Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Efficacy and Safety of Integrated Traditional Chinese and Western Medicine for Corona Virus Disease 2019 (COVID-19): a systematic review and meta-analysis

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ABSTRACT

Corona virus disease (COVID-19) has now spread to all parts of the world and almost all countries are battling against it. This study aimed to assess the efficacy and safety of Integrated Traditional Chinese and Western Medicine (Hereinafter referred to as "Integrated Medicine") to COVID-19. We searched six major Chinese and English databases to identify randomized controlled trials (RCTs) and case-control studies (CCSs) of Integrated Medicine on COVID-19. Two reviewers independently screened, identified studies, and extracted data. Cochrane Risk of Bias tool and the Newcastle-Ottawa Scale were used to assess the quality of included RCTs and CCSs, respectively. Stata (version 13.0; StataCorp) was used to perform meta-analyses with the random-effects model. Risk ratio (RR) was used for dichotomous data while the weighted mean difference (WMD) was adopted for continuous variables as effect size, both of which were demonstrated in effect size and 95% confidence intervals (CI). A total of 11 studies were included. Four were RCTs and seven were CCSs. The sample size of including studies ranged from 42 to 200 (total 982). The traditional Chinese medicine included Chinese medicine compound drugs (QingFei TouXie FuZhengFang) and Chinese patent medicine (e.g. Shufeng Jiedu Capsule, Lianhua Qingwen granules). Compared with the control group, the overall response rate [RR = 1.230, 95%CI (1.113, 1.359), $P = 0.000$], cure rate [RR = 1.604, 95%CI (1.181, 2.177), $P = 0.002$], severity illness rate [RR = 0.350, 95%CI (0.154, 0.792), $P = 0.012$], and hospital stay [WMD = -1.991, 95%CI (-3.278, -0.703), $P = 0.002$] of the intervention group were better. In addition, Integrated Medicine can improve the disappearance rate of fever, cough, expectoration, fatigue, chest tightness and anorexia and reduce patients' fever, and fatigue time ($P < 0.05$). This review found that Integrated Medicine had better effects and did not increase adverse drug reactions for COVID-19. More high-quality RCTs are needed in the future.

Abbreviations: COVID-19, Corona Virus Disease 2019; NCP, Novel Coronavirus Pneumonia; SARS-CoV-2, Severe Acute Respiratory Syndrome CoronaVirus-2; α-INF, alpha-interferon; TCM, Traditional Chinese Medicine; WBC, White blood cell; CRP, C-Reactive Protein; TNF-a, Tumor Necrosis Factor-α; RCTs, Randomized Controlled Trials; CCSs, Case-Control Studies; RoB, Risk of Bias; NOS, Newcastle-Ottawa Scale; RR, Risk Ratio; WMD, Weighted Mean Difference; CI, Confidence Intervals

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1. Introduction

As a member of coronavirus subfamily Coronaviridae, the coronavirus can infect human beings, many kinds of mammals and birds. Some coronavirus can spread between humans, livestock, and poultry. In December 2019, many cases of Novel Coronavirus Pneumonia (NCP) patients have appeared in Wuhan, Hubei, China [1]. The cause is possibly related to contact with a local fish and wild animal market (Huanan Seafood Wholesale Market). WHO named it as Coronavirus Disease 2019 (COVID-19), and the International Classification Committee named the virus as Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2) [2,3]. So far, although transmission in China has been gradually controlled, the rate of infections outside China is rising rapidly, especially in the United States, Italy, and Spain. Till 27 March 2020, about 531,806 cases of COVID-19 and 24,073 deaths have reported [4]. The COVID-19 has posed significant threats to international health. So the effective prevention and treatment of COVID-19 are a very urgent task.

1.1. Western medicine for COVID-19

China has accumulated a lot of experience in prevention, diagnosis, and treatment of COVID-19. So far, China has issued seven versions of COVID-19 clinical guidelines (Trial Version). According to the latest seventh edition, the treatments of COVID-19 still don't have specific medicine [5]. The treatment of COVID-19 involves multiple disciplines, and the current recommendations are mainly based on Western Medicine including supportive care, respiratory assisted ventilation, antiinfection (mainly antiviral agents), and glucocorticoid therapy [5]. Suggested antiviral agents are alpha-interferon (a-INF), lopinavir, ribavirin, chloroquine phosphate, and abidol. At present, there is no evidence to support the general or routine use of Western Medicine, nor is there any evidence to prove the risks and benefits of Western Medicine for COVID-19.

1.2. Integrated Traditional Chinese and Western Medicine for COVID-19

Traditional Chinese Medicine (TCM) has a history of thousands of years and has saved the Chinese from major infectious diseases on many occasions. Now, TCM has been practiced worldwide. During the SARS epidemic in 2003, TCM played a huge role [6–8]. COVID-19 belongs to the category of "Pestilence" in TCM. Its main clinical manifestations are fever, fatigue, dry cough, and the disease is situated in the lung and related to the spleen, stomach, and heart. Like the SARS period, TCM played a major role in the "Fight against the Pestilence in China", saving many people's lives [5,9,10]. Existing evidence showed that compared with the simple treatment of Western Medicine; Integrated Traditional Chinese and Western Medicine (Hereinafter referred to as "Integrated Medicine") for COVID-19 may have better effects [11–15]. However, these studies have small sample sizes, and no convincing evidence is available to demonstrate the benefits and risks of Integrated Medicine for COVID-19.

This study summarized controlled trials and methods of Integrated Medicine treatment of COVID-19, including the changes of clinical symptoms. The secondary objective is to investigate the changes of laboratory indicators and the safety of Integrated Medicine of COVID-19.

2. Materials and Methods

This meta-analysis was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16]. In addition, we also performed this study according to some other methodological study on meta-analysis [17–19]. The protocol for this study has been registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42020177097).

2.1. Literature search

A pre-developed search strategy was used to identify all relevant clinical trials, regardless of languages or types of publication (excluded unpublished trials). We searched the following six databases: PubMed, Embase.com, Cochrane Library, CNKI (China National Knowledge Infrastructure), WanFang and CBM (Chinese Biomedical Database). The search time was limited from December 01, 2019 to March 24, 2020. Search terms included "traditional Chinese medicine", "Western medicine", "Integrated traditional Chinese and Western medicine", "novel coronavirus pneumonia", "2019-nCoV", "COVID-19", "SARS-CoV-2" and "NCP". The search strategy of the PubMed database is presented in Appendix Table 1.

2.2. Inclusion criteria and study selection

Inclusion criteria: (1) Patients: confirm diagnosed COVID-19 patients (Age ≥ 18 years) by laboratory; (2) Intervention: patients in treatment groups were given TCM therapy in addition to the baseline medication similar to the control group (the TCM therapy included Chinese medicine compound drugs, Chinese patent medicine); (3) Comparison: the patients of the control group were given modern Western conventional treatments; (4) Outcomes: a. clinical efficacy (e.g. overall response rate, cure rate, hospital stay), b. clinical symptoms (e.g. fever, cough, expectoration, fatigue, myalgia), c. laboratory indicators (e.g. lymphocyte percentage, white blood cell (WBC) count, C-reactive protein (CRP), tumor necrosis factor-α (TNF-a)), d. adverse drug reactions (e.g. nausea and vomit, diarrhea, liver damage); (5) Study types: randomized controlled trials (RCTs) and case-control studies (CCSs) were included. This followings were excluded: review, abstract, letter, case reports, case series reports, and animal experiments.

Two reviewers independently screened the title/abstract of each record by the inclusion criteria. For the indistinguishable record of the title/abstract, we retrieved the full text for further assessment. Finally, resolve any disagreements through discussion between two reviewers or consultation with a third reviewer.

2.3. Data extraction and quality assessment

A pre-designed data form was used to extract the relevant information, including the author, journal, study type, study location, study time, interventions, the dose of drugs, and outcomes. Primary outcomes including the clinical efficacy and the changes of clinical symptoms, such as cure rate, total effective rate, nausea disappearance rate, fever disappearance rate, and fatigue disappearance rate. Second outcomes including the changes of laboratory indicators and the safety of Integrated Medicine of COVID-19, such as CRP, TNF-α, WBC count, liver damage and diarrhea. The Risk of Bias (RoB) assessment tool from the Cochrane Handbook was used to assess the methodological quality of RCTs [20], and the Newcastle-Ottawa Scale (NOS) was used to assess the quality of CCSs [21]. Each RCT was assessed at low risk, high risk, or unclear risk relating to the following items: sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. The NOS assesses the quality of CCSs with eight questions in three broad categories: (1) patient selection; (2) comparability of study groups; (3) assessment of the outcome. The total score is 9, the higher the score, the better the quality of the study. Two reviewers independently completed the data extraction and quality assessment. Any disagreements between reviewers were resolved by discussion or consultation with a third reviewer.

2.4. Statistical analysis

Stata (version 13.0; StataCorp) was used to perform the statistical analysis. Risk ratio (RR) was used for dichotomous data while weighted

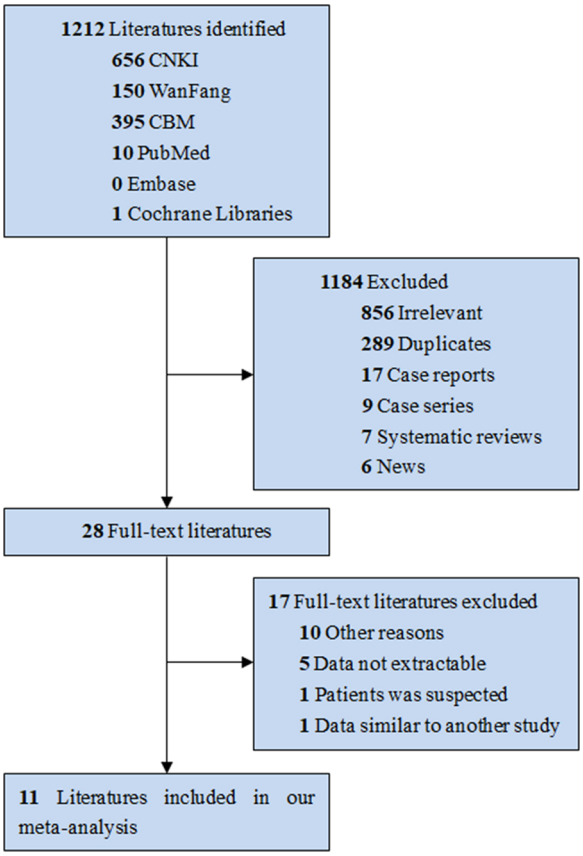

Fig. 1. Flow Diagram of Literature Search and Trial Selection.

mean difference (WMD) was adopted for continuous variables as effect size, both of which were demonstrated with effect size and 95% confidence intervals (CI). Considering heterogeneity of drugs used in different trials, we calculated all results based on the random effect model. We assessed statistical heterogeneity in each pairwise comparison with I^2 statistic, and value of < 25%, 25-50%, and > 50% considered as low, moderate, and high level of heterogeneity, respectively [22]. We would perform subgroup analyses and sensitivity analyses to explore sources of heterogeneity if enough data were available. The Egger's test and funnel plots were used to detect the potential publication bias if the number of included trials was larger than ten for an outcome. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Eligible studies

Fig. 1 showed the study selection process. A total of 11 studies were included in our study. All the articles were published by Chinese, among them, four studies were RCTs [12,23–25] and seven were CCSs [11,12,26–30].

The detail of included studies is shown in Table 1. Except for two studies that did not provide the range of study time [23,24], the study time was from January 01, 2020 to March 02, 2020. The sample size of the included studies ranged from 42 to 200 (total 982). The duration of treatment ranges from 5 to 30 days, with an average of 13.55 days. Two studies did not provide specific Chinese medicine compound drugs and Chinese patent medicine [11,13]. One studies intervention groups were Chinese medicine compound drugs (QingFei TouXie FuZhengFang) [24]. And the other studies were Chinese patent medicine (such as Shufeng Jiedu Capsule, Lianhua Qingwen granules). The drugs used in the control group were Lopinavir, Ribavirin, Arbidol and et al. In addition, both groups of patients received basic treatment, such as oxygen inhalation and nutritional support.

3.2. Study quality

The quality of the included RCTs is shown in Table 2 [12,23–25]. Four RCTs described the adequate random sequence generation process, but only one RCT [25] described the methods used for allocation concealment. Only one RCT [25] described the blinding of participants and personnel and blinding of outcome assessment (High risk), and none described how the incomplete outcome data were processed and reported selective outcome reporting. Overall, the quality of the included RCTs was low.

Seven CCSs were assessed for quality by the NOS [11,13,26–30]. The maximum quality score is 9 and the range of scores was 3 to 7 (Table 3), with a median of 6 (5.4 ± 1.4). Only one study did not report the case definition [13], and all study reported the definition of controls and comparability of cases and controls [11,13,26–30]. None of the studies reported representativeness of the cases and selection of controls [11,13,26–30]. The reporting for exposure was better, but only one study reported non-response rate [30]. These studies showed a moderate quality.

3.3. Clinical Efficacy

Four studies demonstrated the overall response rate: Integrated Medicine was better than Western Medicine alone [RR = 1.230, 95%CI (1.113, 1.359), $P = 0.000$] (Fig. 2). Four studies compared the cure rate of the COVID-19 between Integrated Medicine and Western Medicine. The outcome indicated the cure rate in Integrated Medicine was higher than Western Medicine (Fig. 3). The difference was statistically significant [RR = 1.604, 95%CI (1.181, 2.177), $P = 0.002$]. Besides, Integrated Medicine can reduce the severity of illness rate [RR = 0.350, 95%CI (0.154, 0.792), $P = 0.012$] (Fig. 4). And compared with Western Medicine treatment, the Integrated Medicine treatment can shorten the hospital stay [WMD = -1.991, 95%CI (-3.278, -0.703), $P = 0.002$] (Fig. 5).

3.4. Symptoms disappearance rate or time

We compared the effects of Integrated Medicine and Western Medicine on the clinical symptoms. The results showed that Integrated Medicine can better improve the symptoms disappearance rate and reduced the symptoms disappearance time than Western Medicine (Table 4). Except for the difference in myalgia and nausea is not statistically significant, Integrated Medicine significantly increased the disappearance rate of fever, cough, expectoration, fatigue, chest tightness and anorexia in patients ($P < 0.05$). In addition, Integrated Medicine can reduce patients' fever, and fatigue time ($P < 0.05$).

3.5. Laboratory indicators

Meta-analyses revealed that the Integrated Medicine was more beneficial to the recovery of laboratory indicators. We found that Integrated Medicine was beneficial for IFN-a [WMD = -3.13, 95%CI (-4.23, -2.04), $P = 0.000$] and lymphocyte percentage [WMD = 1.59, 95%CI (0.61, 2.58), $P = 0.002$] to return to normal. And these differences were statistically significant ($P < 0.05$). Besides, as for the CRP and WBC count, there were no significant differences between Integrated Medicine and Western Medicine ($P > 0.05$) (Table 5).

3.6. Adverse Drug Reaction

The common adverse drug reactions of Integrated Medicine were nausea and vomiting, diarrhea, liver damage, and reduced blood cell count. As showed in Table 6, there was no significant difference in the

Table 1
Characteristics of studies included in the meta-analysis.

First author	Type of study	Location of study	Rang of time (2020)	Type of disease	Samples(male)		Treatment		Duration
					Intervention	Control	Intervention	Control	
Zhou WM [23]	RCTs	ChangSha		Light	52(32)	52(28)	Diammonium glycyrrhizinate enteric coated capsules (150 mg,tid) + Lopinavir tablets(500 mg,bid)	Lopinavir tablets(500 mg,bid)	14d
Ding XJ [24]	RCTs	WuHan		Light/ Common/ Severe/ Critical	51(39)	49(39)	Qingfeitouxie fuzhengfang(150 ml,bid) + ifn-α(5 million U,bid) + Ribavirin(0.5 g,bid)	ifn-α(5 million U,bid) + Ribavirin(0.5 g,bid)	10d
Qu XK [26]	CCSs	HaoZhou	01.31～02.11	Light/ Common	40(25)	30(16)	Shufeng Jiedu Capsule(2.08 g,tid) + Arbidol(0.2 g,tid)	Arbidol(0.2 g,tid)	10d
Xia WG [11]	CCSs	WuHan	01.15～02.08	Common/ Severe/ Critical	34(17)	18(6)	Integrated Traditional Chinese and Western Medicine	Western Medicine	23d
Yao KT [27]	CCSs	WuHan	01.11～01.30	Common	21(16)	21(12)	Lianhua Qingwen granules(6 g,tid) + Western Medicine	Western Medicine	19d
Xiao Q [28]	CCSs	WuHan	01.24～01.30	Light/ Common	100(64)	100(66)	Shufeng Jiedu Capsule(2.08 g,tid) + Arbidol(0.2 g,tid)	Arbidol(0.2 g,tid)	14d
Cheng DZ [29]	CCSs	WuHan	01.01～01.30	Light/ Common	51(26)	51(27)	Lianhua Qingwen granules(6 g,tid) + Western Medicine	Western Medicine	7d
Shi J [13]	CCSs	ShangHai	01.01～02.01	Light/ Common/ Severe	49(26)	18(10)	Traditional Chinese Medicine	Western Medicine	30d
Yang MB [30]	CCSs	GuangZhou	01.21～03.02	Light/ Common	26(16)	23(9)	Reyanning mixture(10-20 ml,bid) + Lopinavir(100 mg,bid) + ifn-α(5 million U,bid) + abidol(0.2 g,tid) + ribavirin(0.5 g,bid)	Lopinavir(100 mg,bid) + ifn-α(5 million U,bid) + abidol(0.2 g,tid) + ribavirin(0.5 g,bid)	7d
Fu XX [12]	RCTs	GuangZhou	01.20～02.23	Common	37(19)	36(19)	Tongjiequwen granule formula(150 ml,bid) + Arbidol(0.2 g,tid)	Arbidol(0.2 g,tid)	10d
Duan C [25]	RCTs	WuHan	02.01～02.05	Light	82(39)	41(23)	Jinhua Qinggan granules(10 g,tid) + Western Medicine	Western Medicine	5d

Table 2
The risk of bias of included Randomized Controlled Trials.

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Fu XX [12]	L	U	U	U	U	U	U
Zhou WM [23]	L	U	U	U	U	U	U
Ding XJ [24]	L	U	U	U	U	U	U
Duan C [25]	L	L	L	H	U	U	U

H: High risk, L: Low risk, U: Unclear risk

Table 3
The quality of included Case-Control Studies.

Study	Is the Case Definition Adequate?	Representativeness of the Cases	Selection of Controls	Definition of Controls	Comparability of Cases and Controls	Ascertainment of Exposure	Use the same method to determine case and control exposure factors	Non-Response Rate	Total
Qu XK [26]	★			★	★★	★	★		6
Xia WG [11]	★			★	★★	★	★		6
Yao KT [27]	★			★	★★				4
Xiao Q [28]	★			★	★★	★	★		6
Cheng DZ [29]	★			★	★★	★	★		6
Shi J [13]				★	★★				3
Yang MB [30]	★			★	★★	★	★	★	7

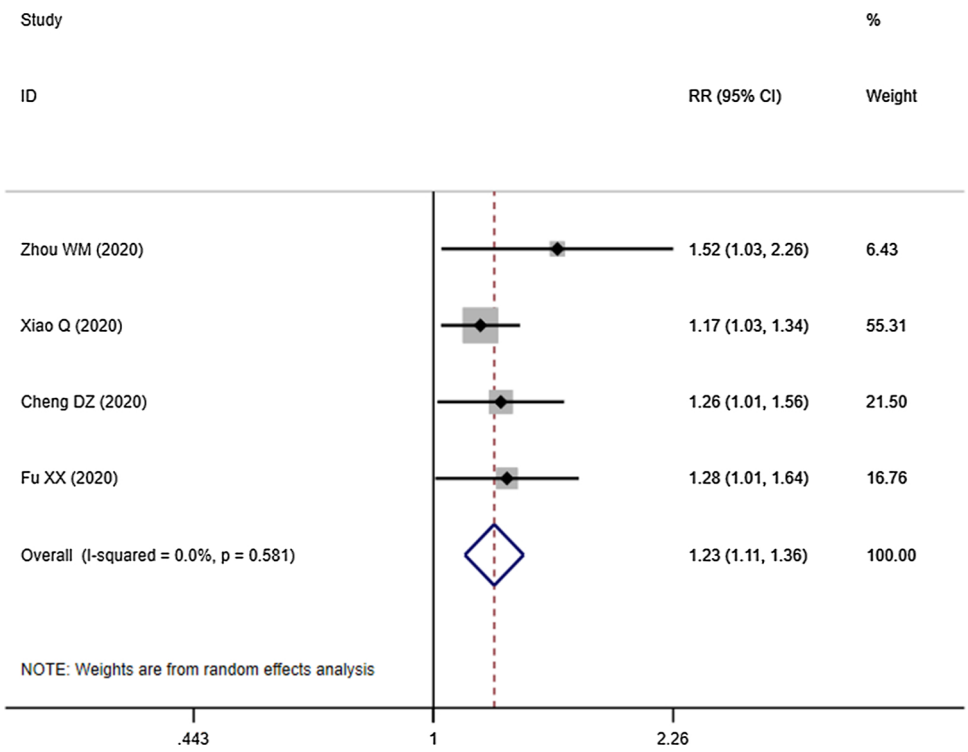

Fig. 2. Overall response rate of the COVID-19 between Integrated Medicine and Western Medicine.

adverse drug reactions caused by the two different interventions ($P > 0.05$).

3.7. Subgroup analysis of the primary outcomes

Results of subgroup analyses of the Chinese medicine compound drugs and Chinese patent medicine for the primary outcome were shown in Appendix Tables 2 and 3. When the Integrated Medicine included *Diammonium glycyrrhizinate enteric coated capsules*, it can improve the cure rate compared with Western Medicine ($P = 0.036$). *Lianhua Qingwen granules* can improv the total effective rate ($P = 0.037$), fever disappearance rate ($P = 0.003$), fatigue disappearance rate ($P = 0.032$), myalgia disappearance rate ($P = 0.025$), expectoration disappearance rate ($P = 0.004$), and chest tightness

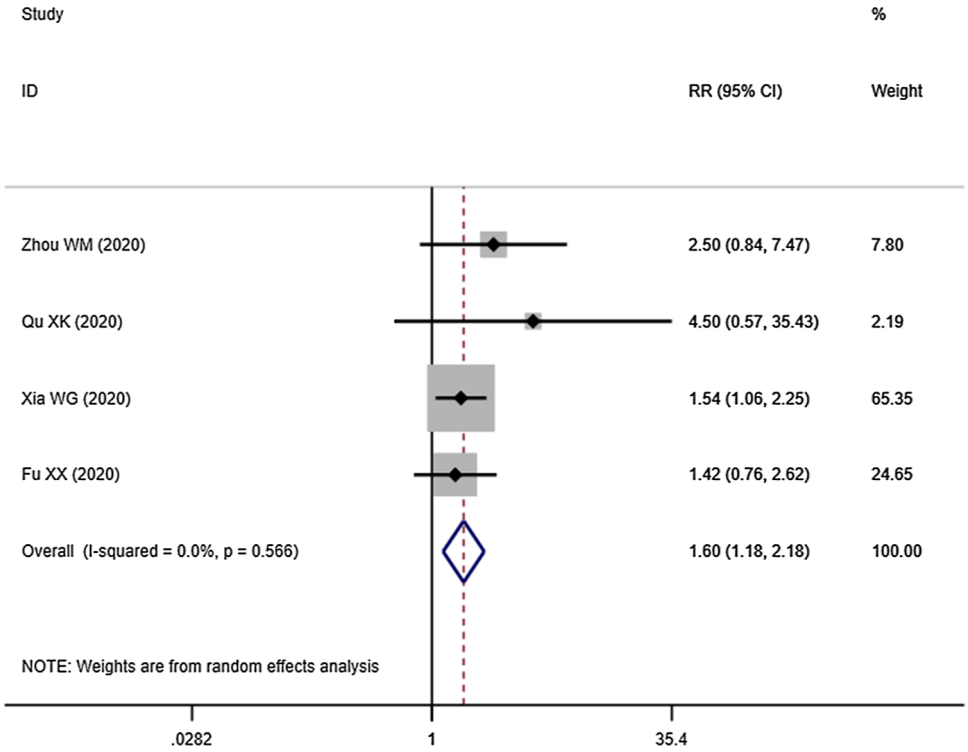

Fig. 3. Cure rate of the COVID-19 between Integrated Medicine and Western Medicine.

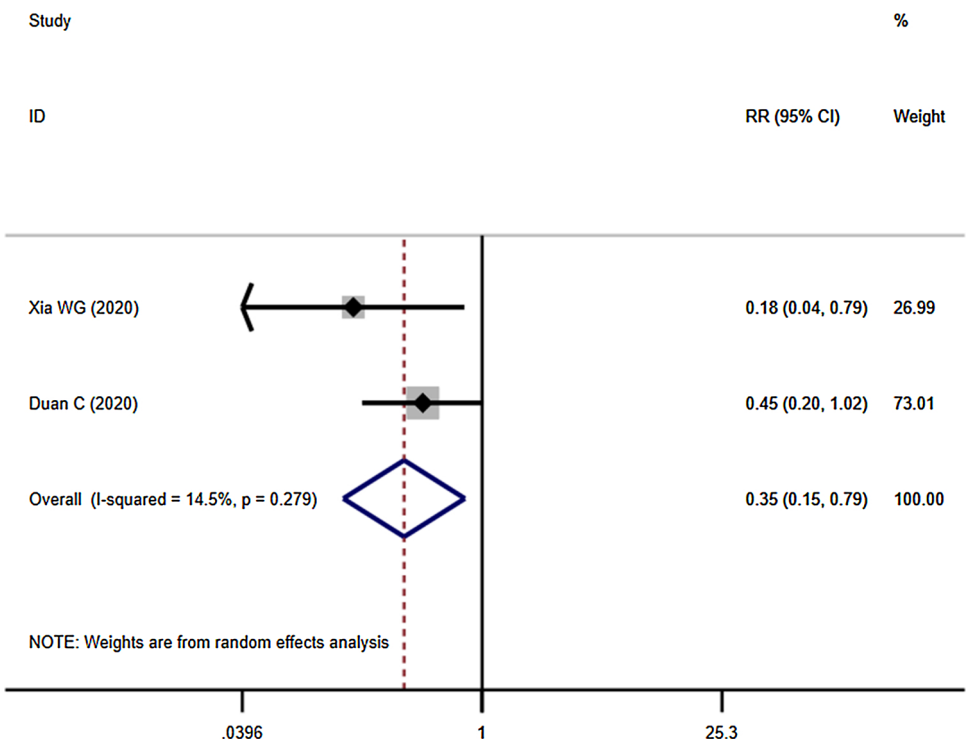

Fig. 4. Severity illness rate of the COVID-19 between Integrated Medicine and Western Medicine.

disappearance rate ($P = 0.007$). In addition, *Lianhua Qingwen granules* shorten the fever ($P = 0.01$), fatigue ($P = 0.02$), and cough ($P = 0.038$) time. *Shufeng Jiedu Capsule* can improvthe total effective rate ($P = 0.02$) and shorten the fever ($P = 0.003$) time. *Tongjiequwen granule formula* can improve the total effective rate ($P = 0.044$). *Jinhua Qinggan granules* can improve fever disappearance rate ($P = 0.02$), cough disappearance rate ($P = 0.023$), and expectoration disappearance rate ($P = 0.003$). *Qingfeitouxie fuzhengfang* can improve cough disappearance rate ($p = 0.032$) and chest tightness disappearance rate ($P = 0.025$).

3.8. Publication bias

Since the number of studies in any comparative analysis did not exceed ten, we did not assess the publication bias.

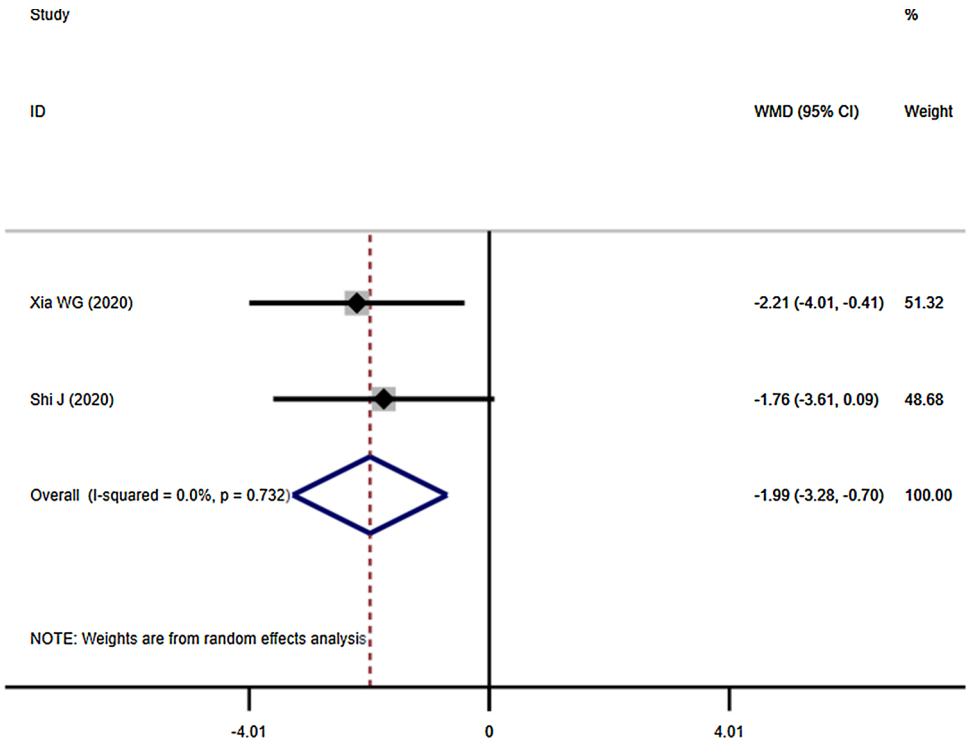

Fig. 5. Hospital stay of the COVID-19 between Integrated Medicine and Western Medicine.

Table 4
Comparison of the symptoms disappearance rate or time between integrated Chinese and Western medicine.

Outcome measure	No. of studies	Samples			Statistical method	Effect estimate	*P-value*
		Total	Events/Intervention	Events/Control			
Fever disappearance rate	4	324	157/181	97/143	RR (Random) 95%CI	1.320(1.048,1.663)	0.018
Cough disappearance rate	4	283	113/157	55/126	RR (Random) 95%CI	1.590(1.122,2.253)	0.009
Expectoration disappearance rate	3	126	49/68	16/58	RR (Random) 95%CI	2.549(1.390,4.678)	0.003
Fatigue disappearance rate	3	175	69/101	30/74	RR (Random) 95%CI	1.532(1.137,2.065)	0.005
Myalgia disappearance rate	3	63	24/33	12/30	RR (Random) 95%CI	1.783(0.812,3.913)	0.149
Chest tightness disappearance rate	3	81	25/36	11/45	RR (Random) 95%CI	2.587(1.506,4.444)	0.001
Nausea disappearance rate	3	38	16/23	9/15	RR (Random) 95%CI	1.132(0.717,1.787)	0.596
Anorexia disappearance rate	2	57	12/19	4/38	RR (Random) 95%CI	5.043(1.116,22.783)	0.035
Diarrhea disappearance rate	3	38	9/22	12/16	RR (Random) 95%CI	0.681(0.199,2.332)	0.541
Fever disappearance time	5	425			WMD (Random) 95%CI	−1.319(-1.842,-0.796)	0.000
Cough disappearance time	3	307			WMD (Random) 95%CI	−0.993(-2.397,-0.532)	0.212
Fatigue disappearance time	3	301			WMD (Random) 95%CI	−1.129(-2.221,-0.037)	0.043
Nasal congestion disappearance time	2	270			WMD (Random) 95%CI	0.033(-0.281,0.348)	0.835
Runny nose disappearance time	2	270			WMD (Random) 95%CI	−0.800(-2.515,0.915)	0.360

4. Discussion

Our study systematically evaluated the effect of Integrated Medicine for COVID-19. After a comprehensive search of six databases, we included four RCTs and seven CCTs. The study results showed that the Integrated Medicine had better effects and fewer adverse drug reactions compared with Western Medicine. This study is not the first to find that Integrated Medicine has a greater effect on acute infectious diseases. Similar studies have shown that it has positive effects on lung infiltrate absorption in SARS patients [31]. Facing such a severe epidemic situation in the world, the Western countries should pay attention to the therapeutic effect of TCM. We think it is necessary to hire TCM experts to participate in the treatment of COVID-19 in Western countries.

TCM has served the Chinese people since ancient times and has played an important role in today's medical care. And it especially has a very systematic understanding of the etiology and pathogenesis of acute infectious diseases. And in TCM, the dosage, composition, treatment time, withdrawal and follow-up criteria, and treatment plan of the compound Chinese herbal medicine can be adjusted according to the situation of the patient. In the included studies, eight different herbal medicine or Chinese patent medicine were used. This means that in terms of treatment, TCM can make more choices to make the best treatment. In addition, TCM was involved in the treatment of COVID-19 with different severity from light to critical [11,24]. However, the use of these traditional herbs has been controversial due to unclear composition and lack of scientific evidence [32]. In our study, we found that the quality of these studies was low. In the treatment of many diseases, TCM is only used as adjuvant therapy [33,34]. So, standard treatment and outcome index need to be developed. In this way, the best evidence can be systematically reviewed, summarized and disseminated to better provide evidence-based TCM decision-making.

TCM is superior to western medicine in improving the symptoms and quality of life of patients. This study found that Integrated Medicine can improve the disappearance rate of fever, cough, expectoration, fatigue, chest tightness and anorexia and reduce patients' fever, and fatigue time. This is related to TCMs can affect immune cells and cytokine production associated with immune responses [35]. Immune regulation maintains the homeostasis of the immune system, protects the body from sources of infection or other harmful substances, thereby alleviating the clinical symptoms. It is essential for normal health. However, we found that the outcome indicators were not uniform in the included studies. This situation is dangerous and increases the waste of research resources, may cause some ineffective or adverse interventions to be applied clinically [36]. The diversity of outcome indicators also exists in the laboratory indicators and the adverse reaction indicators. Although we found that the Integrated Medicine may change the inflammation index and have fewer adverse drug reactions than western medicine. But these are not enough, we found that many important indicators cannot be analyzed due to outcome indicators were not uniform. Such as erythrocyte sedimentation rate, each interleukin type, macrophage ratio [13,24].

As a new kind of respiratory disease, COVID-19 has many unknown factors to be solved. We found that included studies had a short duration, the ranges from 5 to 30 days. COVID-19 is likely to require a longer period of follow-up. In this way, the efficacy and possible adverse drug reaction of COVID-19 can be better observed. Besides, adverse events should be monitored through standardized and effective reporting systems, and some serious adverse events should be observed through epidemiological studies [37,38].

However, this study also has the following limitations. The TCM and Western Medicine used in the intervention group and the control group is different. But we did not perform subgroup analysis or sensitivity analysis. And many merger statistical analysis studies have more heterogeneity. In addition, most of the included trials had flaws in the methodological design, including randomization, concealment of allocation, and inadequate reports on blinding, withdrawal, and sample size estimates. We also tried to contact the authors who participated in the trial for detailed information; however, we did not get a response at the end. And we did not perform a subgroup analysis according to the severity of the disease in patients withCOVID-19. In COVID-19 patients with different syndromes, the treatment effect may be different.

Above all, COVID-19 is a sudden outbreak disease. There are difficulties for clinicians to conduct RCTs, especially in the acute or critical period. So we included both RCTs and CCTs in this study. Therefore,

Table 5
Comparison of the laboratory indicators between integrated Chinese and Western medicine.

Outcome measure	No. of studies	Samples	Statistical method	Effect estimate	*P-value*
CRP	4	326	WMD (Random)95%CI	−1.16(-6.96,4.65)	0.695
TNF-α	2	204	WMD (Random)95%CI	−3.13(-4.23,-2.04)	0.000
Lymphocyte percentage	2	273	WMD (Random)95%CI	1.59(0.61,2.58)	0.002
WBC count	2	273	WMD (Random)95%CI	0.66(-0.03,1.34)	0.060

CRP, C - reactive protein; TNF-a, Tumor Necrosis Factor-α; WBC, White blood cell; CI, Confidence Intervals

Table 6
Comparison of the adverse drug reaction between integrated Chinese and Western medicine.

Outcome measure	No. of studies	Samples			Statistical method	Effect estimate	*P-value*
		Total	Events/Intervention	Events/Control			
Nausea and vomiting	2	172	5/92	5/80	RR (Random) 95%CI	0.915(0.267,3.138)	0.888
Diarrhea	2	225	32/134	3/91	RR (Random) 95%CI	5.598(0.267,166.774)	0.320
Liver damage	2	202	3/103	12/99	RR (Random) 95%CI	0.281(0.046,1.706)	0.168

RR, Risk Ratio; CI, Confidence Intervals

some high-quality RCTs are needed to evaluate the effect of Integrated Medicine for COVID-19.

5. Conclusion

The study results showed that compared with Western Medicine, the Integrated Medicine for COVID-19 has better effects and did not increase adverse drug reactions. However, due to the low number of included studies, low quality, and inadequate methodologies, high-quality RCTs are needed to evaluate the effect of Integrated Medicine for COVID-19 in future.

Ethical approval

Ethical approval and patient consent are not required since this is an overview based on published studies.

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Conflicts of Interest

The authors declare that they have no competing interests.

Author Contributions

Jinhui Tian, and Junhua Zhang designed this study; Ming Liu and Ya Gao ran the search strategy; Ming Liu and Yuan Yuan collected data, Shuzhen Shi and Ya Gao re-checked data; Ya Gao performed analysis and Jinhui Tian re-checked; Ming Liu and Kelu Yang assess the quality of studies, Shuzhen Shi and Junhua Zhang re-checked; Ming Liu wrote the manuscript, Ya Gao, Jinhui Tian and Junhua Zhang edited. All listed authors reviewed and revised the manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.phrs.2020.104896.

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