1, 2021. Analyzed information included language, received date, quantity, citations, affiliation, number of authors, research type (randomized controlled trial or non-randomized controlled trial), trial registry information, disease severity, sample size, specific interventions, outcomes, and adverse reactions, among others. Based on the aforementioned information, a quantitative and qualitative literature analysis was done. A total of 47 articles were retrieved, most of which were published in Chinese (42 articles, 89.36%). Based on the results of the number of trial registrations (12 articles), the number of citations (the maximum for a single article was 62), and the modified Chalmers scale (total: 100 points, average: 61.40 points), the overall study quality still needs improvement. Most patients presented with the mild and common type of COVID-19 and were recruited in Hubei Province, while researchers from these studies were from all over the country (135 institutions). TCM interventions included 66 different formulas and 134 herbs, of which *Armeniacae semen amarum* (Kuxingren), *Agastache rugosa* (Huoxiang), *Ephedra sinica* stapf (Mahuang), *Gypsum fibrosum* (Shigao), *Glycyrrhizae radix et rhizome* (Gancao), and *Gtractylodes rhizoma* (Cangzhu) appeared at high frequencies. Highlighted outcomes from these studies included the following: Clinical symptoms (fever, cough, fatigue, etc.), progression rate from normal stage to heavy stage, laboratory indices including leukocyte and lymphocyte counts, and c-reactive protein levels, imaging diversity of lung computed tomography (CT), and recorded adverse reactions. With a certain number of published clinical trials, the landscape of TCM clinical trials for COVID-19 was established. Most studies have a relatively low quality and impact, and standardized implementation of evidence-based research in TCM was lacking. The mainstay TCM treatment for COVID-19 involved clearing heat, releasing the exterior, and resolving its dampness. Additionally, the Maxing Shigan Decoction was one of the most common classical prescriptions for COVID-19, and the “three drugs and three perceptions” were also widely used. Some symptoms, laboratory indicators, and imaging diversity of lung CT were found to have significantly improved after taking these decoctions. Overall, TCM is safe, and no serious adverse reactions have been reported. Through multiple mechanisms, TCM has shown great clinical effects, but its underlying mechanisms and patterns should be further explored. It is of great practical significance to enhance the level of clinical and evidence-based research for TCM application in the prevention and treatment of acute and emergent infectious diseases. Furthermore, such research will help strengthen clinical expertise in this field and further standardize the implementation of evidence-based TCM medical research.

COVID-19, Traditional Chinese Medicine, clinical trials, bibliometrics

doi: [10.1360/TB-2021-0125](https://doi.org/10.1360/TB-2021-0125)