Outcome reporting from protocols of clinical trials of Coronavirus Disease 2019 (COVID-19): a review

Ruijin Qiu,[1] Xuxu Wei,[1] Mengzhu Zhao,[2] Changming Zhong,[1] Chen Zhao,[3] Jiayuan Hu,[1] Min Li,[4] Ya Huang,[1] Songjie Han,[1] Tianmai He,[1] Jing Chen,[5]* Hongcai Shang[1]*

1. Key Laboratory of Chinese Internal Medicine of Ministry of Education and Beijing, Dongzhimen Hospital, Beijing University of Chinese Medicine.

2. First Teaching Hospital of Tianjin University of Traditional Chinese Medicine.

3. Institute of Basic Research In Clinical Medicine, China Academy of Chinese Medical Sciences

4. Beijing University of Chinese Medicine Third Affiliated Hospital

5. Baokang Affiliated Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin China.

*__Corresponding author:__

1. Jing Chen

Postal address: 88th Yuquan Road, Nankai District, Tianjin, China, 300193

Tel: +86 022 27474998

Email: cjshcsyc@126.com

2. Hongcai Shang

Postal address: Hai Yun Cang on the 5th Zip, Dongcheng District, Beijing, China, 100700.

Tel: +86 010 84012510

Email: shanghongcai@foxmail.com

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Objectives

To examine heterogeneity of outcomes in protocols of clinical trials of Coronavirus Disease 2019 (COVID-19) and to identify outcomes for prioritization in developing a core outcome set (COS) in this field.

Design

This study is a review.

Data sources

Databases of ICMJE-accepted clinical trial registry platform were searched on February 14, 2020.

Eligibility Criteria

Randomized controlled trials (RCTs) and non-RCTs of COVID-19 were considered. Conditions of patients include common type, severe type or critical type. Interventions include traditional Chinese medicine (TCM) and Western medicine. We excluded trials that for discharged patients, psychological intervention and complications of COVID-19.

Data extraction and synthesis

The general information and outcomes, outcome measurement instruments and measurement times were extracted. The results were analysed by descriptive analysis.

Results

19 registry platforms were searched. A total of 97 protocols were included from 160 protocols. For protocols of TCM clinical trials, 76 outcomes from 16 outcome domains were reported, and almost half (34/76, 44.74%) of outcomes were reported only once; the most frequently reported outcome was time of SARS-CoV-2 RNA turns to negative. 27 (27/76, 35.53%) outcomes were provided one or more outcome measurement instruments. 10 outcomes were provided one or more measurement time frame. For protocols of western medicine clinical trials, 126 outcomes from 17 outcome domains were reported; almost half (62/126, 49.21%) of outcomes were reported only once; the most frequently reported outcome was proportion of patients with negative SARS-CoV-2. 27 outcomes were provided one or more outcome measurement instruments. 40 (40/126, 31.75%) outcomes were provided one or more measurement time frame.

Conclusion

Outcome reporting in protocols of clinical trials of COVID-19 is inconsistent. Thus, developing a core outcome set is necessary.

Keywords: Outcomes; clinical trials, COVID-19; review.

Strengths and limitations of this study

1. This review is the first to describe variation in outcomes, outcome measurement instruments and outcome measurement time reporting in clinical trials for Coronavirus Disease 2019 (COVID-19).

2. All the database of ICMJE-accepted clinical trial registry platform were searched, and randomized controlled trials and observational studies were considered.

4. The aim of this review was to provide a list of outcomes for clinical trials of COVID-19, both interventions of Traditional Chinese Medicine and western medicine were considered.

5. When the searching was conducted, no clinical trials were registered by countries out of China, so all of included protocols were from China.

INTRODUCTION

Since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection occurred in Wuhan, Hubei Province from December 2019, the disease, which was named as Coronavirus Disease 2019 (COVID-19) by World Health Organization (WHO) on February 12, 2020. According to the website of National Health Commission of the People's Republic of China (NHC-PRC), 77,658 confirmed cases have been reported from all areas of China until 0 o'clock, February 25, 2020. 27,323 cured patients discharged, 2,663 patients died [1]. On the website of WHO showed that 2559 confirmed cases have been reported in 33 countries out of China, 34 patients died at 10AM CET, February 25 2020 [2].

However, there is still no specific medicine for COVID-19 now. In China, the government encourages traditional Chinese medicine (herbal medicine, moxibustion, Baduanjin, etc.) to take an important role in clinical practice. The NHC-PRC and National Administration of Traditional Chinese Medicine (NATCM) have released the Version 6.0 of Diagnosis and Treatment Guideline for COVID-19 (informal version) on February 18, 2020 [3]. The guideline recommended general therapy methods, such as oxygen support, or trying to use alpha-interferon, Lopinavir/Ritonavir, Ribavirin, Chloroquine phosphate, Abidol, etc. For severe and critical type of disease, high flow nasal catheter oxygen therapy, invasive or non-invasive mechanical ventilation, extracorporeal membrane oxygenation (ECMO), plasma of survivors, glucocorticoid, plasma exchange or according to the patients' situation. The guideline also recommended TCM therapy methods, including herbal medicine formulas and proprietary Chinese medicine according to TCM syndromes, which are analyzed by clinical symptoms and signs through four methods of diagnosis: inspection, auscultation and olfaction, interrogation, and palpation.

At the same time, an increasing number of clinical trials are conducting. After searching some protocols of clinical trials from Chinese Clinical Trial Registry (ChiTCR) and ClinicalTrials.gov, we found that different researchers chose different outcomes. It is very important for clinical trials to provide evidence in treating COVID-19. However, the heterogeneity of outcomes make it impossible to conduct meta-analysis in the future, which may reduce the value of clinical trials and improve waste.

We are going to develop a core outcome set (COS) for clinical trials of COVID-19. The study have been registered in Core Outcome Measures in Effectiveness Trials (COMET) database [4]. The first clinical trial of COVID-19 was registered on January 23, 2020 [5]. When we registered the COS study, there were about 50 clinical trials registered [4]. On February 25, 2020, the number of registered trials increased to 297. Before we finish the COS, we believe that it is very important to draw researchers' attention to concern about outcomes in their research. So we conducted a review of outcome reporting from registered clinical trials of COVID-19. Because

TCM and western medicine take the same role in the treatment of COVID-19 in China, so the review includes both interventions.

METHODS

Search strategy

All the databases of ICMJE-accepted clinical trial registry platform [6] were considered. Search terms for ChiCTR included “COVID-19”, “2019-novel Corona Virus (2019-nCoV)”, “Novel Coronavirus Pneumonia (NCP)”, “Severe Acute Respiratory Infection (SARI)”, “Severe Acute Respiratory Syndrome - Corona Virus- 2 (SARS-CoV-2)”. Search terms for Netherlands National Trial Register (NTR) included “nCoV”, “Coronavirus”, “SARS”, “SARI”, “NCP”, “COVID”. Search terms for other databases included “2019-nCoV OR Novel Coronavirus OR New Coronavirus OR SARS-CoV-2 OR SARI OR NCP OR Novel Coronavirus Pneumonia OR COVID-19 OR Wuhan pneumonia”. The searching conducted on n February 14, 2020.

Inclusion criteria

1. The population should include conformed patients of COVID-19.
2. Patients’ conditions include common type, severe type or critical type.
3. The interventions include any type of TCM therapy or western therapy.
4. The study types include randomized controlled trial (RCT) and observation study.

Exclusion criteria

1. Studies for discharged patients.
2. Studies for psychological intervention.
3. Studies for complications of COVID-19.

Study identification

Two reviewers (RQ and XW) independently assessed all the registered protocols. Any disagreement was resolved by discussion.

Date extraction

Two reviewers (RQ and MZ) independently extracted information. The information included the primary investigators’ name, study type, type of disease, primary sponsor, number of settings, sample size, population’s age, course of treatment, interventions, outcomes, outcome definition/measurement instruments, measurement time frame. Any disagreement was resolved by discussion.

Merging outcomes and grouping under outcome domains

Two researchers (RQ and CZ) merged the overlapping outcomes according to the definition

of outcomes independently. If the researchers did not provide definition of outcome, they discussed and achieved consensus if necessary. For example, “PaO2/FiO2”, “oxygenation index”, “oxygen index”, “the difference of PaO2/FiO2 between two groups” were aggregated as “PaO2/FiO2”. Many protocols presented composite outcomes. If definitions were provided, or all of the single outcomes in the composite one can be measured in one test, it was listed in the review. If a single outcome which belongs to a composite outcome was reported by one or more protocols, the composite outcome was removed from the review. But when we conduct Delphi survey in further research, the composite outcome will be list to consult the participants’ opinion.

After the original outcomes were aggregated, two researchers (RQ and CZ) grouped individual outcomes into the appropriate outcome domain together and achieved consensus. The taxonomy of outcome domains were developed by the researchers from COMET initiative [7].

Statistical analysis

The results were analysed by descriptive analysis.

Patient and public involvement

The COVID-19 is highly infectious. For the safety of patients and public, they were not involved in the design or planning of the study.

RESULTS

Characteristics of literature

In this review, a total of 160 protocols from 19 different clinical trials registry platforms were searched. After reading titles and study details, 63 non-relevant or ineligible study protocols were excluded. In the end, 97 eligible study protocols were included from ChiCTR and ClinicalTrials.gov. The searching results and inclusion numbers were shown in Table 1.

In the included protocols, 34 clinical trials were for TCM therapy and 63 clinical trials were for western medicine therapy. All of clinical trials will be conducted in China. These clinical trials include 75 RCTs (53 for western medicine and 22 for TCM medicine) and 22 non-RCTs (10 for western medicine and 12 for TCM medicine). The first registered clinical trial for western medicine was on January 23, 2020, while the first registered clinical trial for TCM medicine was on January 27, 2020. The general characteristics of the included protocols are shown in table 2 and table 3.

According to the information of primary sponsor, we found that the clinical trials were registered from 13 different provinces of China. Researchers from Hubei province registered more clinical trials (31/97, 31.96%) than researchers from other provinces. The distribution of clinical trials is

shown in Figure 1.

Table 1 The global registry of COVID-19 related clinical trials searching results and inclusion

ICMJE-accepted clinical trials registry	Results	Inclusion	Official website
WHO Primary Registries			
Australian New Zealand Clinical Trials Registry (ANZCTR)	0	0	https://www.anzctr.org.au/
Brazilian Clinical Trials Registry (ReBec)	0	0	http://www.ensaiosclinicos.gov.br/
Chinese Clinical Trial Registry (ChiCTR)	111*	77	http://www.chictr.org.cn/index.aspx
Clinical Research Information Service (CRiS), Republic of Korea	0	0	http://cris.nih.go.kr/cris/en/use_guide/cris_introduce.jsp
Clinical Trials Registry - India (CTRI)	0	0	http://ctri.nic.in/Clinicaltrials/login.php
Cuban Public Registry of Clinical Trials (RPCEC)	0	0	http://registroclinico.sld.cu/en/home
EU Clinical Trials Register (EU-CTR)	0	0	https://www.clinicaltrialsregister.eu/
German Clinical Trials Register (DRKS)	0	0	https://www.drks.de/drks_web/
Iranian Registry of Clinical Trials (IRCT)	0	0	https://www.irct.ir/
ISRCTN	0	0	http://www.isrctn.com/
Japan Primary Registries Network (JPRN)	0	0	https://rctportal.niph.go.jp/en/
Lebanese Clinical Trials Registry (LBCTR)	0	0	http://lbctr.emro.who.int/
Thai Clinical Trials Registry (TCTR)	0	0	http://www.clinicaltrials.in.th/
The Netherlands National Trial Register (NTR)	24*	0	https://www.trialregister.nl/
Pan African Clinical Trial Registry (PACTR)	0	0	https://pactr.samrc.ac.za/Search.aspx
Peruvian Clinical Trial Registry (REPEC)	0	0	https://ensayosclinicos-repec.ins.gob.pe/en/
Other Registries			
ClinicalTrials.gov	25*	20	https://www.clinicaltrials.gov/
UMIN Clinical Trials Registry (UMIN-CTR)	0	0	https://www.umin.ac.jp/ctr/index/htm/
EudraCT	0	0	https://eudract.ema.europa.eu/index.html

Table 2 The characteristics of included protocols for TCM clinical trials

Study ID	Study type	Type of disease	Primary sponsor	Number of settings	Sample size	Population' age (years)	Intervention	Number of outcomes
Zhong N [8]	Non RCT	COVID-19	Guangdong Province, China	21	400	18-75	Group 1: Xue-Bi-Jing injection Group 2: CT	Primary outcomes: 1 Secondary outcomes: 14
Huang L [9]	Non RCT	COVID-19 (without severe type)	Beijing, China	1	60	≥ 18	Group 1:TCM treatment Group 2: TCM treatment and Lopinavir / Ritonavir Group3: Lopinavir / Ritonavir;	Primary outcomes: 1 Secondary outcomes: 8
Liang T [10]	RCT	COVID-19	Beijing, China	1	42	≥ 18	Group 1: TCM + CT Group 2: CT	Primary outcomes: 1 Secondary outcomes: 3
Liu Q [11]	RCT	severe and critical COVID-19	Beijing, China	1	100	Unclear	Group 1: Conventional medicine + TCM Group 2:western medical therapies	Primary outcomes: 4 Secondary outcomes: 7
Xia W [12]	OS	COVID-19	Hubei Province, China	1	300	Unclear	Group 1: according to guidelines	Primary outcomes: 1 Secondary outcomes: 0
Wang Y [13]	RCT	Common type of COVID-19	Beijing, China	2	120	Unclear	Group 1: TCM standard decoctions + CT Group 2: basic western medical therapies	Primary outcomes: 2 Secondary outcomes: 6
Li J [14]	Non RCT	COVID-19	Henan Province, China	8	100	Unclear	Group 1: TCM syndrome differentiation treatment + CT Group 2: CT	Primary outcomes: 2 Secondary outcomes: 8
Zhong N [15]	RCT	COVID-19	Hebei Province, China	7	400	≥ 18	Group 1: CT + low dose of Lianhua Qingwen Group 2: CT + Lianhua Qingwen medium dose Group 3: CT + high dose of Lianhua Qingwen Group 4: CT	Primary outcomes: 1 Secondary outcomes: 6
Yang Z [16]	OS	COVID-19	Guangdong Province, China	1	72	18-75	Group 1: Tanreqing injection	Primary outcomes: 2 Secondary outcomes: 8
Zhang J [17]	RCT	COVID-19 (virus turned negative after treatment)	Hubei Province, China	1	100	18-70	Group 1: TCM decoctions+basic western medical therapies Group 2: CT	Primary outcomes: 3 Secondary outcomes: 1

Study ID	Study type	Type of disease	Primary sponsor	Number of settings	Sample size	Population' age (years)	Intervention	Number of outcomes
Zheng C [18]	RCT	COVID-19 (virus turned negative after treatment)	Hubei Province, China	1	100	18-70	Group 1: shadowboxing + CT Group 2: CT	Primary outcomes: 4 Secondary outcomes: 1
Xia W [19]	RCT	COVID-19 (virus turned negative after treatment)	Hubei Province, China	1	100	18-70	Group 1: Pulmonary rehabilitation+ CT Group 2: CT	Primary outcomes: 2 Secondary outcomes: 3
Xia W [20]	RCT	Common type of COVID-19	Hubei Province, China	1	100	18-70	Group 1: TCM decoctions+ CT Group 2: CT	Primary outcomes: 3 Secondary outcomes: 5
Wen C [21]	RCT	common or severe type of COVID-19	Zhejiang Province, China	1	140	14-80	Group 1 (ordinary): CT Group 2 (ordinary): TCM + CT Group 3 (severe): CT Group 4 (severe): TCM + CT	Primary outcomes: 3 Secondary outcomes: 6
Xie C [22]	RCT	Suspected and confirmed diagnosis of COVID-19	Sichuan Province, China	1	400	Unclear	Group 1: TCM treatment + CT Group 2: CT	Primary outcomes: 4 Secondary outcomes: 0
Xie C [23]	OS	suspected and confirmed diagnosis of COVID-19	Sichuan Province, China	1	200	Unclear	Group 1: TCM treatment + CT	Primary outcomes: 13 Secondary outcomes: 0
Wen C [24]	OS	COVID-19	Zhejiang Province, China	1	1000	Unclear	Group 1: Integrated Traditional Chinese and Western Medicine	Primary outcomes: 4 Secondary outcomes: 5
Liu Q [25]	Non-RCT	Common type of COVID-19	Beijing, China	5	60	≥ 18	Group 1: Reduning injection + CT Group 2: CT	Primary outcomes: 1 Secondary outcomes: 5

Study ID	Study type	Type of disease	Primary sponsor	Number of settings	Sample size	Population' age (years)	Intervention	Number of outcomes
Wang D [26]	RCT	COVID-19	Hubei Province, China	2	400	≥ 18	Group 1: Low dose of Shuanghuanglian + CT Group 2: Medium dose of Shuanghuanglian + CT Group 3: High dose of Shuanghuanglian + CT Group 4: CT	Primary outcomes: 1 Secondary outcomes: 6
Zhang Z [27]	OS	COVID-19	Guangdong Province, China	1	100	Unclear	Group 1: Xinguan-1 formula + CT Group 2: CT	Primary outcomes: 2 Secondary outcomes: 10
Xiao X [28]	RCT	COVID-19	Beijing, China	1	150	14-80	Group 1: TCM + CT Group 2: CT	Primary outcomes:1 Secondary outcomes:5 Other outcomes: 4
Zhang N [29]	RCT	COVID-19	Anhui Province, China	4	200	12-80	Group 1: TCM Group 2: CT	Primary outcomes: 4 Secondary outcomes: 0
Mao W [30]	OS	suspected or confirmed COVID-19	Zhejiang Province, China	9	350	18-85	Group 1 (Suspected patients): Routine respiratory disease treatment Group 2 (Suspected patients): TCM + control group Group 3 (Common COVID-19 patients): treatment according to the guideline Group 4 (Common COVID-19 patients): TCM + control group Group 5 (Severe COVID-19 patients) : TCM + treatment according to the guideline	Primary outcomes: 6 Secondary outcomes: 4
Liu D [31]	RCT	COVID-19	Hubei Province, China	1	120	≥ 18	Group 1: Jinyebaidu granule + CT Group 2: CT	Primary outcomes: 1 Secondary outcomes: 1
Huang L [32]	RCT	Common type of COVID-19	Beijing, China	1	408	18-75	Group 1: TCM + CT Group 2: CT	Primary outcomes: 1 Secondary outcomes: 7
Lv D [33]	RCT	Severe type of COVID-19	Zhejiang Province, China	1	40	18-80	Group 1: Babaodan + CT Group 2: CT	Primary outcomes: 2 Secondary outcomes: 0

Study ID	Study type	Type of disease	Primary sponsor	Number of settings	Sample size	Population' age (years)	Intervention	Number of outcomes
Huang T [34]	RCT	Severe type of COVID-19	Hubei Province, China	3	160	18-80	Group 1: Truncation and Torsion Formula + CT Group 2: CT	Primary outcomes: 2 Secondary outcomes: 7
Zhang W [35]	Non-RCT	COVID-19	Shanghai, China	1	600	15-85	Group 1: herbal medicine based on TCM syndrome + CT Group 2: Qing-Fei-Pai-Du decoction + CT Group 3: Shu-Feng-Jie-Du capsuale + CT Group 4: CT	Primary outcomes: 2 Secondary outcomes: 6
Zheng X [36]	RCT	COVID-19	Hubei Province, China	6	160	≥ 18	Group 1: Shenqi Fuzheng Injection + CT Group 2: CT	Primary outcomes: 1 Secondary outcomes: 3
Zheng X [37]	RCT	COVID-19	Hubei Province, China	5	160	≥ 18	Group 1: Kangbingdu granules + CT Group 2: CT	Primary outcomes: 1 Secondary outcomes: 0
Zhang Y [38]	RCT	COVID-19	Beijing, China	1	60	18-80	Group 1: CT Group 2: TCM syndrome differentiation treatment + CT	Primary outcomes: 4 Secondary outcomes: 0
Wang L [39]	RCT	COVID-19	Shanghai, China	1	120	18-81	Group 1: CT Group 2: TCM + CT	Primary outcomes: 1 Secondary outcomes: 4
Lu H [40]	RCT	Mild and common type of COVID-19	Shanghai, China	1	72	18-75	Group 1: Tanreqing Capsules + CT Group 2: CT	Primary outcomes: 2 Secondary outcomes: 5
Zhai X [41]	Non-RCT	COVID-19	Shanghai, China	1	30	0-18	Group 1: CT Group 2: TCM + CT	Primary outcomes: 4 Secondary outcomes: 1

CT: conventional therapy (including any western routine treatment); OS: observational study; RCT: randomized controlled trial; TCM: traditional Chinese medicine

Table 3 The characteristics of included protocols for western medicine clinical trials

Study ID	Study type	Type of disease	Primary sponsor	Number of settings	Sample size	Population' age (years)	Course of treatment	Intervention	Number of outcomes
Huang C [5]	RCT	Unexplained viral pneumonia or COVID-19	Hubei province, China	1	160	≥18		Group: Lopinavir-ritonavir tablets + interferon-α2b Group 2: CT	Primary outcomes: 2 Secondary outcomes: 9
Chen Y [42]	RCT	COVID-19	Chongqing, China	1	40	≥18		Group 1: Lopinavir-ritonavir tablets + Aerosolized interferon-α + Methylprednisolone Group 2: Lopinavir-ritonavir tablets + Aerosolized interferon-α	Primary outcomes: 3 Secondary outcomes: 3
Zhao D [43]	RCT	COVID-19	Liaoning Province, China	2	45	≥18	Unclear	Group 1: Critical Treatment in Critical Period + Ankylosaurus Group2: Critical Treatment in Critical Period + Ankylosaurus+M1 suppression therapy Group 3: Critical Treatment in Critical Period	Primary outcomes: 2 Secondary outcomes: 0
Jiang H [44]	Non-RCT	COVID-19	Sichuan Province, China	2	120	18-80	Unclear	Group 1: Lopinavir/litonavir (LPV/r)+ emtritabine (FTC)/ Tenofovir alafenamide Fumarate tablets (TAF) Group 2: LPV/r	Primary outcomes: 1 Secondary outcomes: 3
Jiang S [45]	Non-RCT	COVID-19	Guangdong Province, China	1	20	≥18	Unclear	Group 1: chloroquine Group 2:CT	Primary outcomes: 2 Secondary outcomes: 5 Other outcomes: 4
Wang X [46]	RCT	COVID-19	Hubei province, China	1	100	18-65	14 days	Group 1: Darunavir/cobicistat + thymosin α1 + CT Group 2: LPV/r + hymosin α1+ CT Group 3: hymosin α1	Primary outcomes: 1 Secondary outcomes: 8
Zhao J [47]	RCT	Mild COVID-19	Hubei province, China	1	328	≥18	Unclear	Group 1: Lopinavir-Ritonavir + CT Group 2: CT	Primary outcomes: 1 Secondary outcomes: 8
Gong G [48]	RCT	Mild and severe COVID-19	Hunan province, China	6	240	18-70	7-14 days	Group 1: Novaferon Atomization inhalation + CT Group 2: lopinavir / ritonavir tablets (Kaletra) + CT Group 3: Novafron + Kaletra + CT Group 4: CT	Primary outcomes: 1 Secondary outcomes: 3

Study ID	Study type	Type of disease	Primary sponsor	Number of settings	Sample size	Population' age (years)	Course of treatment	Intervention	Number of outcomes
Qiu Y [49]	RCT	COVID-19	Zhejiang Province, China	1	30	18-75	≤14 days	Group 1: Baloxavir Marboxil Group 2: Favipiravir Group 3: Lopinavir-Ritonavir	Primary outcomes: 2 Secondary outcomes: 8
Zhang Z [50]	RCT	COVID-19	Hubei province, China	1	300	30-65	Unclear	Group 1: Low dose of Hydroxychloroquine Group 2: High dose of Hydroxychloroquine Group 3: Placebo	Primary outcomes: 1 Secondary outcomes: 1
Lv Q [51]	RCT	COVID-19	Zhejiang Province, China	1	600	18-65	Unclear	Group 1: Arbidol Tablets Group 2: Novaferon injection, atomized inhalation + Arbidol Tablets Group 3: Lopinavir/litonavir Group 4: Arbidol Tablets Group 5: Novaferon injection, atomized inhalation + Lopinavir/litonavir Group 6: Novaferon injection, atomized inhalation + Arbidol Tablets	Primary outcomes: 1 Secondary outcomes: 0
Zhou J [52]	RCT	Severe type of COVID-19	Hubei province, China	1	70	18-75	Unclear	Group 1: Ruxolitinib combined with mesenchymal stem cell Group 2: CT	Primary outcomes: 1 Secondary outcomes: 0
Qiu Y [53]	RCT	COVID-19 (Severe and critical types are excluded)	Zhejiang Province, China	5	160	18-75	Unclear	Group 1: ASC09/Ritonavir + CT Group 2: Lopinavir/Ritonavir + CT	Primary outcomes: 1 Secondary outcomes: 9
Liu Y [54]	Non-RCT	COVID-19	Shenzhen Province, China	1	90	16-75	Unclear	Group 1: alpha-Interferon atomization Group 2: Lopinavir and Ritonavir + alpha-Interferon atomization Group 3: Favipiravir + alpha-Interferon atomization	Primary outcomes: 5 Secondary outcomes: 0
Chen Y [55]	RCT	Mild type of COVID-19	Chongqing, China	1	108	18-65	Unclear	Group 1: Ribavirin + Interferon alpha-1b Group 2: lopinavir / ritonavir + interferon alpha-1b Group 3: Ribavirin + LPV/r+Interferon alpha-1b	Primary outcomes: 1 Secondary outcomes: 5

Study ID	Study type	Type of disease	Primary sponsor	Number of settings	Sample size	Population' age (years)	Course of treatment	Intervention	Number of outcomes
Shan H [56]	OS	COVID-19	Guangdong Province, China	2	205	≥18	Unclear	Group 1: mild-moderate chloroquine Group 2: mild-moderate Lopinavir/ ritonavir Group 3: mild-moderate combination group (chloroquine phosphate + Lopinavir/ritonavir) Group 4: severe-chloroquine Group 5: severe- Lopinavir/ritonavir	Primary outcomes: 1 Secondary outcomes: 4
Pei B [57]	RCT	Severe and critical type of COVID-19	Hubei province, China	1	30	≥18	Unclear	Group 1: CT Group 2: umbilical cord blood mononuclear cells + CT	Primary outcomes: 1 Secondary outcomes: 8
Pei B [58]	RCT	Severe and critical type of COVID-19	Hubei province, China	1	30	≥18	Unclear	Group 1: CT Group 2: umbilical cord mesenchymal stem cell conditioned medium + CT	Primary outcomes: 1 Secondary outcomes: 8
Qiu Y [59]	RCT	COVID-19	Zhejiang Province, China	1	30	18-75	Unclear	Group 1: current antiviral treatment + Baloxavir Marboxil tablets Group 2: current antiviral treatment + fabiravir tablets Group 3: current antiviral treatment	Primary outcomes: 2 Secondary outcomes: 6
Hu B [60]	OS	Common or severe type of COVID-19	Hubei province, China	1	40	≥18	Unclear	Group 1: vMIP atomized inhalation + CT	Primary outcomes: 2 Secondary outcomes: 2
Liu L [61]	RCT	COVID-19	Sichuan Province, China	8	60	18-75	Unclear	Group 1: nebulization of novel gene recombinant super compound interferon Group 2: nebulization of alpha-interferon	Primary outcomes: 9 Secondary outcomes: 6
Li L [62]	RCT	COVID-19	Zhejiang Province, China	1	63	1-99	Unclear	Group 1a: CT + Intravenous infusion of Human Menstrual Blood-derived Stem Cells preparations Group 1b: CT Group 2a: Artificial liver therapy + CT Group 2b: Artificial liver therapy + Intravenous infusion of Human Menstrual Blood-derived Stem Cells preparations +	Primary outcomes: 1 Secondary outcomes: 8

Study ID	Study type	Type of disease	Primary sponsor	Number of settings	Sample size	Population' age (years)	Course of treatment	Intervention	Number of outcomes
								CT	
Wu C [63]	RCT	critical COVID-19	Guangdong Province, China	1	60	18-80	Unclear	Group 1: high-fow therapy by nasal cannulae (HFNC) Group 2: bag- valve mask oxygenation (SMO)	Primary outcomes: 1 Secondary outcomes: 6
Du R [64]	RCT	COVID-19	Hubei province, China	1	100	≥18	Unclear	Group 1: CT Group 2: methylprednisolone + CT	Primary outcomes: 5 Secondary outcomes: 0
Qu J [65]	RCT	COVID-19 (Mild/common type)	Shanghai, China	1	380	≥18	Unclear	Group 1: Arbidol tablets + CT Group 2: CT	Primary outcomes: 1 Secondary outcomes: 8
Not Provided [66]	RCT	COVID-19	Beijing, China	4	80	≥18	5 days	Group 1: standard care Group 2: standard care + Methylprednisolone	Primary outcomes: 2 Secondary outcomes: 8
Lu H [67]	RCT	COVID-19	Shanghai, China	1	30	Child, Adult, Older Adult	Unclear	Group 1: Darunavir + Cobicistat + CT Group 2: CT	Primary outcomes: 1 Secondary outcomes: 5
Qin N [68]	RCT	COVID-19	Hubei province, China	1	100	≥18	2 weeks	Group 1: Abidol hydrochloride Group 2: Abidol Hydrochloride + Interferon atomization	Primary outcomes: 2 Secondary outcomes: 5
Qin N [69]	RCT	COVID-19	Hubei province, China	1	400	≥18	2 weeks	Group 1: Symptomatic supportive treatment Group 2: Abidol hydrochloride was added on the basis of group 1. Group 3: Oseltamivir was added on the basis of group 1. Group 4: Lopinavir/ritonavir was added on the basis of group 1.	Primary outcomes: 2 Secondary outcomes: 5

Study ID	Study type	Type of disease	Primary sponsor	Number of settings	Sample size	Population' age (years)	Course of treatment	Intervention	Number of outcomes
Cao B [70]	RCT	COVID-19	Beijing, China	2	308	≥18	9 days	Group 1: Remdesivir group active remdesivir Group 2: Control group Placebos matched remdesivir	Primary outcomes: 1 Secondary outcomes: 10
Cao B [71]	RCT	Severe COVID-19	Beijing, China	1	452	≥18	9 days	Group 1: Remdesivir Group 2: Remdesivir Placebo	Primary outcomes: 1 Secondary outcomes: 10
Qu J [72]	RCT	Mild or common type of COVID-19	Shanghai, China	1	380	18-75	14-20 days	Group 1: Arbidol tablets + basic treatment Group 2: basic treatment	Primary outcomes: 1 Secondary outcomes: 8
Qin N [73]	RCT	COVID-19 (without severe type)	Hubei province, China	1	60	18-55	14 days	Group 1: ASC09F+Oseltamivir Group 2: Ritonavir+Oseltamivir Group 3: Oseltamivir	Primary outcomes: 1 Secondary outcomes: 9
Li T [74]	RCT	Severe type of COVID-19	Beijing, China	2	80	≥18	Unclear	Group 1: IVIG therapy+ standard care Group 2: Standard care	Primary outcomes: 3 Secondary outcomes: 8
Lu H [75]	RCT	COVID-19	Shanghai, China	1	30	≥18	5 days	Group 1: Hydroxychloroquine + CT Group 2: CT	Primary outcomes: 4 Secondary outcomes: 2
Zhang Z [76]	RCT	COVID-19	Beijing, China	1	200	16-99	Unclear	Group 1: hydroxycholoroquine Group 2: CT	Primary outcomes: 7 Secondary outcomes: 4 Other outcomes: 1
Xia J [77]	RCT	Mild/generalCOVID-19	Guangdong Province, China	1	112	≥18	Unclear	Group 1: Chloroquine Phosphate Group 2: Lopinavir / Ritonavir	Primary outcomes: 10 Secondary outcomes: 2 Other outcomes: 1
Ning Q [78]	RCT	OVID-19	Hubei province, China	1	90	18-70	Unclear	General patients group 1: CT General patients group 2: Sodium Aescinate + CT Severe patients control group 1: CT + hormonotherapy Severe patients control group 2: CT Severe patients experimental group: Sodium Aescinate + CT	Primary outcomes: 1 Secondary outcomes: 4

Study ID	Study type	Type of disease	Primary sponsor	Number of settings	Sample size	Population' age (years)	Course of treatment	Intervention	Number of outcomes
Ning Q [79]	RCT	severe OVID-19	Hubei province, China	1	100	≥18	7 days	Group 1: Methylprednisolone (<40mg/d) Group 2: Methylprednisolone (40~80mg/d)	Primary outcomes: 2 Secondary outcomes: 5
Qiu Y [80]	RCT	OVID-19	Zhejiang Province, China	2	160	18-75	14 days	Group 1: ASC09/ritonavir Group 2: lopinavir/ritonavir	Primary outcomes: 1 Secondary outcomes: 9
Li L [81]	RCT	OVID-19	Guangdong Province, China	1	125	7-14 days	Unclear	Group 1: CT + lopinavir/ritonavir Group 2: CT + arbidol Group 3: CT	Primary outcomes: 1 Secondary outcomes: 4 Other outcomes: 5
Wang F [82]	Non-RCT	OVID-19	Beijing, China	7	40	18-65	Unclear	Group 1: Mesenchymal Stem Cell + CT Group 2: CT	Primary outcomes: 2 Secondary outcomes: 7
F Zhang [83]	RCT	Severe type of COVID-19	Jiangsu Province, China	1	40	14-70	Unclear	Group 1: 5u washed microbiota suspension administered + CT Group 2: 5u placebo + CT	Primary outcomes: 1 Secondary outcomes: 0
Peng Z [84]	RCT	Severe type of COVID-19	Hubei province, China	1	140	≥18	7 days	Group 1: Vit C + water for injection Group 2: Water for injection	Primary outcomes: 1 Secondary outcomes: 8
Cheng X [85]	Non-RCT	Severe type of COVID-19	Hubei province, China	1	10	≥18	3 days	Group 1: Immunoglobulin of cured patients Group 2: γ-Globulin	Primary outcomes: 1 Secondary outcomes: 10
Zhang Z [86]	RCT	COVID-19	Hubei province, China	1	238	18-60	Unclear	Group 1: Xiyanping injection Group 2: alpha-interferon	Primary outcomes: 7 Secondary outcomes: 5
Liu Z [87]	RCT	Severe type of COVID-19	Sichuan Province, China	3	300	≥18	Unclear	Group 1: convalescent plasma therapy + CT Group 2: CT	Primary outcomes: 1 Secondary outcomes: 13
Kang Y [88]	OS	Severe type of COVID-19	Sichuan Province, China	1	100	Unclear	Unclear	NA	Primary outcomes: 6 Secondary outcomes: 0
Hu P [89]	RCT	Mild and common type of COVID-19	Chongqing, China	2	60	18-80	Unclear	Group 1: Lopinavir / Ritonavir (Kaletra) + IFN aerosol inhalation Group 2: Abidol and IFN aerosol inhalation Group 3: ASC09/ Ritonavir (ASC09F) + IFN aerosol inhalation	Primary outcomes: 1 Secondary outcomes: 8

Study ID	Study type	Type of disease	Primary sponsor	Number of settings	Sample size	Population' age (years)	Course of treatment	Intervention	Number of outcomes
Mao H [90]	RCT	mild and moderate COVID-19	Chongqing, China	2	240	Unclear	Unclear	Group 1: Hydroxychloroquin Group 2: Lopinavir /Ritonavir	Primary outcomes: 1 Secondary outcomes: 11
Huang W [91]	RCT	Common type of COVID-19	Chongqing, China	4	240	≥18	Unclear	Group 1: Low-dose hydroxychloroquine + CT Group 2: Medium-dose hydroxychloroquine + CT Group 3: High-dose hydroxychloroquine + CT Group 4: CT	Primary outcomes: 2 Secondary outcomes: 5 Other outcomes: 3
Huang W [92]	RCT	Severe and critical type of COVID-19	Chongqing, China	4	60	≥18	Unclear	Group 1: Hydroxychloroquine + CT Group 2: CT	Primary outcomes: 2 Secondary outcomes: 7 Other outcomes: 3
Xu X [93]	RCT	common type of COVID-19	Anhui Province, China	1	188	18-85	Unclear	Group1: CT Group 2: tocilizumab + CT	Primary outcomes: 1 Secondary outcomes: 3
Lin J [94]	RCT	common type of COVID-19	Hubei province, China	1	60	18-75	Unclear	Group 1: Diammonium Glycyrrhizinate Enteric-coated Capsules + Vitamin C tablets+ CT Group 2: clinical standard antiviral treatment	Primary outcomes: 3 Secondary outcomes: 4
Huang X [95]	RCT	COVID-19	Zhejiang Province, China	2	40	≥18	Unclear	Group 1: Polyinosinic-Polycytidylic Acid Injection + CT Group 2: CT	Primary outcomes: 1 Secondary outcomes: 5
Wu W [96]	Cohort study	Severe COVID-19	Hubei province, China	3	100	≤75	Unclear	NA	Primary outcomes: 1 Secondary outcomes: 3
Xia J [97]	RCT	Severe COVID-19	Hubei province, China	1	120	≥18	Unclear	Group 1: Thymosin Group 2: Camrelizumab Group 3: CT	Primary outcomes: 1 Secondary outcomes: 0
Xu C [98]	RCT	COVID-19 (without severe type)	Guangdong Province, China	NA	60	≥18	Unclear	Group 1: Anti-aging Active Freeze-dried Powder Granules + CT Group 2: CT	Primary outcomes: 1 Secondary outcomes: 6

Study ID	Study type	Type of disease	Primary sponsor	Number of settings	Sample size	Population' age (years)	Course of treatment	Intervention	Number of outcomes
Xu C [99]	RCT	COVID-19 (without severe type)	Guangdong Province, China	NA	60	≥18	Unclear	Group 1: Intravenous infusion of Umbilical Cord Blood Mononuclear Cells preparations + CT Group 2: CT	Primary outcomes: 1 Secondary outcomes: 6
Xu C [100]	RCT	COVID-19 (without severe type)	Guangdong Province, China	NA	60	≥18	Unclear	Group 1: Intravenous infusion of Cord Blood Mesenchymal Stem Cells preparations + CT Group 2: CT	Primary outcomes: 1 Secondary outcomes: 6
Xu C [101]	RCT	COVID-19 (without severe type)	Guangdong Province, China	NA	60	≥18	Unclear	Group 1: High-dose NK cells + mesenchymal stem cells Group 2: Conventional dose NK cells + mesenchymal stem cells Group 3: Preventive dose NK cells + mesenchymal stem cells	Primary outcomes: 1 Secondary outcomes: 6
Xie J [102]	RCT	COVID-19	Chongqing, China	1	120	≥18	Unclear	Group 1: Anti-PD-1 antibody Group 2: Thymosin Group 3: CT	Primary outcomes: 1 Secondary outcomes: 6
Peng Z [103]	OS	COVID-19	Hubei Province, China	2	10	18-75	Unclear	Group 1: Umbilical Cord-Derived Mesenchymal Stem Cells	Primary outcomes: 1 Secondary outcomes: 15

CT: conventional therapy (including any western routine treatment); OS: observational study; RCT: randomized controlled trial

The list of outcomes

In protocols of TCM clinical trials, the number of primary outcomes are from 1 (13/34, 38.24%) to 13 (1/34, 2.94%), the number of secondary outcomes are from 1 (7/34, 20.59%) to 14 (1/34, 2.94%). 1(1/34, 2.94%) protocol of clinical trial reports other outcomes. For individual clinical trial, the number of outcomes are from 1 (2/34, 5.88%) to 15 (1/34, 2.94%). The number of outcomes in protocols of TCM clinical trials is shown in Figure 2.

In protocols of western medicine clinical trials, the number of primary outcomes are from 1 (39/63, 61.90%) to 10 (1/63, 1.59%), the number of secondary outcomes are from 0 (8/63, 12.70%) to 15(1/63, 1.59%). 5 (5/63, 7.94%) protocols of clinical trials reported other outcomes (the number of outcomes are from 1 to 5). For individual clinical trial, the number of outcomes are from 1 (4/63, 6.35%) to 16 (1/63, 1.59%). The number of outcomes in protocols of western medicine clinical trials is shown in Figure 3.

After merging and grouping outcomes, there are 76 different outcomes from 16 outcome domains in 34 protocols of TCM clinical trials (table 4). Almost half of outcomes are reported only once (34/76, 44.74%). The most frequently reported outcome is “time of SARS-CoV-2 RNA turns to negative”, which is reported 16 times. Only 3 (3/76, 3.95%) outcomes are reported more than 10 times. Only 27 (27/76, 35.53%) outcomes are provided one or more outcome measurement instruments. Only 10 outcomes are provided one or more measurement time frame. The summary of outcome reporting for protocols of TCM clinical trials is shown in Figure 4.

In the 16 outcome domains of protocols of TCM clinical trials, 4 outcome domains (adverse events/effects, hepatobiliary outcomes, mortality/survival, psychiatric outcomes) consisted of only one outcome. These outcomes are reported between 1 and 9 times, and the median outcome reporting time was 6.5. Respiratory, thoracic and mediastinal outcomes have the largest number of outcomes, which includes 17 outcomes; chest imaging is reported more frequently than other outcomes. The number of outcomes in different outcome domains in protocols of TCM clinical trials is shown in Figure 5.

After merging and grouping, there are 126 different outcomes from 17 outcome domains in 63 protocols of western medicine clinical trials (table 5). Almost half of outcomes are reported only once (62/126, 49.21%). The most frequently reported outcome is “proportion of patients with negative SARS-CoV-2”, which is reported 40 times. Only 11 (11/126, 8.73%) outcomes are reported more than 10 times. Only 27 outcomes are provided one or more outcome measurement instruments. Only 40 (40/126, 31.75%) outcomes are provided one or more measurement time frame. The summary of outcome reporting for protocols of TCM clinical trials is shown in Figure 6.

In the 17 outcome domains of protocols of western medicine clinical trials, 5 outcome domains (adverse events/effects, delivery of care, economic, metabolism and nutrition outcomes, mortality/survival) consisted of only one outcome. These outcomes are reported between 1 and 36 times, and the median outcome reporting time is 1. Respiratory, thoracic and mediastinal outcomes included the largest number of outcomes, which includes 31 outcomes; chest imaging is reported more frequently than other outcomes. The number of outcomes in different outcome domains in protocols of western medicine clinical trials is shown in Figure 7.

DISCUSSION

This review is the first to evaluate the outcome reporting of protocols of TCM and western medicine clinical trials for treating COVID-19. The results showed variations in the outcome reporting. For outcome measurement instruments/outcome definitions and outcome measurement time, there is also heterogeneity. However, many primary investigators did not provide outcome measurement instruments/outcome definitions or outcome measurement time. It is difficult to predict results of clinical trials now. But it is obvious that these problems may result in the exclusion of some studies from systematic reviews/meta-analyses due to the heterogeneity of outcomes or outcome measurements. It is a waste.

In this review, we find that there are more than 40 duplicated outcomes between protocols of TCM and western medicine clinical trials. No matter for clinical trials of TCM or western medicine, etiological test, chest imaging, respiratory symptoms, temperature, mortality/survival and adverse events are very important. These outcomes are relevant to the prognosis of disease and safety of therapy.

Because of no specific therapy can be used in the treatment of COVID-19, it is necessary and urgent to conduct clinical trials, no matter what the interventions are. We believe that it is important to develop a COS for clinical trials of TCM and western medicine for treating COVID-19, so that the efficacy of different interventions can be compared and merged in systematic review/meta-analysis.

Table 4 Outcomes from protocols of TCM clinical trials

Outcome domain	Outcomes	Number of outcomes	Defination/ outcome measurement	Time point
Mortality/survival				
	Mortality/survival	8	0	28 days, 84 days
Physiological/clinical				
Blood and lymphatic system outcomes				
	Blood routine test	10	0	Not provided
	Biochemical outcomes	6	0	Not provided
	CRP	5	0	Not provided
	Coagulation outcomes	3	0	Not provided
	Erythrocyte sedimentation rate	1	0	Not provided
	High-sensitive CRP	1	0	Not provided
Cardiac outcomes				
	ECG	1	1	Not provided
	Heart function	1	0	Not provided
	Heart rate	1	0	Not provided
	Myocardial enzyme	2	0	Not provided
	Myoglobin	1	0	Not provided
	Troponin	1	0	Not provided
Gastrointestinal outcomes				
	Clearance time of gastrointestinal symptoms	1	0	Not provided
	Remission of clinical symptoms: gastrointestinal discomfort	4	0	Not provided

Outcome domain	Outcomes	Number of outcomes	Defination/ outcome measurement	Time point
General outcomes				
	Blood pressure	1	0	Not provided
	Clearance time of fatigue	1	0	Not provided
	Clearance time of fever	14	1	1. 8 o'clock, 12 o'clock, 16 o'clock, and 20 o'clock, 2.28 days
	Clinical symptom score	1	0	Not provided
	Propotion of patients without fatigue	9	0	Not provided
	Proportion of patients without fever	3	0	Not provided
	Remission of clinical symptoms: fever	4	0	Not provided
	Temperature	3	0	Not provided
	TCM syndromes	7	0	Not provided
	The proportion of patients without fever	1	0	Not provided
	Time to remission/disappearance of primary symptoms	1	1	Not provided
Hepatobiliary outcomes				
	Liver function	5	0	Not provided
Immune system outcomes				
	HLA-DR	1	0	Not provided
	Immunoglobulin	1	0	Not provided
	Procalcitonin	5	0	Not provided
	Rate of subjects receiving systematic corticosteroids	1	1	28 days

Outcome domain	Outcomes	Number of outcomes	Defination/ outcome measurement	Time point
Infection and infestation outcomes				
	Incidence of antibiotic treatment	1	0	Not provided
	Proportion of patients with negative SARS-CoV-2	6	0	at the end of the treatment, on the 28th day of treatment
	Time of SARS-CoV-2 RNA turns to negative	16	2	Not provided
Renal and urinary outcomes				
	Urine routine	2	0	Not provided
	kidney function	5	0	Not provided
Psychiatric outcomes				
	Psychological outcomes	1	0	Not provided
Respiratory, thoracic and mediastinal outcomes				
	PaO2/FiO2	4	0	Not provided
	Chest imaging	12	1	Not provided
	Blood oxygen saturation	3	0	Not provided
	CURB-65	1	1	Not provided
	Clearance time of cough	4	0	Not provided
	Pulmonary function	6	0	Not provided
	Duration of mechanical ventilation	3	1	28 days
	Improvement of lung HRCT score	2	1	Not provided
	Pneumonia severity index	4	1	Not provided
	Proportion of patients without	6	0	Not provided

Outcome domain	Outcomes	Number of outcomes	Defination/ outcome measurement	Time point
	cough			
	Proportion of patients without sputum	2	0	Not provided
	Proportion of patients without wheezing	2	0	Not provided
	Respiratory rate	1	0	Not provided
	St Georges respiratory questionnaire (SGRQ)	4	1	Not provided
	Time to improvement of abnormalities in Chest radiology	1	1	28 days
	The incidence of dyspnea with low oxygen saturation level and high respiratory rate	1	1	28 days
	Time of improvement in respiratory symptoms	1	0	Not provided
Functioning				
Physical functioning				
	6-minute walk test (6MWT)	4	1	Not provided
	APACHE II scores	1	1	Not provided
	Clinical outcome	1	1	14 day
	DIC	1	0	Not provided
	Modified Barthel Index (MBI)	4	1	Not provided
	Major organ function	1	0	Not provided
	Incidence of medical complications during hospitalization	1	1	Not provided
	Incidence of multiple organ dysfunction	1	0	Not provided
	Patients with complications of 2019-nCoV infection	1	1	28 days

Outcome domain	Outcomes	Number of outcomes	Defination/ outcome measurement	Time point
	Recovery rate	2	0	Not provided
	SOFA score	1	1	Not provided
	Time to disease recovery	5	0	Not provided
	Time to release from isolation	2	0	Not provided
	Time to Clinical Recovery	1	1	Not provided
Global quality of life				
	EQ-5D	1	1	Not provided
	SF-36	2	1	Not provided
Resource use				
Hospital				
	Duration of hospitalization	10	1	28 days
	Length of stay in ICU	1	0	Not provided
Need for further intervention				
	The time when the condition becomes worse	6	3	Not provided
	Rate of progressing to the severe stage	7	1	Not provided
	Rate of progressing to the critical stage	10	1	Not provided
Adverse events/effects				
	Adverse events	9	0	Not provided

CRP: C-reactive protein; CURB-65: Confusion, Urea, Respiratory Rate and Age 65; ECG: electrocardiogram; HLA-DR: Human leukocyte antigen-DR; HRCT: chest high-resolution computed tomography; ICU: Intensive Care Unit; RNA: ribonucleic acid; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; SOFA: Sequential Organ Failure Assessment; TCM: traditional Chinese medicine.

Table 5 Outcomes from protocols of western medicine clinical trials

Outcome domain	Outcomes	Number of outcomes	Definition/ outcome measurement	Time point
Mortality/survival				
	Mortality/survival	36	1	2 weeks, 4 weeks, 12 weeks, 14-20 days, 28 days.
Physiological/clinical				
Blood and lymphatic system outcomes				
	Blood routine test	16	1	At baseline, day 1, 3, 4, 5, 7, 10, 14, 21, 28.
	Biochemical outcomes	7		Not provided
	CRP	9	0	At Baseline, day1, 3, 5, 6, 7, 10,14, 21, 28, 90
	Time of CRP recovery	1	0	28 days
	Coagulation outcomes	2	1	Day 1, 3, 5, 7, 10, 14, 21, 28
	ES rate	1	0	Not provided
	Rate of ES recovery	4	0	Two weeks, 28 days
	Time of ES recovery	1	0	28 days
Cardiac outcomes				
	ECG	3	1	Not provided
	Heart rate	6	0	Baseline, week 1, week 2, week 3, week 4
	Myocardial enzymes	2	0	Day 0, 3, 4, 6, 7, 10, 14, 28, 90

Outcome domain	Outcomes	Number of outcomes	Definition/ outcome measurement	Time point
	Mb	1	0	Day 1, 3, 5, 7, 10, 14, 21, 28
	Rate of Mb recovery	4	0	Two weeks, 28 days
	Rate of CK recovery	4	0	Two weeks, 28 days
	Time of Mb recovery	1	0	28 days
	Time of CK recovery	1	0	28 days
General outcomes				
	Abnormal time of temperature during infection	1	0	Not provided
	Antipyretic rate	2	1	14-20 days
	Blood pressure	6	0	Day 0 till day 21
	Clearance time of fever	15	0	14-20 days, up to 28 days
	Clearance time of fatigue	6	0	Not provided
	Clearance time of myalgia	2	0	14-20 days
	Proportion of patients without fatigue	6	0	Not provided
	Proportion of patients without dyspnea	5	0	14 days
	Proportion of patients without fever	14	0	Day 7, within 14 days
	Temperature	6	0	Baseline, 1 week, 2 weeks, 3 weeks, 4weeks
Hepatobiliary outcomes				
	ALT	1	0	At baseline , day 3, 6, 10, 14, 28 and 90
	Rate of ALT recovery	4	0	Two weeks, 28 days
	Time to ALT recovery	1	0	28 days

Outcome domain	Outcomes	Number of outcomes	Definition/ outcome measurement	Time point
Immune system outcomes				
	CD4+ T celll count	1	0	At Baseline , day 3, 6, 10, 14, 28 and 90
	CD8+ T celll count	1	0	At Baseline , day 3, 6, 10, 14, 28 and 90
	IL-2	1	0	Day 7, 14, 28
	IL-4	1	0	Day 7, 14, 28
	IL-6	8	0	Day 1, 3, 5, 7, 10, 14, 21, 28
	IL-8	1	0	On the Day28
	IL-10	1	0	Day 7, 14, 28
	Immunoglobulin	1	0	Not provided
	Lymphocyte subsets and complement	1	0	Day 1, 3, 5, 7, 10, 14, 21, 28
	Procalcitonin	4	0	Day 1, 3, 5, 7, 10, 14, 21, 28
	Recovery time of lymphocyte	1	0	Not provided
	Time to CD4+ T cell recovery	1	0	Not provided
	Time to CD8+ T cell recovery	1	0	Not provided
	TNF-α	4	0	Day 7, 14, 28
	γ-interferon	1	0	Day 7,14, 28
Infection and infestation outcomes				
	Chloroquine blood concentration	1	0	Day 1, 3, 5, 7, 10, 14, 21, 28
	Declining speed of SARS-CoV-2	1	1	Not provided
	Duration of antibiotic treatment	1	0	Not provided

Outcome domain	Outcomes	Number of outcomes	Definition/ outcome measurement	Time point
	Hemodiafiltration	1	0	Not provided
	Incidence of antibiotic treatment	2	0	Not provided
	Level of virus antibody in blood sample	1	0	Not provided
	Other infection	1	0	Not provided
	Proportion of patients with negative SARS-CoV-2	40	1	Day 0, 1, 2, 3, 4, 5, 7, 10, 14, 16, 21, 28
	Time of SARS-CoV-2 RNA turns to negative	23	1	At baseline, day 3, 6, 7, 10, 14, 28, 90
Metabolism and nutrition outcomes				
	Liquid balance	1	0	Not provided
Musculoskeletal and connective tissue outcomes				
	MRI of hip	1	1	Not provided
	CT of hip	1	1	Not provided
Renal and urinary outcomes				
	Urine routine	1	0	Not provided
	kidney function	2	1	Day 0, 1, 3, 4, 5, 7, 10, 14, 21, 28
	Incidence rate of kidney damage	1	0	Not provided
Respiratory, thoracic and mediastinal outcomes				
	Application of pulmonary surfactant	1	0	Not provided
	Blood oxygen saturation	2	0	Day 0 till day 21

Outcome domain	Outcomes	Number of outcomes	Definition/ outcome measurement	Time point
	PaO2/FiO2	7	1	Day 1, 3, 5, 7, 10, 14, 21, 28
	Chest imaging	25	2	At baseline , day 3, 4, 6, 7, 10, 14, 21, 28
	Clearance time of cough	9	0	14-20 days
	Clearance time of dyspnea	3	0	14-20 days, up to 28 days
	Duration of extracorporeal membrane oxygenation	2	0	Up to 28 days
	Duration of supplemental oxygenation	6	0	Up to 28 days
	Duration of mechanical ventilation	10	0	From Day 0 through Day 28
	Finger oxygen improvement rate	2	1	14-20 days
	Frequency of requirement for mechanical ventilation	1	0	Up to 28 days
	Frequency of requirement for supplemental oxygen	1	0	14 days, 28 days
	Frequency of respiratory progression	2	1	Up to 28 days
	Murray lung injury score	5	1	7 days, 14 days
	Oxygen intake methods	1	1	Up to 28 days
	Pneumonia severity index	2	0	Not provided
	Proportion of patients without cough	12	0	Within 14 days, up to 28 days
	Respiratory rate	6	1	Baseline, 1 week, 2 weeks, 3weeks, 4weeks
	Rate of mechanical ventilation	9	1	Day 7, 14, 15
	Time to normalization of respiratory rate	1	0	Not provided
	The duration of intubation	1	0	Not provided

Outcome domain	Outcomes	Number of outcomes	Definition/ outcome measurement	Time point
	The incidence of hypoxia	1	0	Not provided
	The lowest SpO2 during intubation	1	0	Not provided
	Time to chest imaging recovery	2	1	Two weeks
	The times of intubation	1	0	Not provided
	Time of improvement in respiratory symptoms	2	0	Not provided
	Time of using assisted breathing	2	0	Not provided
	Time to cough reported as mild	1	0	Not provided
	Time to dyspnea reported as mild	1	1	Up to 28 days
	Rate of no requiring supplemental oxygen	11	0	14 days
	Ventilator parameters	5	1	Day 10 and 28
Functioning				
Physical functioning				
	7-point scale	1	1	Not provided
	APACHE II scores	1	1	Day 10
	Complications	2	0	Not provided
	Demand for first aid measurements	1	1	On the day 28
	Disease progression rate	4	1	14-20 days
	Incidence of multiple organ dysfunction	1	0	Not provided
	Incidence of shock	1	0	Not provided
	Lower SOFA score	2	1	7 days, 14 days

Outcome domain	Outcomes	Number of outcomes	Definition/ outcome measurement	Time point
	NEWS2 score	1	1	Not provided
	Number of participants with improvement from severe type to common type	1	1	2 weeks
	Organ function support measures	1	0	Not provided
	Organ support intensity	1	0	Not provided
	Rate of severe type of disease	2	0	Not provided
	Rate of preventing mild to moderate patients from shifting to severe patients	1	0	Not provided
	Rate of disease remission	5	1	Day 7, within 14 days
	SOFA score	3	1	Day 7, 10
	Time to treatment failure	2	1	Not provided
	Time to NEWS2 of ≤ 2 maintained for 24 hours.	1	0	Up to 28 days
	Time to release from isolation	1	0	Not provided
	Time to severe stage	2	0	Not provided
	The rate of critical stage	3	1	2 weeks
	Time to Clinical Recovery	7	4	14 days, 28 days
	Time to Clinical Improvement	8	2	Up to 28 days
Delivery of care				
	The rate of discontinuations due to adverse events	1	0	Not provided
Resource use				
Economic	Hospitalization costs	1	0	Not provided
Hospital				

Outcome domain	Outcomes	Number of outcomes	Definition/ outcome measurement	Time point
	Duration of hospitalization	23	0	From day 0 through day 28
	Length of stay in ICU	10	1	Day 28
	ICU free days	1	0	Up to 28 days
	Incidence of ICU admission	9	0	Day7, 14, 15, 28
	The proportion of inpatients	1	0	Within 28 days
Need for further intervention				
	The time when the condition becomes worse	5	1	Not provided
	Jaw thrust maneuver	1	0	Not provided
	Rate of progressing to the critical stage	1	1	Day 7
	Time to the critical stage	1	1	Day 7
Adverse events/effects				
	Adverse events	29	5	At baseline, day 3, 6, 10, 14, 28, 90

APACHE-II: Acute Physiology and Chronic Health Evaluation; ALT: Alanine aminotransferase; CK: Creatine Kinase; CRP: C-reactive protein; ES: Erythrocyte sedimentation; ECG: electrocardiogram; ICU: Intensive Care Unit; IL: Interleukin; Mb: Myoglobin; NEWS2: National Early Warning Score 2; RNA: ribonucleic acid; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; SOFA: Sequential Organ Failure Assessment.

Contributors

RQ and HS contributed to the study design. XW and MZ conducted searching and extracted data from databases. RQ, CZ, JH, YH, TH contributed to the data analysis. RQ drafted the manuscript. ML, HS, CZ, JC, HS revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that there is no conflict of interest.

Patient consent

Not required.

Data sharing statement

The data is from public database and does not include identifiable patient data.

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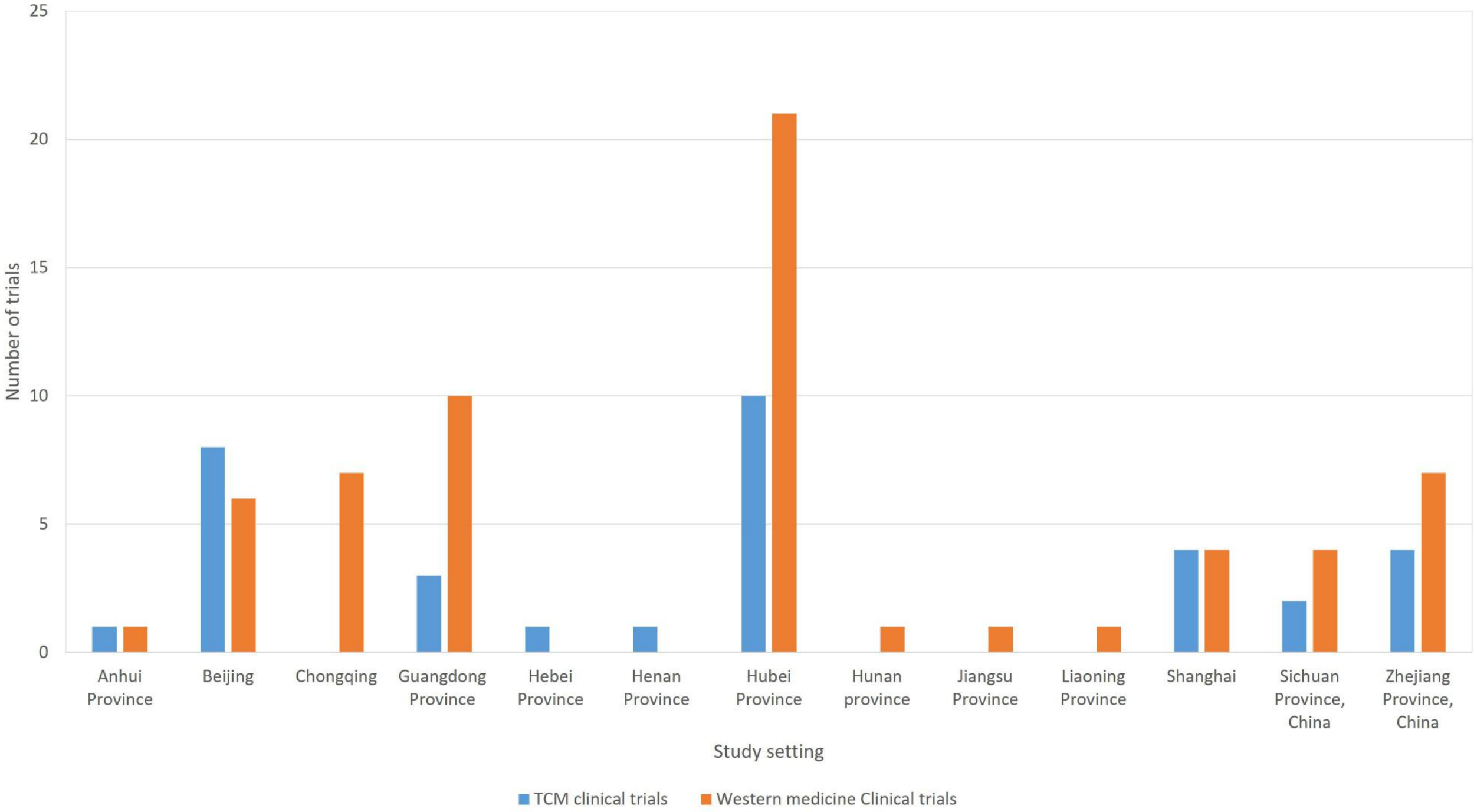
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Hebei Province
Henan Province
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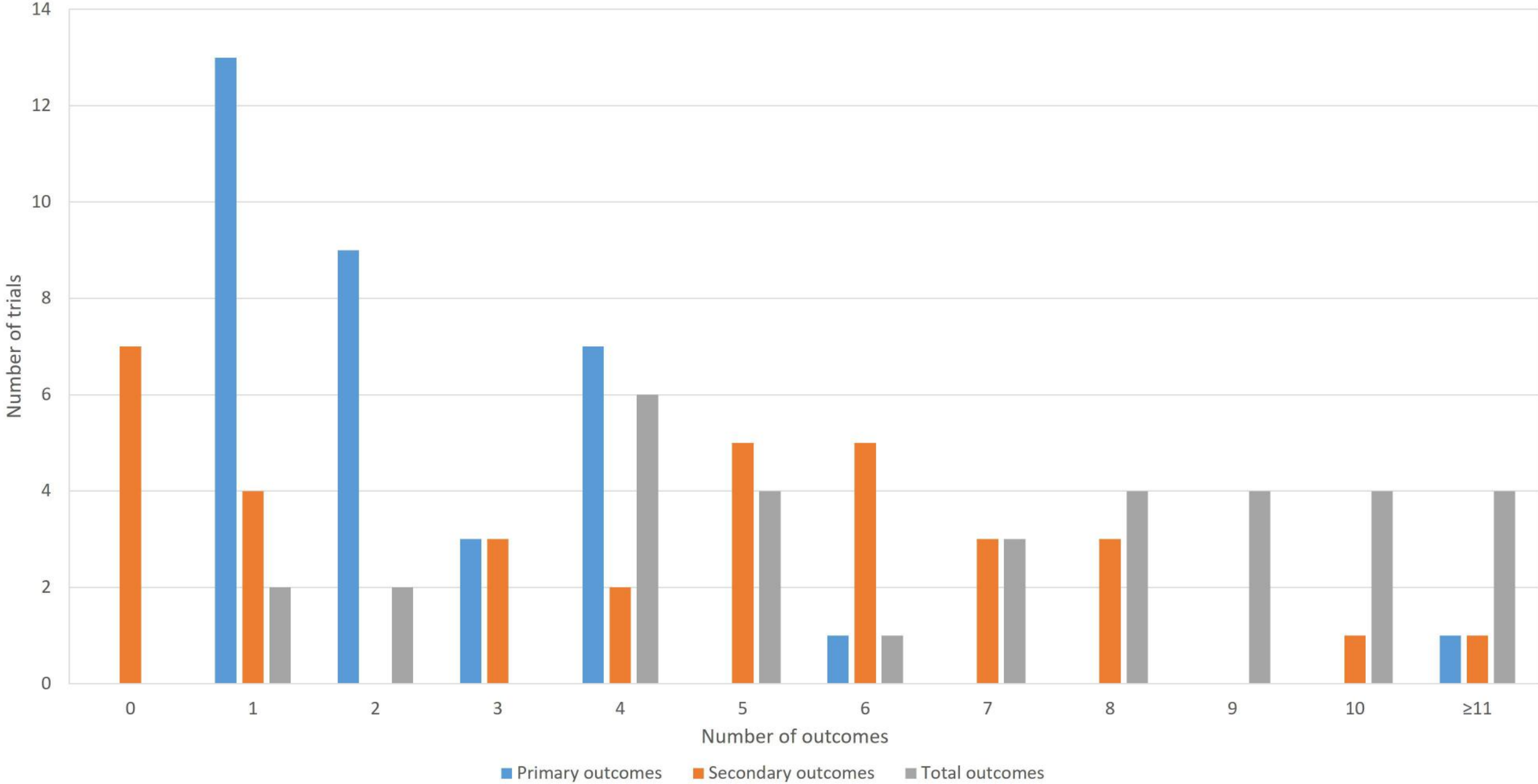
Study setting
TCM clinical trials
Western medicine Clinical trials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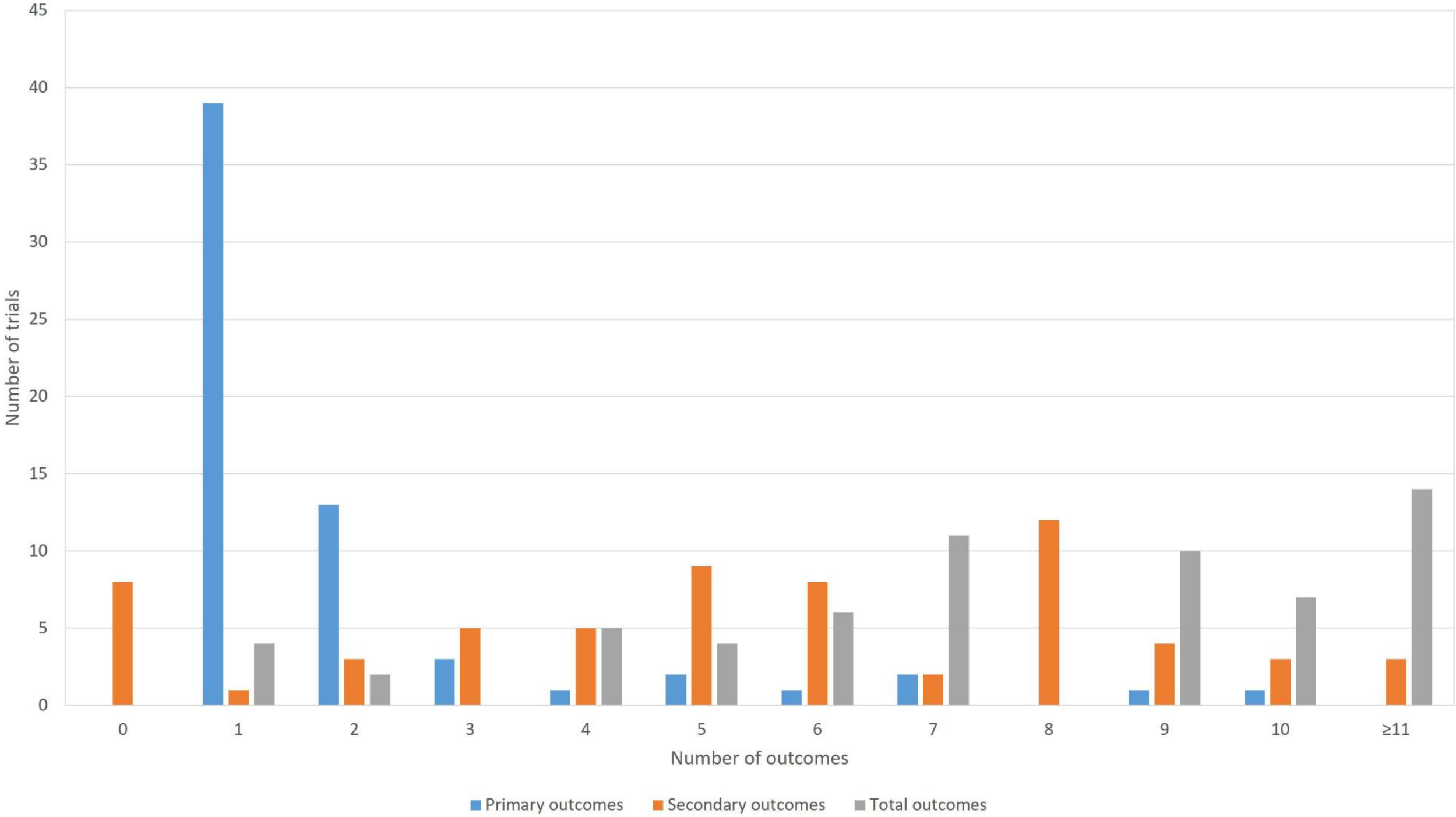
Total outcomes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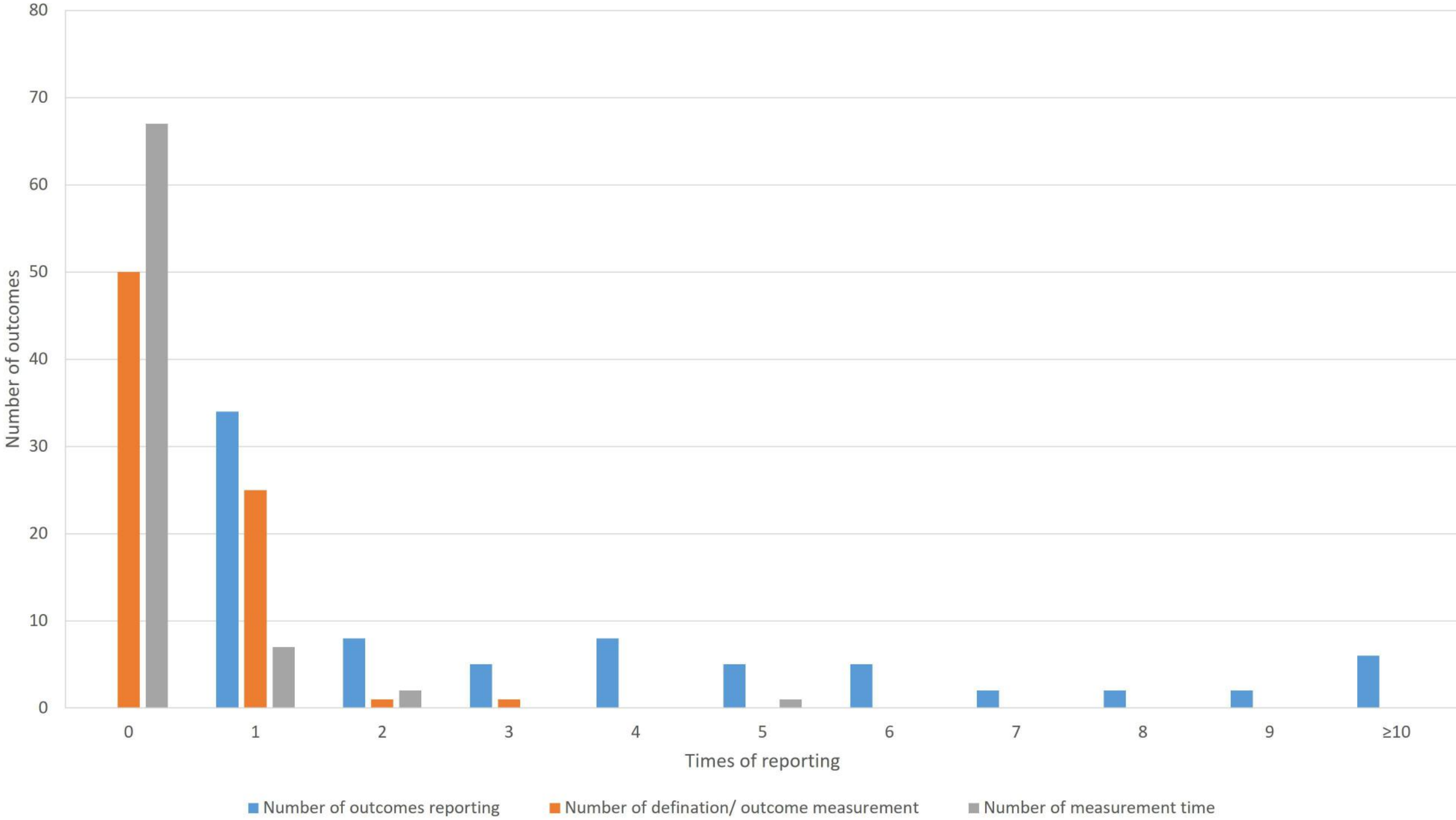
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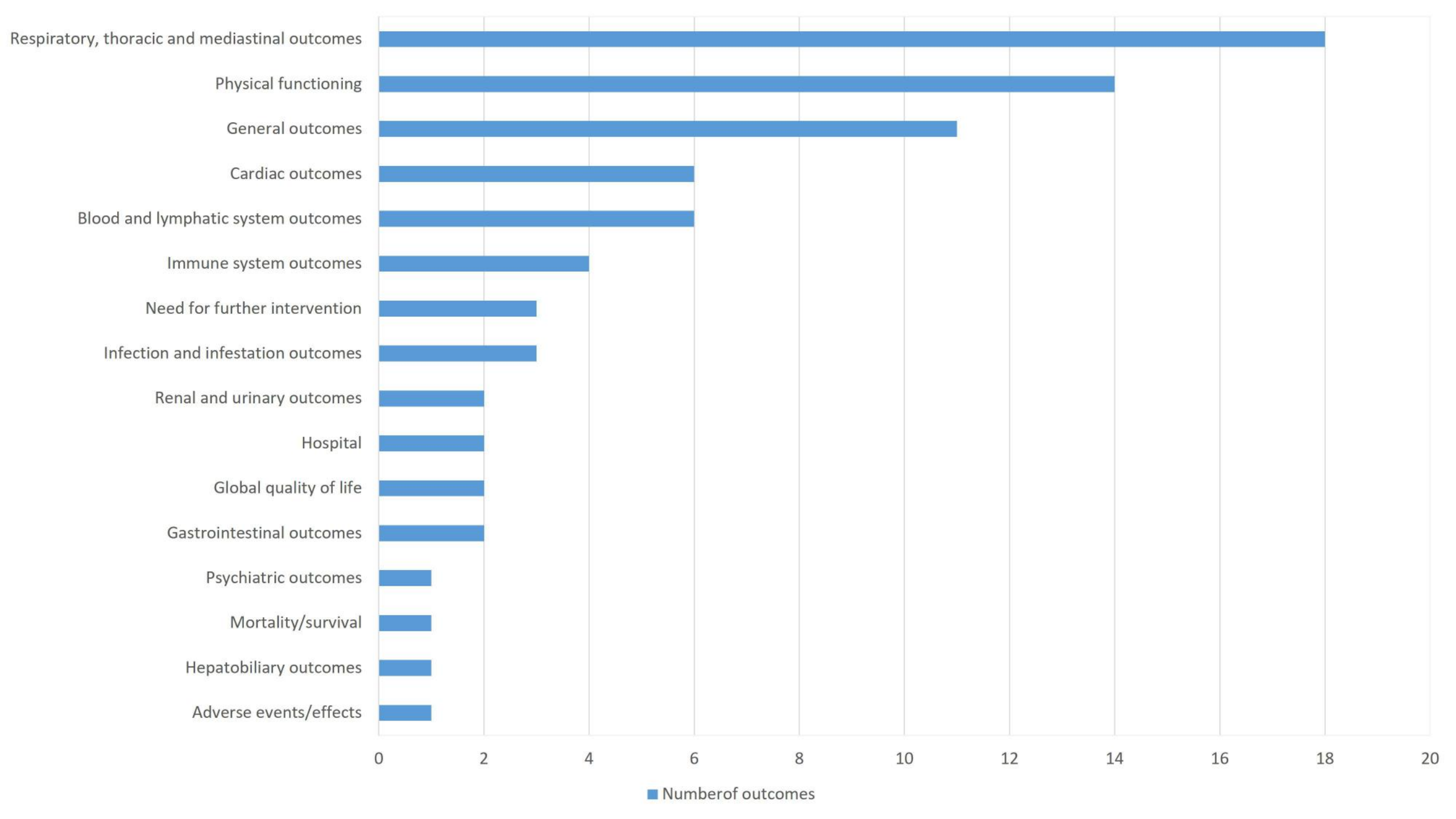
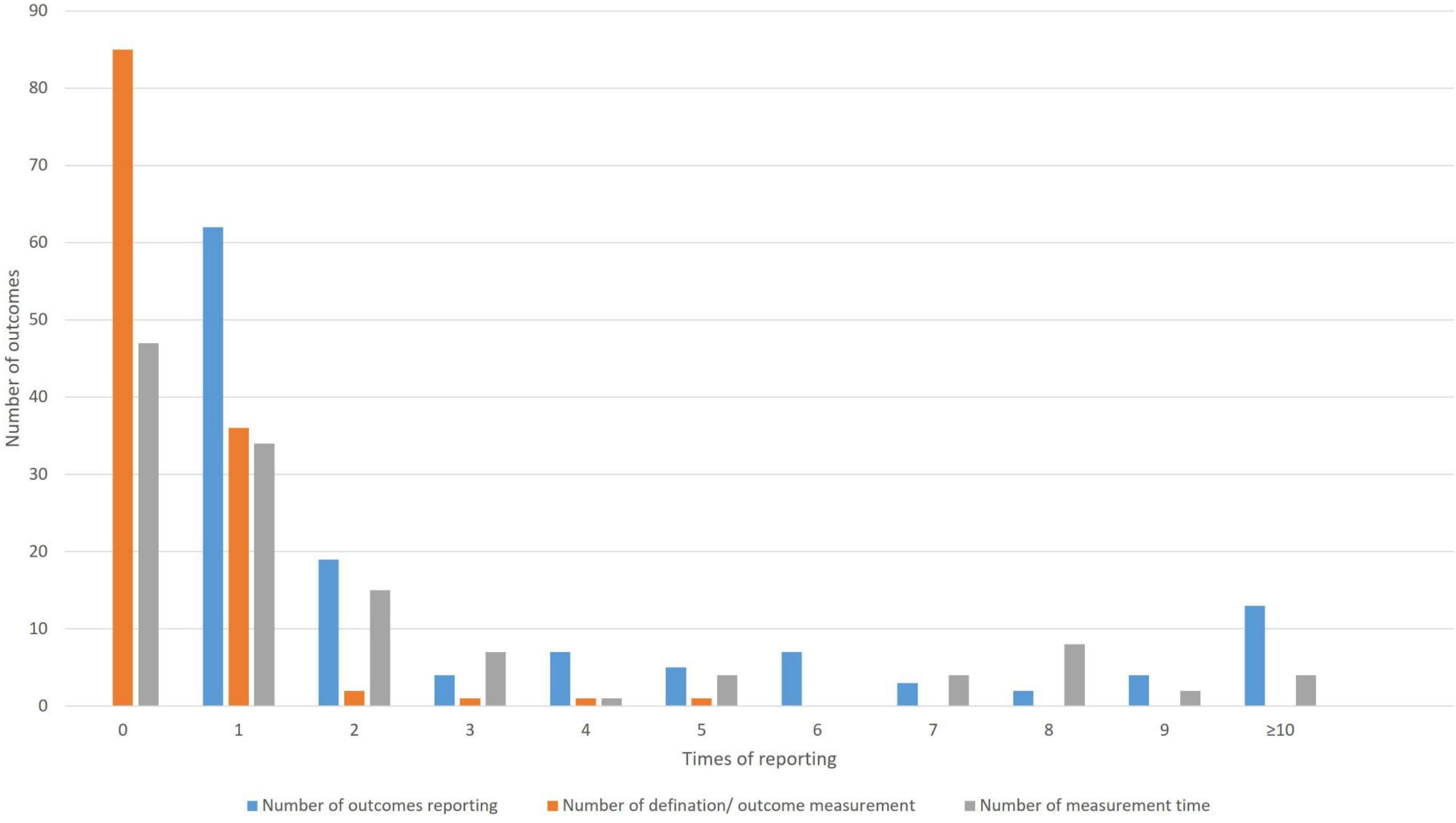
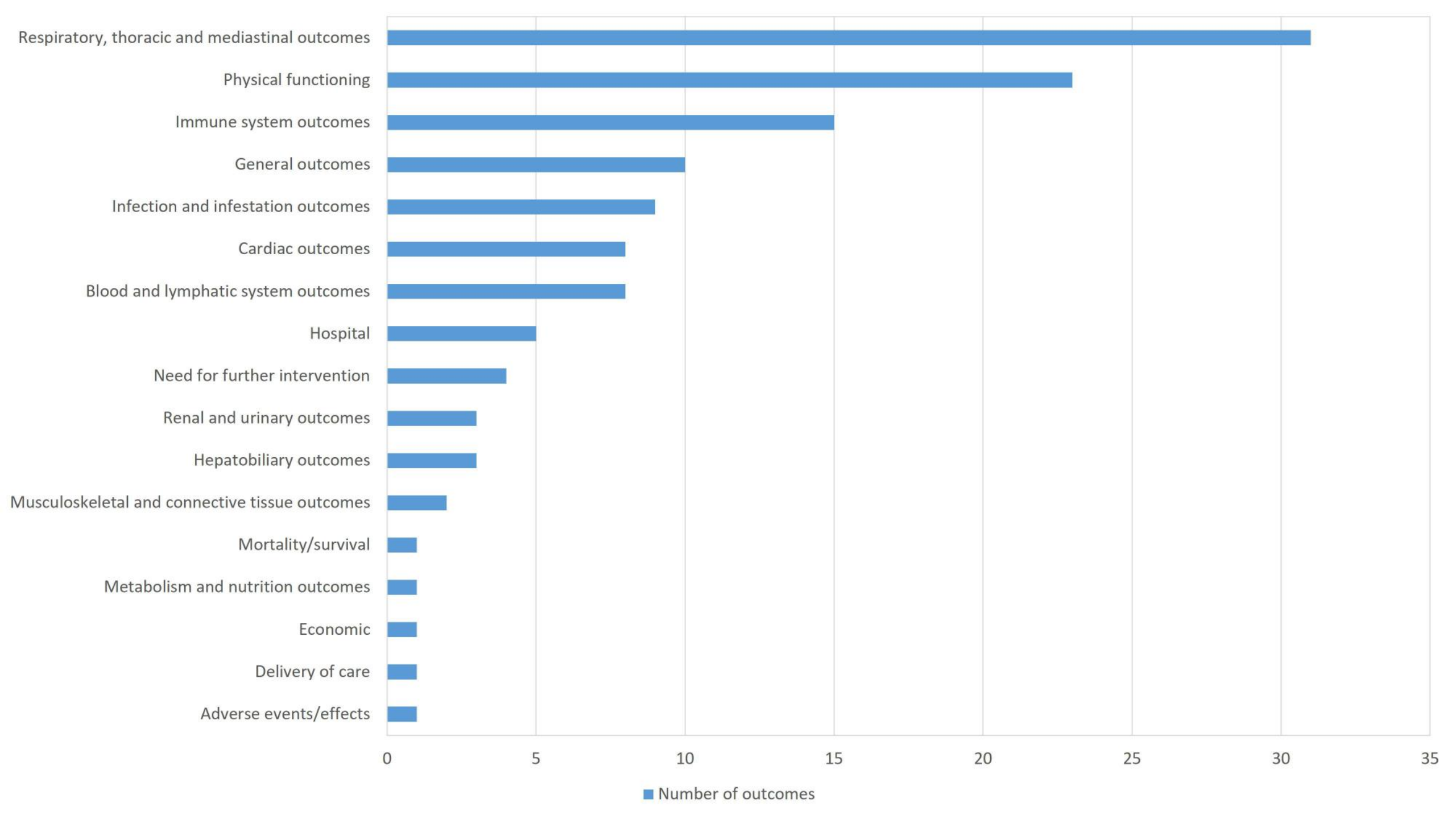

Respiratory, thoracic and mediastinal outcomes
Physical functioning
General outcomes
Cardiac outcomes
Blood and lymphatic system outcomes
Immune system outcomes
Need for further intervention
Infection and infestation outcomes
Renal and urinary outcomes
Hospital
Global quality of life
Gastrointestinal outcomes
Psychiatric outcomes
Mortality/survival
Hepatobiliary outcomes
Adverse events/effects
0
2
4
6
8
10
12
14
16
18
20
Numberof outcomes


90
80
70
60
50
40
30
20
10
0
Number of outcomes
0
1
2
3
4
5
6
7
8
9
≥10
Times of reporting
Number of outcomes reporting
Number of defination/ outcome measurement
Number of measurement time


Respiratory, thoracic and mediastinal outcomes
Physical functioning
Immune system outcomes
General outcomes
Infection and infestation outcomes
Cardiac outcomes
Blood and lymphatic system outcomes
Hospital
Need for further intervention
Renal and urinary outcomes
Hepatobiliary outcomes
Musculoskeletal and connective tissue outcomes
Mortality/survival
Metabolism and nutrition outcomes
Economic
Delivery of care
Adverse events/effects
0
5
10
15
20
25
30
35
Number of outcomes