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.

Journal of Clinical Epidemiology 152 (2022) 36–46

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Three out of four published systematic reviews on COVID-19 treatments were not registered and one-third of those registered were published: a meta-research study

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Accepted 21 September 2022; Published online 27 September 2022

Abstract

Objectives: The aim of this study is to describe (1) registered and (2) published systematic reviews (SRs) on COVID-19 treatments, and to analyze (3) the proportion of publications among registered SRs and (4) the proportion of registrations among published SRs.

Study Design and Setting: This meta-research study (CRD42021240423) is part of CEOsys (http://www.covid-evidenz.de/). Two reviewers identified protocols in PROSPERO (registered January 2020 to September 2020) and SRs published as preprint or peer-reviewed article in L·OVE (Living OVerview of the Evidence) COVID-19 (by May 2021). SRs of all types assessing COVID-19 treatments in humans were included.

Results: We included 239 PROSPERO protocols and 346 SRs published in L·OVE. In both samples, the affiliation of the corresponding author with an Asian institution, standard SR as review type, and meta-analysis as synthesis method were the most frequent characteristics. Living SRs made up ≤10%. A total of 71 of 239 (29.7%) PROSPERO protocols were published as SR by February 2022, that is, after at least 17 months of follow-up (25 of 71 as preprints, 35.2%). In L·OVE, 261 of 346 (75.4%) SRs published by May 2021 were not registered in PROSPERO.

Conclusion: Overall, one-third PROSPERO protocols were published and three-fourth published SRs were not registered. We strongly encourage authors to register and publish their SRs promptly to reduce research waste and to allocate resources efficiently during the pandemic and beyond.

Keywords: Meta-research; COVID-19; Treatment; Dissemination; Systematic reviews; PROSPERO

1. Background

In March 2020, the World Health Organization declared the coronavirus disease 2019 (COVID-19) a pandemic [1]. The massive global spread of COVID-19 is monitored with great caution and has resulted up to now in over 500 million total cases and over 6 million deaths as of August 2022 [2].

Meta-researchers observed a dynamic trend in publications on COVID-19 of papers "without data" and other

W. S. and J. N. contributed equally to this work.

Funding: This work was supported as part of the CEOsys project by Federal Ministry of Education and Research (BMBF), Germany, grant number 01KX2021.

Ethical Approval: Not required.

Conflicts of interest: The authors have no competing interests to declare. Waldemar Siemens was employed at Roche Pharma AG, Grenzach-Wyhlen, Germany, from April 2020 to June 2021. Roche Pharma AG was not involved in the project and had no influence at any time in the project. Waldemar Siemens is employed at the Institute for Evidence in Medicine (Medical Center, University of Freiburg, Germany) and Cochrane Germany in Freiburg since September 2021.

Data sharing statement: The data analyzed in this study are available at https://osf.io/w4nsa/.

Review registration: PROSPERO-ID: CRD42021240423.

Author Contributions: Conception and design: J.N., J.J.M., and C.S. Collection and assembly of data: J.N., J.S., and C.S. Analysis and interpretation: W.S., J.N., J.S., C.S., and J.J.M. Manuscript writing: W.S. and J.N. Accountable for all aspects of the work: W.S., J.N., J.S., J.J.M., and C.S.

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https://doi.org/10.1016/j.jclinepi.2022.09.011

What is new?

Key findings

- A total of 71 of 239 PROSPERO protocols (29.7%) were published as full systematic review.
- In the L·OVE sample, 261 of 346 systematic reviews (75.4%) were not registered in PROSPERO before publication.

What this study adds to what is known?

- This meta-research study adds important information on characteristics of systematic reviews on COVID-19 treatments.
- The emerging relevance of living systematic reviews and preprints is highlighted.
- One-third PROSPERO protocols were published and three-fourth published SRs were not registered.

What is the implication and what should change now?

- Researchers should take into account utilizing a living approach to synthesize the evidence on COVID-19 treatments.
- Preprints are a legitimate and important way of dissemination but should ideally be followed by a peer-reviewed publication as soon as possible.
- Timely publication and registration of systematic reviews is of highest importance to inform physicians and policy-makers during the ongoing COVID-19 pandemic.

publication types such as systematic reviews [3]. Although systematic reviews are a highly important source for clinical guidelines and for political decision-making [4], readers are often challenged by their number and partially low quality [5–7].

To facilitate transparency and to avoid duplication or flawed research it is highly recommended that clinical studies are prospectively registered [8]. Moreover, the registration of systematic reviews has also been endorsed [9–11], for example, in the widely accepted International Register of Prospective Systematic Reviews (PROSPERO, https://www.crd.york.ac.uk/prospero/) [12] or in databases like INPLASY (https://inplasy.com/) or OSF (https://osf.io/). Published systematic reviews addressing COVID-19 questions have often been conducted under severe time pressure [13] and therefore may be at risk of not having been registered. Also, many systematic reviews may have been registered [14], but not conducted because of a lack of resources [15].

Additionally, understanding the PICO approach and methodological aspects in COVID-19 systematic reviews, for example, the review type (systematic review, living review) and the type of publications evaluated (peer-reviewed journal publication, preprint), are relevant for planning further research, avoiding duplications, and getting an overview of the systematic review research landscape [16–18].

Therefore, the aims of this meta-research study are to identify and describe systematic reviews on COVID-19 treatments (1) registered in PROSPERO and (2) published in the COVID-19 Living OVerview of the Evidence (L·OVE) platform. Furthermore, we analyzed (3) the proportion of publications of the PROSPERO sample and (4) the proportion of registered systematic reviews of the L·OVE sample.

2. Methods

2.1. Study design

This meta-research study followed a systematic review approach and is reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guideline [19]. We registered the work prospectively in PROSPERO (CRD42021240423).

Our study is part of the CEOsys project, which is an association of 20 German university hospitals and partner organizations aiming at summarizing and assessing the certainty of study results regarding COVID-19 (https://covid-evidenz.de/, funded by the German Federal Ministry of Education and Research, grant number 01KX2021).

We structured this meta-research project in the analysis of systematic reviews evaluating prevention measures (part I) [20] and the analysis of treatment measures for COVID-19 patients (part II), which is presented in this article.

2.2. Eligibility criteria

We included PROSPERO protocols of systematic reviews (PROSPERO sample) and systematic reviews published in the L·OVE platform (L·OVE sample) as of January 2020 addressing any treatment measures for COVID-19 in patients of any age. Treatment measures were defined as any pharmacological or nonpharmacological measure to treat acute COVID-19. There were no restrictions regarding the control group. Furthermore, the systematic review protocols (PROSPERO sample) and published systematic reviews (L·OVE sample) had to report at least one health-related outcome, that is, an outcome assessing patients' health in a broad sense (e.g., dyspnea, hospitalization, antibody titers). Taking into account that the L·OVE sample (focusing on published systematic reviews) includes any types of reviews, we used additional criteria to define a review as systematic review: (1) a clear interventional research question had to be reported, (2) at least two

medical databases must have been searched, (3) a flowchart or a description of the screening process had to be provided, and (4) definite inclusion and exclusion criteria of the included primary studies had to be reported in the Methods section of the systematic review.

We excluded PROSPERO protocols and published systematic reviews if they assessed treatments against other viruses (e.g., influenza) or interventions for rehabilitation after COVID-19, if they were duplicates, if information were lacking, or if they did not meet the systematic review definition. Furthermore, we neither included systematic reviews (at the protocol stage or after being published) focusing on other meta-research (e.g., a review of review) nor systematic reviews written in other languages than the English.

2.3. Systematic literature searches

2.3.1. PROSPERO sample of protocols.

We searched PROSPERO protocols registered on https://www.crd.york.ac.uk/prospero/ by September 2020, focusing on COVID-19 treatments. We applied the COVID-19 treatment filter provided on PROSPERO (Appendix A).

2.3.2. COVID-19 Living OVerview of the Evidence sample of published systematic reviews.

We searched for systematic reviews published in the COVID-19 L·OVE platform (Living OVerview of the Evidence; https://app.iloveevidence.com/) by May 2021. COVID-19 L·OVE includes more than 40 medical databases, trial registries, and preprint servers. We applied the implemented ‘‘Prevention and treatment’’ and ‘‘Systematic reviews’’ filters without further restrictions.

2.4. Study selection

Two reviewers (J.N., J.S.) independently screened the full PROSPERO protocols for eligibility because abstracts are not separately available for PROSPERO protocols.

The (1) title and abstract and (2) full text from records identified in COVID-19 L·OVE were screened by one reviewer (J.N.) and checked by a second reviewer (J.S.). We resolved disagreements by discussion (J.N., J.S.). In the absence of consensus, a third reviewer (C.S.) was involved.

2.5. Data extraction

Data extraction was performed by one reviewer (J.N.) and thoroughly checked by a second reviewer (J.S.). Disagreements were resolved by discussion (J.N., J.S.) or, in case of remaining disagreements, by involving a third reviewer (C.S.).

We extracted the following main characteristics in both samples, that is, the identified PROSPERO protocols and published systematic reviews identified in COVID-19 L·OVE: author, year, population, intervention, primary and secondary outcomes, institutional affiliation of corresponding author, review type (e.g., living systematic review, rapid systematic review), study designs included, synthesis method (e.g., meta-analysis, network meta-analysis), and date of registration and publication.

The data are available at https://osf.io/w4nsa/.

2.6. Definition and data synthesis of main outcomes

Based on the aims of this meta-research study, we included various outcomes to describe the characteristics of (aim 1) the PROSPERO protocols and (aim 2) the systematic reviews published in COVID-19 L·OVE.

Additionally, the proportion of PROSPERO protocols (aim 3), for which a published systematic review existed, was used to estimate the extent of dissemination (i.e., conversion rate) of systematic reviews on COVID-19 treatments. For this purpose, the PROSPERO sample first was matched with the L·OVE sample using PROSPERO's unique CRD number (CRD: Centre for Reviews and Dissemination). Second, we additionally checked the PROSPERO protocols regarding information on a final publication and, as third step, we conducted a search in Google Scholar (by February 2022) to extend the time between registration and possible publication to at least 17 months to avoid bias by missing publications with a shorter time available for dissemination.

Subsequently, we analyzed the proportion of PROSPERO protocols published over time for documenting the registration date and the publication date of the corresponding systematic review (published as peer-reviewed journal article or preprint or both).

For identifying the proportion of systematic reviews published in COVID-19 L OVE and registered a priori in PROSPERO (aim 4), we thoroughly checked whether the published systematic reviews (up to May 2021) were a priori registered in PROSPERO by searching the register and checking the full texts for the keywords ‘‘PROSPERO’’ and ‘‘CRD.’’ In addition, we analyzed the currentness of evidence in the L·OVE sample considering the publication date of the systematic review and the date of the latest search (conducted by the review authors).

2.7. Statistical analysis

We performed data extraction and management as well as data analysis in Excel (version 2016) and R version 4.1.2 [21]. We summarized study results with descriptive statistics. Exploratory subgroup analyses were calculated for both samples for (1) proportion of published PROSPERO protocols over time and (2) time between search and publication date for the L·OVE sample regarding the following variables: review type, synthesis method, and publication status. The results are presented by means of cumulative incidence plots. We used R version 4.2.1 [22] and the packages survival [23] survminer [24] and ggplot2 [25].

3. Results

3.1. PROSPERO sample: registered protocols

Of 595 entries identified in PROSPERO, 356 were excluded because eligibility criteria (e.g., wrong patient population or intervention, systematic review criteria not met) were not applicable. Finally, 239 PROSPERO protocols were included focusing on treatment measures for COVID-19 (Fig. 1).

3.2. PROSPERO sample: characteristics

In the PROSPERO sample (identified between January 2020 and September 2020, $N = 239$), most protocols (62, 25.9%) focused on Traditional Chinese Medicine to treat COVID-19 (Table 1). Antiviral and antimicrobial agents were considered in 50 (20.9%) PROSPERO protocols. Immunological agents (e.g., immunosuppressive drugs, corticosteroids, tocilizumab) were considered in 33 (13.8%) PROSPERO protocols. In total, approximately in two out of three (150, 62.7%) protocols the corresponding author was affiliated with institutions in Asia. Regarding the review type, most PROSPERO protocols were planned as standard systematic review (208, 87.0%). Only 7 (3.0%) were planned as rapid review and 24 (10.0%) were planned as living systematic review or the authors were planning to provide updates regularly.

3.3. PROSPERO sample: proportion of published protocols over time

Figure 2 shows the proportion of PROSPERO protocols over time (by February 2022) for which a corresponding

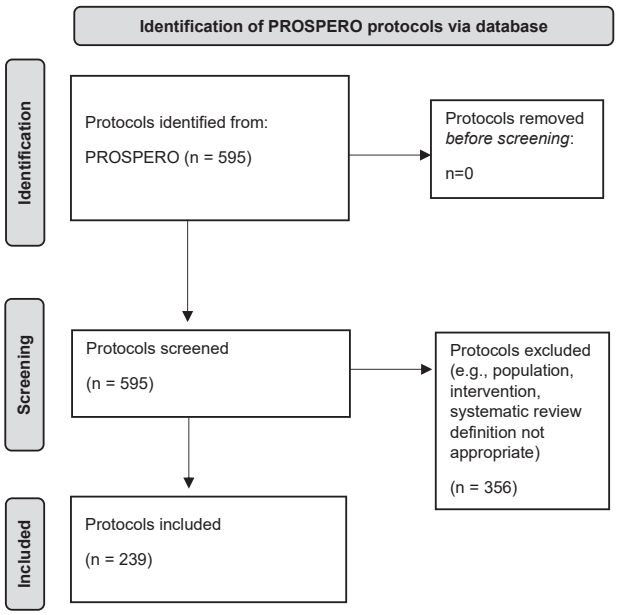

Fig. 1. Flow diagram of the PROSPERO sample (identified between January 2020 and September 2020).

Table 1. Characteristics of PROSPERO sample (identified between January 2020 and September 2020)

Characteristics	*N* = 239	100%
Population: age		
All ages[a]	172	72.0%
Adults (>18 yr)	60	25.1%
Children (<18 yr)	4	1.6%
Women of childbearing age (pregnant, postpartum)	2	0.8%
Older adults (>64 yr)	1	0.4%
Population: severity		
All grades of severity[a]	163	68.2%
Severely ill (i.e., in hospital)	37	15.5%
Patients with predefined severe symptoms	29	12.1%
Critically ill (i.e., in ICU)	7	2.9%
Nonsevere patients	3	1.3%
Population: disease		
SARS-CoV-2 only	226	94.6%
Other coronaviruses also included	13	5.4%
Intervention		
Traditional Chinese Medicine	62	25.9%
Antiviral and antimicrobial	50	20.9%
Immunological agents	33	13.8%
Any or several in comparison	28	11.7%
Oxygenation and ventilation	18	7.5%
Cell-based therapies	14	5.9%
Anticoagulants	13	5.4%
Other	21	8.8%
Main outcomes[b]		
Mortality and efficacy	70	29.3%
Efficacy	70	29.3%
Mortality	46	19.2%
Mortality, efficacy, and safety	37	15.5%
Efficacy and safety	13	5.4%
Mortality and safety	2	0.8%
Safety	1	0.4%
Institutional affiliation		
Asia	150	62.7%
South America	29	12.1%
Europe	26	10.9%
North America	15	6.3%
Africa	15	6.3%
Australia	3	1.3%
No institutional affiliation	1	0.4%
Review type		
(Standard) systematic review	208	87.0%
Living SR or updated SR	24	10.0%
Rapid review	7	3.0%
Study designs included		
NRSI + RCT	147	61.5%
RCT	83	34.7%
NRSI	8	3.3%

(*Continued*)

Table 1. Continued

Characteristics	*N* = 239	100%
No information	1	0.4%
Synthesis method		
Meta-analysis	180	75.3%
SR without meta-analysis	42	17.6%
Network meta-analysis	17	7.1%
Anticipated completion		
Before February 2022	234	97.9%
After February 2022	5	2.1%
Publication status[c]		
Published as full SR	71	29.7%
Published as a peer-reviewed journal article only	46	19.2%
Published as a preprint only	13	5.4%
Published as both (preprint/peer-reviewed)	12	5.0%
No publication identified	168	70.3%

Abbreviations: ICU, intensive care unit; *N*, number; NRSI, non-randomized studies of interventions; RCT, randomized controlled trial; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SR, systematic review.

[a] In this category, systematic reviews were included if (1) all ages/all grades of severity were included or (2) the age range/grades of severity to be included was not predefined in the inclusion criteria.

[b] Main outcomes as defined in the PROSPERO entry.

[c] Last update search: February 2022.

publication of a systematic review was identified. In total, 29.7% (i.e., 71 of 239 PROSPERO protocols registered up to September 2020) were published. After 400 days of registration, publication probability did not change anymore.

Of the published 29.7%, about two-thirds (19.2%) were published as peer-reviewed journal article. In almost all PROSPERO protocols (97.9%) the authors stated a completion date before February 2022 (Table 1). Three PROSPERO protocols were registered only after the publication of the corresponding systematic reviews (Fig. 2).

When compared to standard systematic reviews, our results indicated that living or updated systematic reviews are probably more likely being published [hazard ratio (HR) 2.30, 95% confidence interval (CI) 1.24–4.29], whereas there were no such signals for rapid reviews (HR 1.16, 95% CI 0.28–4.74) (Fig. B.1/Appendix B).

The second subgroup analysis regarding synthesis method (Fig. B.2/Appendix B) was inconclusive and resulted in a HR of 0.68 (95% CI 0.34–1.37) for systematic reviews without meta-analysis and a HR of 1.17 (95% CI 0.51–2.73) for network meta-analysis, both compared to the reference category meta-analysis.

The subgroup analysis for publication status (Fig. B.3/Appendix B) indicated that preprints might have a larger likelihood of publication than journal publications in this sample (HR 2.2, 95% CI 1.16–4.17).

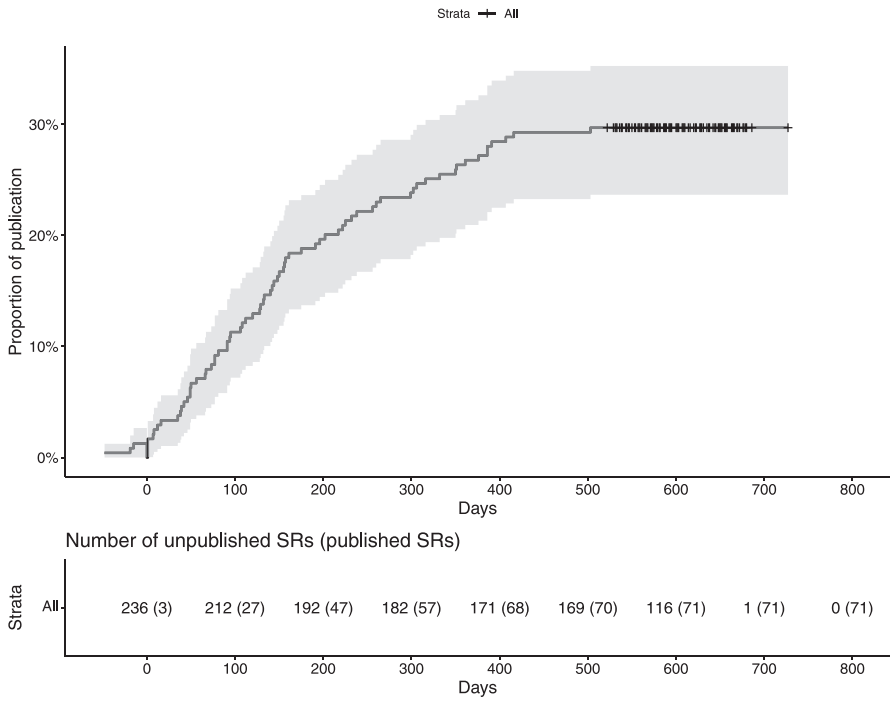

Fig. 2. Proportion of published PROSPERO protocols over time (*N* = 239).

3.4. Living OVerview of the Evidence sample: published systematic reviews

Of 2,179 entries identified in COVID-19 L·OVE, 413 were included for the analysis focusing on various COVID-19 treatments in humans. Because some systematic reviews could be assigned to more than one report (e.g., preprint and peer-reviewed publication, updated versions, preprints published on more than one platform), our final number of unique systematic reviews for the analysis was 346 (Fig. 3).

3.5. Living OVerview of the Evidence sample: characteristics

In the L·OVE sample (N = 346), antiviral and antimicrobial interventions (121, 35.0%) were assessed most frequently (Table 2). In about half of the systematic reviews (175, 50.6%) the corresponding author was affiliated with institutions in Asia. Regarding the review type, 84.7% were standard systematic reviews and 6.1% were living systematic review. In total, 217 (62.7%) systematic reviews were peer-reviewed journal articles followed by preprint publications (81, 23.4%), 39 (11.3%) were published both as journal article and preprint. A total of 261 (75.4%) systematic reviews from the L·OVE sample were not registered in PROSPERO.

We identified 49 systematic reviews with the same PROSPERO CRD number in both samples corresponding to an overlap of 20.5% for the PROSPERO sample and 14.2% for the L·OVE sample.

3.6. Living OVerview of the Evidence sample: currentness of evidence

Fig. 4 shows the month of last literature search of 324 systematic reviews (22 missing values: no search date or/

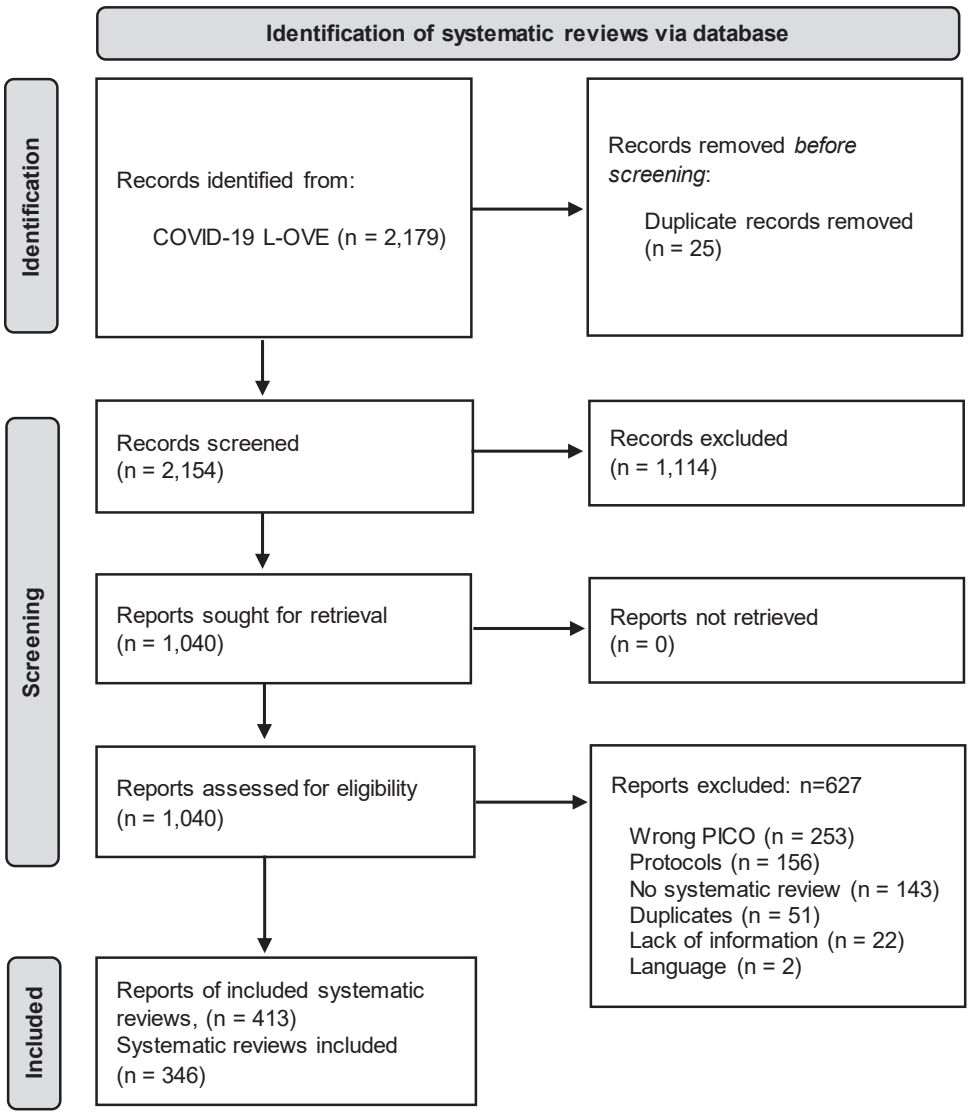

Fig. 3. Flow diagram of the L·OVE sample (searched May 2021).

Table 2. Characteristics of L·OVE sample (searched May 2021)

Characteristics	*N* = 346	100%
Population: age		
All ages[a]	322	93.1%
Adults (>18 yr)	15	4.3%
>12 yr	5	1.4%
Children (<18 yr)	3	0.9%
Older adults (>64 yr)	1	0.3%
Population: severity		
All grades of severity[a]	292	84.4%
Severely ill (i.e., in hospital)	35	10.1%
Patients with predefined severe symptoms	11	3.2%
Critically ill (i.e., in ICU)	6	1.7%
Nonsevere patients	2	0.6%
Population: disease		
SARS-CoV-2 only	319	92.2%
Other coronaviruses also included	27	7.8%
Intervention		
Antiviral and antimicrobial	121	35.0%
Immunological agents	81	23.4%
Any or several in comparison	46	13.3%
Cell-based therapies	35	10.1%
Traditional Chinese Medicine	20	5.8%
Oxygenation and ventilation	15	4.3%
Anticoagulants	10	2.9%
Other	18	5.2%
Main outcomes[b]		
Mortality, efficacy, and safety	133	38.4%
Mortality and efficacy	90	26.0%
Mortality	59	17.1%
Efficacy	37	10.7%
Efficacy and safety	16	4.6%
Mortality and safety	3	0.9%
Safety	8	2.3%
Institutional affiliation		
Asia	175	50.6%
North America	64	18.5%
Europe	57	16.5%
South America	33	9.5%
Africa	9	2.6%
No institutional affiliation	5	1.4%
Australia	3	0.9%
Review type		
Standard systematic review	293	84.7%
Rapid review	32	9.2%
Living SR or updated SR	21	6.1%
Study designs included		
NRSI + RCT	152	44.0%
NRSI	76	22.0%
RCT	56	16.2%
No information	49	14.2%
Empty review	13	3.8%
Synthesis method		
Meta-analysis	209	60.4%
SR without meta-analysis	125	36.1%
Network meta-analysis	9	2.6%
Other (benefit-risk assessment; IPD analysis)	3	0.9%
Publication type		
Peer-reviewed journal	217	62.7%
Preprint	81	23.4%
Both: peer-reviewed journal and preprint	39	11.3%
Published online without peer-review	9	2.6%
Studies per review, median (IQR)	12	(6–24)
PROSPERO registration		
No	261	75.4%
Yes	85	24.6%

Abbreviations: ICU, intensive care unit; IPD, individual patient data; IQR, interquartile range; *N*, number; NRSI, nonrandomized studies of interventions; RCT, randomized controlled trial; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SR, systematic review.

[a] In this category, systematic reviews were included if (1) all ages/all grades of severity were included or (2) the age range/grades of severity to be included was not predefined in the inclusion criteria.

[b] Main outcomes were extracted according to the review aims and refinements in the Methods section of each systematic review.

and no publication date reported). The white dotted gray area displays the cumulative sum of the latest reported search dates when starting in March 2021. The data indicate that the search date of 50% of the systematic reviews identified in L·OVE (published up to May 2021) was before July 2020.

The median time between search date reported by the review authors and publication date were 59 days (95% CI 49–65) (Fig. C.1/Appendix C). The exploratory subgroup analyses identified no differences for the variables review type and synthesis methods (Figs. C.2 and C.3/Appendix C). When compared to peer-reviewed journal, results indicated that preprints (HR 2.11, 95% CI 1.60–2.78), both peer-reviewed journal publication and preprint publications (HR 2.36, 95% CI 1.66–3.35), and published online without peer-review systematic reviews (HR 9.01, 95% CI 4.37–18.59) were probably more likely of having fewer days between publication and latest search (Fig. C.4/Appendix C).

4. Discussion

4.1. Summary of findings

In this meta-research study, we identified a sample of 239 PROSPERO protocols, registered during the early

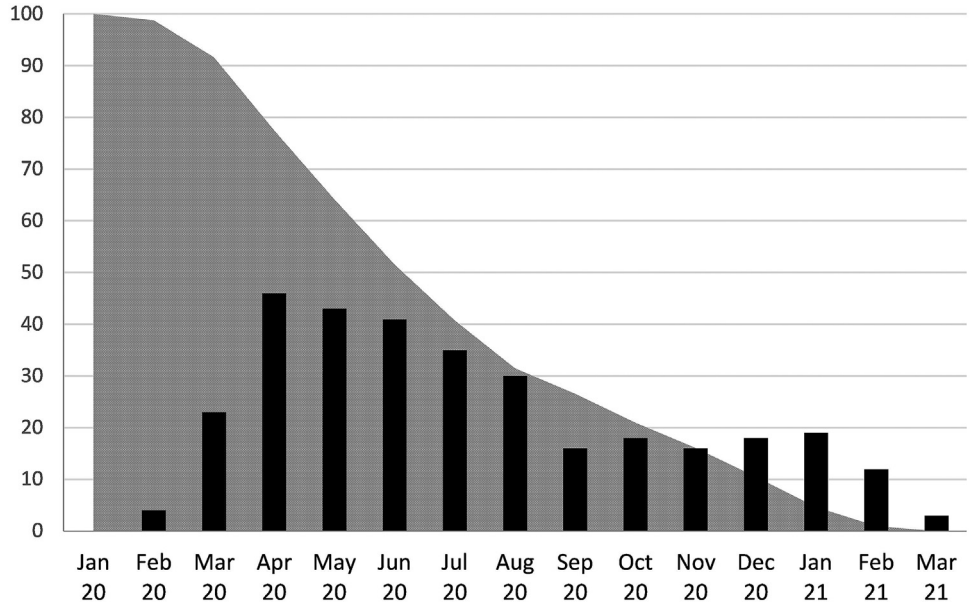

Fig. 4. Last literature search (as reported by authors of the systematic review) in the L·OVE sample (N = 324): per month and cumulative.

phase of the pandemic between January 2020 and September 2020, and 346 L·OVE publications up to May 2021.

Less than one-third of PROSPERO protocols were published as completed systematic review. About three-quarters of the published systematic reviews of the L·OVE sample were not registered.

Characterizing the samples, we noted that a quarter of PROSPERO protocols focused on Traditional Chinese Medicine as intervention for COVID-19. These were followed by antiviral and antimicrobial agents making up one-fifth. In the L·OVE sample, antiviral and antimicrobial interventions and immunological agents were assessed most frequently, that is, in about one-third and one-quarter, respectively. In contrast, to the PROSPERO sample, only 1 out of 20 published systematic reviews of the L·OVE sample assessed Traditional Chinese Medicine as intervention.

The affiliation of the corresponding author with an Asian institution, standard systematic review as review type, and meta-analysis as synthesis method were the most frequent categories for both the PROSPERO and the L·OVE sample. Living systematic reviews as review type made up less than 10% in both samples.

4.2. Results in context of other meta-research studies

4.2.1. Characteristics

In a meta-research study analyzing the characteristics and quality of published systematic reviews addressing a research question relating to COVID-19 (N = 280), Abbott et al. [26] found that the lead author institution was most frequently based in China. This finding is supported by another meta-research study of systematic reviews on COVID-19 treatments in which China contributed 36.5% (69/189) [18], which is in general in agreement with our results. Although many protocols on PROSPERO were registered with Traditional Chinese Medicine as intervention, we only identified about 5% of systematic review publications in the L·OVE sample with Traditional Chinese Medicine, even though L·OVE includes three biweekly updated Chinese databases (CBM: Chinese Biomedical Literature Database, CNKI: Chinese National Knowledge Infrastructure, VIP: Chinese Scientific Journal Database). We suspect that these not (yet) published systematic reviews might be poorly funded or were abandoned due to the urgency of patient care during the pandemic or other unknown reasons.

The COVID-19 pandemic raises awareness for the need of living systematic reviews [8,27–30]. In 5 out of 88 (5.7%) systematic reviews from a meta-research study, the review authors stated planning to update their systematic review [26], which is close to the 6.1% of living systematic reviews identified in our L·OVE sample. The low proportion of living systematic reviews could have multiple reasons, for example, no need to label the review as living due to other overlapping reviews, lack of resources, unawareness, or lacking expertise in living evidence synthesis. Nevertheless, searching PubMed publications including ‘‘living systematic review’’ in the title (search date: August 5, 2022) reveals that about three-fourth are associated with COVID-19 and that about 90% were published not before 2020 which suggests that the pandemic may be a catalyst for living systematic reviews.

During the pandemic, preprint publications on COVID-19 were produced more frequently, accessed more, cited more, and shared more on various online platforms than

non-COVID-19 preprints [16,31]. This is not surprising because rapid communication of findings is of high relevance to inform physicians, researchers, and policymakers [32].

Interestingly, our meta-research showed that of the few published systematic reviews (71/239, 29.7%) of the PROSPERO sample, approximately one-third (25/71, 35.2%) were published as preprints, which is in line with the number of preprints in the L·OVE sample (120/346, 34.7%) indicating the use and acceptance of preprint servers.

Although there is no doubt that preprint publications have become more relevant in the pandemic [16], it has to be taken into account that preprints are not peer-reviewed and that there may be substantial differences between preprints and peer-reviewed publications—taking into account that reviewer comments may impact the overall content of a publication [17,32].

4.2.2. Proportion of published PROSPERO protocols over time

Although the 97.9% of the included PROSPERO protocols stated a completion date for the planned systematic review before February 2022, our mature time-to-event data showed that only 29.7% of these protocols were published as systematic review. In contrast, an analysis of PROSPERO protocols focusing on pain therapy revealed that 53.6% (742/1,384) of this sample had been published within at least 1.3 years following their registration [15]. The reasons for the lower proportion of publication found in our research may be associated with scarcity of resources, awareness of other similar systematic reviews, or the fact that review results are out-of-date within a short time during a dynamically changing pandemic situation. These factors may have discouraged systematic review authors from continuing and publishing their registered systematic reviews.

4.2.3. Proportion of published systematic reviews registered in PROSPERO

Abbott et al. [26] defined a subsample of 88 from 280 systematic reviews that met the authors' systematic review criteria. Twenty-nine systematic reviews of these 88 were registered (33%), which is slightly higher than the percentage of registered systematic reviews in our L OVE sample (24.6%). This is slightly higher compared to the proportion of registered systematic reviews on remdesivir for COVID-19 treatment (8/38, 21.1%) [33] or systematic reviews of various treatments in advanced cancer patients (39/261, 14.9%) [34].

4.3. Limitations

In regards to the generalizability of our findings, we have to acknowledge that this meta-research project refers to systematic reviews from the early phase of the pandemic with PROSPERO protocols registered between January 2020 and September 2020 and systematic reviews published on COVID-19 L·OVE up to May 2021. However, for evaluating the proportion of published PROSPERO protocols we searched for published systematic reviews up to February 2022 to allow a time between registration and publication of 17–25 months. This should be sufficient regarding the pandemic situation and the possibility to publish as preprint (without undergoing a delaying peer-review process) or peer-reviewed journal article. Although COVID-19 L·OVE is highly comprehensive and current, we acknowledge that the applied search filters and also the filter provided by PROSPERO have not been validated. In addition, only protocols and publications in English were considered, which might further limit the generalizability of our findings.

Another limitation is that our subgroup analyses were exploratory. Many categories (e.g., rapid reviews, Fig. B.1/Appendix B) were based on few systematic reviews and therefore leading to underpowered results.

The analysis of registered protocols was limited to PROSPERO, which is a widely accepted international database for systematic reviews registrations and explicitly mentioned in the PRISMA-P reporting guideline [35,36]. However, we did not include systematic review protocols published, for example, in peer-reviewed journals, or databases like INPLASY (https://inplasy.com/) or OSF (https://osf.io/).

Initially, we also planned to analyze redundancy of the included systematic review protocols and publications (CRD42021240423). However, the data quality was insufficient and a meaningful analysis of redundancy would not have been possible.

Another limitation is that title/abstract screening for the L·OVE sample and the data extraction were not performed by two independent reviewers but by one reviewer. Although a second reviewer checked the screening results and the data extraction this could have had an impact on selection of reviews.

Finally, we had no a priori categorization system for data extraction of outcomes and interventions resulting in a general categorization for the many heterogeneous outcomes. The structure for categorizing the interventions was adapted a posteriori from the US National Institutes of Health [37].

5. Conclusion

This meta-research project provides important data from the early phase of the pandemic:

1.Despite the importance of living systematic reviews in pandemic situations and beyond (e.g., to inform stakeholders with the most up-to-date evidence), less than one-tenth in both samples were labeled as living systematic. Triggered by the pandemic, we expect that a

growing number of researchers will be prepared to conduct living systematic reviews in future.

2. Less than one-third of the PROSPERO protocols were published as a full systematic review. This is a strong signal for systematic review authors to publish their review results in a peer-reviewed journal or at least as preprint.
3. Approximately three-quarter of the published systematic reviews (in the COVID-19 L·OVE platform) were not registered. Taking into account the advantages of a priori registration, research waste could be reduced and resources could be allocated more efficiently—particularly in pandemic situations.
4. Overall, we strongly encourage authors to register and efficiently publish their systematic reviews as well as to update their PROSPERO record when they finalize or abandon their review. This would most likely result in greater efficiency in research and would inform other researchers, physicians, society, and policymakers on COVID-19 research and beyond.

Appendix A

Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2022.09.011.

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