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Integration of Various Types of Information in Living Systematic Reviews

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Abstract in English

Title: Integration of various types of information in living systematic reviews

Abstract: The landscape of scientific research is complex, offering a wealth of information from various sources including journal articles and grey literature. Living systematic reviews provide comprehensive and continuously updated summaries of the literature as new evidence emerges. Questions remain about the reliability of data from informal sources. My research aims to investigate the benefits and risks of integrating these types of information into traditional processes.

To achieve this aim, I first considered the influence of publication type on treatment effect. I conducted a meta-epidemiological study to evaluate whether summary treatment effect estimates differ between preprint and journal article trials. From this study, I did not find an important difference between summary treatment effects of preprints and summary treatment effects of journal articles.

Second, building on the findings of the first study, I evaluated the consistency in effect estimates between preprint and subsequent journal article trials, for a one-to-one comparison of the different publication types of the same trial. I found effect estimates to be generally consistent between preprints and subsequent journal articles. Also, the main results and interpretation did not change in any trial. Nevertheless, few trials had a minor discrepancy in effect estimate, and some trial outcomes were added and deleted in the journal article.

Overall, based on the results of these first two studies, I considered that in the context of a fast-moving pandemic, incorporating preprint results may be reasonable, once caution is taken to assess risk of bias and completeness of reporting.

Third, given the limitations of peer review, I conducted a qualitative study to assess the role of systematic reviews and post-publication peer reviews in the identification of methodological and reporting issues of trials. Through risk of bias and outcome reporting bias assessments, systematic reviewers identified issues in the majority of trials that could be easily resolved by trial authors. Post-publication peer review poorly identified key issues in

research quality. From this study, I proposed a feedback loop between systematic reviewers and trial authors to supplement peer review, as well as a method for incorporating post-preprint peer review into the formal workflow.

Finally, I investigated the consistency of outcome reporting between RCTs with results available in clinical trial registries and the final published report. Preliminary analysis showed that the majority of the data is inconsistent.

All data in this thesis concern COVID-19 trials from the COVID-NMA living systematic review.

In conclusion, this thesis showcases the importance and utility of different types of information, and emphasized the need to streamline all data sources to improve the reliability and robustness of evidence synthesis. It also suggests a framework for creating an evidence ecosystem with strong links between research enterprises.

Keywords: preprint, post-publication peer review, clinical trial registry, risk of bias, living systematic review

Résumé court en français

Titre : Intégration de divers types d'informations dans des revues systématiques dynamiques

Résumé : Le paysage de la recherche scientifique est complexe et offre une multitude d'informations provenant de diverses sources, notamment des articles de revues et de la littérature grise. Les revues systématiques dynamiques fournissent des résumés complets et continuellement mis à jour de la littérature à mesure que de nouvelles preuves émergent. Des questions subsistent quant à la fiabilité des données provenant de sources informelles. Mes recherches visent à étudier les avantages et les risques de l'intégration de ces types d'informations dans les processus traditionnels.

Pour atteindre cet objectif, j'ai d'abord examiné l'influence du type de publication sur l'effet du traitement. J'ai mené une étude méta-épidémiologique pour évaluer si les estimations de l'effet du traitement sommaire diffèrent entre les essais prépublications (preprints) et les essais d'articles de revues. À partir de cette étude, je n'ai pas trouvé de différence importante entre les effets du traitement sommaire des preprints et les effets du traitement sommaire des articles de revues.

Ensuite, en m'appuyant sur les implications de la première étude, j'ai évalué la cohérence des estimations d'effet entre les essais preprints et les essais d'articles de revues ultérieurs, pour une comparaison un à un des différents types de publication du même essai. J'ai constaté que les estimations d'effet étaient généralement cohérentes entre les preprints et les articles de revues ultérieurs. De plus, les principaux résultats et l'interprétation n'ont pas changé dans aucun essai. Néanmoins, peu d'essais présentaient une légère divergence dans l'estimation de l'effet, et certains résultats d'essai ont été ajoutés et supprimés dans l'article de la revue.

Dans l'ensemble, sur la base des résultats de ces deux premières études, j'ai considéré que dans le contexte d'une pandémie à évolution rapide, l'intégration des résultats de preprints peut être raisonnable, à condition de prendre soin d'évaluer le risque de biais et l'exhaustivité du rapport.

Troisièmement, compte tenu des limites de l'évaluation par les pairs, j'ai mené une étude qualitative pour évaluer le rôle des revues systématiques et des revues par les pairs post-

publication dans l'identification des problèmes méthodologiques et de rapport des essais. Grâce aux évaluations du risque de biais et des biais de rapport des résultats, les examinateurs systématiques ont identifié des problèmes dans la majorité des essais qui pourraient être facilement résolus par les auteurs des essais. L'évaluation par les pairs post-publication a mal identifié les problèmes clés de la qualité de la recherche. À partir de cette étude, j'ai proposé une boucle de rétroaction entre les examinateurs systématiques et les auteurs d'essais pour compléter l'évaluation par les pairs et une méthode pour intégrer l'évaluation par les pairs post-preprint dans le flux de travail formel.

Enfin, j'ai étudié la cohérence dans les rapports entre les registres d'essais cliniques et le rapport final publié. L'analyse préliminaire a montré que la majorité des données sont divergentes.

Toutes les données de cette thèse concernent les essais COVID-19 de la revue systématique dynamique COVID-NMA.

En conclusion, cette thèse met en évidence l'importance et l'utilité de différents types d'informations, et souligne la nécessité de rationaliser toutes les sources d'information pour améliorer la fiabilité et la robustesse de la synthèse des données probantes. Elle propose également un cadre pour créer un écosystème de données probantes avec des liens forts entre les entreprises de recherche.

Mots clefs : preprint, post-publication peer review, registres d'essais cliniques, risque de biais, revue systématique dynamique

Résumé substantiel en français

Le concept de l'évaluation par les pairs est apparu au XVIIe siècle, remontant à la fondation des sociétés savantes et des revues académiques. La Royal Society de Londres, à travers sa revue *Philosophical Transactions*, a posé les bases de ce qui deviendra une pratique fondamentale dans la publication scientifique. Initialement, les décisions sur la publication des manuscrits étaient prises par les éditeurs de revues ou les conseils des sociétés savantes, mais l'utilisation d'évaluateurs externes a été intégrée au processus au milieu du XXe siècle, en raison de l'augmentation du volume de la recherche et du besoin de contrôle de qualité.

L'évaluation par les pairs permet de déterminer quels manuscrits répondent suffisamment aux normes de la revue en s'assurant que le travail est significatif, original et, surtout, scientifiquement et éthiquement solide. Ce faisant, elle vise à améliorer la qualité des manuscrits et à identifier les contributions les plus marquantes à la science. Aujourd'hui, l'évaluation par les pairs s'est imposée comme la référence absolue (« *gold standard* ») pour valider la recherche dans toutes les disciplines ; les articles de revues évalués par les pairs étant souvent considérés comme la source d'information la plus fiable et la plus fiable.

Cependant, l'évaluation par les pairs a ses défauts. Des problèmes tels que la lenteur des délais d'évaluation, la difficulté à trouver des évaluateurs et la subjectivité de l'évaluation, entre autres biais potentiels, ont été reconnus. En raison de ces limites, le recours exclusif au processus d'évaluation par les pairs et, par extension, aux articles de revues sont de plus en plus considérés comme insuffisants, en particulier dans les domaines en évolution rapide. Des sources de données alternatives sont nécessaires pour fournir des informations plus immédiates et plus complètes.

Les registres d'essais cliniques, comme ClinicalTrials.gov, offrent des perspectives précieuses sur les recherches en cours et les tendances émergentes. Cependant, ces registres souffrent souvent d'un manque de détails méthodologiques. Malgré cela, ils renforcent la transparence et la responsabilité dans la recherche clinique, en aidant à identifier le biais de publication, c'est-à-dire la publication de résultats en fonction de leur nature ou de leur direction plutôt que sur la base d'une spécification préétablie. Les preprints sont une autre source d'information essentielle, dont l'utilisation a connu une forte augmentation pendant la

pandémie. Comme ces manuscrits ne sont pas retardés par le processus d'évaluation par les pairs, ils peuvent fournir des données scientifiques précoces, par exemple sur les interventions thérapeutiques et préventives pour la COVID-19, ainsi que sur la physiopathologie du virus lui-même à ce moment-là. Cependant, l'absence d'évaluation par les pairs de ces manuscrits est une arme à double tranchant, car des inquiétudes sont soulevées quant à la fiabilité des résultats. Il convient d'être prudent lors de l'interprétation des résultats des preprints. Enfin, l'évaluation par les pairs après la preprint et après la publication (post-preprint and post-publication peer review (PPPR)) est un processus informel par lequel la communauté scientifique évalue la recherche après sa publication en preprint ou la publication de son article dans une revue. Des plateformes comme PubPeer facilitent ce commentaire ouvert sur les méthodes et les résultats des études, ce qui peut conduire à l'identification de défauts et même à des actions éditoriales majeures, comme des rétractations et des expressions de préoccupations.

L'écosystème de la recherche peut être écrasant face à la quantité vaste et complexe de données disponibles à partir de diverses sources. Les revues systématiques et les méta-analyses synthétisent ces vastes corpus de preuves existantes dans des résumés complets. Les revues systématiques utilisent des méthodes qualitatives prédéfinies pour synthétiser les résultats sur un sujet spécifique, tandis que les méta-analyses ont recours à des techniques statistiques pour combiner les résultats de plusieurs études en une seule estimation quantitative ou une taille d'effet globale. Ces revues aident à identifier les lacunes dans la recherche afin que les études ultérieures puissent concevoir et rendre compte de leurs études de manière à réduire ces lacunes au fil du temps. Elles sont devenues des outils précieux pour orienter les décisions en matière de soins de santé et sont considérées comme le summum de la médecine fondée sur les preuves.

Pour mener une revue systématique et une méta-analyse, les chercheurs commencent par définir une question de recherche, en prêtant attention au PICO (population, intervention, comparateur et résultat). Le protocole détaillant le plan d'action est ensuite publié en ligne. Les chercheurs effectuent ensuite une recherche exhaustive dans la littérature pour identifier les études éligibles, puis l'extraction des données, l'évaluation du risque de biais et la synthèse des données sont effectuées. Des outils comme le Cochrane RoB 2 sont utilisés pour évaluer

le risque de biais, tandis que les lignes directrices PRISMA aident à garantir la transparence du processus de revue.

Il convient de noter que les revues systématiques deviennent rapidement obsolètes en raison de la nature évolutive rapide de la recherche. Le temps nécessaire à la réalisation de ces revues entraîne des retards importants, ce qui limite la capacité des décideurs à s'y fier pour obtenir rapidement des informations. De plus, des défauts méthodologiques, un biais de publication et des portées trop restreintes peuvent compromettre leur efficacité.

Les revues systématiques dynamiques (living systematic reviews, LSR) représentent une approche innovante de la synthèse des preuves, répondant aux limitations des méthodes traditionnelles. Les LSR sont continuellement mises à jour à mesure que de nouvelles preuves émergent, garantissant qu'elles restent actuelles et pertinentes. Cette approche est particulièrement utile lorsque des informations précises et rapides sont essentielles pour la prise de décision, comme lors de la pandémie de COVID-19. Les outils numériques et les méthodes automatisées ont facilité la mise en œuvre des LSR, en faisant une ressource précieuse dans l'écosystème de la synthèse des preuves. La revue systématique dynamique COVID-NMA (covid-nma.com) est un exemple notable de cette approche, reposant sur un processus complexe de screening quotidien, d'extraction de données et d'évaluations RoB, par des paires de chercheurs, indépendamment et en double, avec des désaccords résolus par consensus et un troisième évaluateur, si nécessaire. La méta-analyse et la hiérarchisation des preuves ont été réalisées chaque semaine et tous les résultats ont été mis à disposition sur une plateforme accessible au public. La revue systématique dynamique COVID-NMA a exploité des données provenant de diverses sources formelles et informelles, notamment des articles de revues, des prépublications, des registres d'essais cliniques et des rapports réglementaires pour fournir des preuves actualisées sur l'efficacité et la sécurité des différentes options thérapeutiques.

L'objectif central de cette thèse de doctorat était d'explorer les avantages et les risques de l'intégration de différents types d'informations dans les revues systématiques dynamiques. Plus spécifiquement, la recherche a été menée en utilisant la revue systématique dynamique COVID-NMA et guidée par trois objectifs principaux :

1. Examiner l'influence du type de publication (preprint vs article de revue) sur l'effet du traitement.

2. Évaluer le rôle de l'évaluation par les pairs après publication dans l'identification des problèmes méthodologiques et de rapport des ECR.
3. Comparer la cohérence des rapports entre les registres d'essais cliniques et le rapport final publié.

Objectif 1 : Examiner l'influence du type de publication (preprint vs article de revue) sur l'effet du traitement.

Ce premier objectif a été divisé en deux projets.

Au début, j'ai cherché à évaluer si les estimations des effets du traitement diffèrent entre les essais prépubliés et ceux des revues à comité de lecture via une étude méta-épidémiologique.

Au moment de la synthèse des preuves, il n'est pas clair quelles preprints seront finalement publiées dans des revues à comité de lecture. Par conséquent, en examinant les méta-analyses elles-mêmes par le biais de ce type d'étude, en se concentrant sur celles qui incluent différents essais de différents types de publication et en estimant s'il existe une différence statistique, nous pouvons mieux évaluer la fiabilité des résultats des preprints.

J'ai dérivé des données de la revue systématique dynamique COVID-NMA jusqu'au 20 juillet 2022. J'ai identifié toutes les méta-analyses évaluant les traitements pharmacologiques contre les soins standards/placebo pour les patients atteints de COVID-19 incluant au moins une preprint et un article de revue à comité de lecture. J'ai considéré les critères de jugement critiques définis par COVID-NMA. Comme COVID-NMA est une revue systématique dynamique, toutes les analyses étaient mises à jour chaque semaine puis toutes les deux semaines à mesure que de nouvelles études étaient identifiées et extraites, et la base de données sauvegardée. Par conséquent, la base de données est formatée en plusieurs versions temporelles d'une méta-analyse donnée. Les méta-analyses ont été sélectionnées pour inclusion dans le jeu de données final en deux étapes. Premièrement, j'ai sélectionné au hasard un moment où une méta-analyse incluait au moins un article prépublié et au moins un article de revue à comité de lecture. La sélection a été automatisée à l'aide d'un code R. Deuxièmement, si à ce moment donné une méta-analyse répondant aux critères d'éligibilité (en termes de comparaison des traitements et de critères de jugement) était disponible pour plus d'un des critères de jugement critiques définis par COVID-NMA, la méta-analyse incluant

le plus grand nombre d'essais a été sélectionnée. La différence dans les estimations des effets entre les essais preprint et ceux des revues à comité de lecture a été estimée par le ratio des odds ratio (ROR). Pour chaque méta-analyse, j'ai d'abord estimé l'effet du traitement (c'est-à-dire l'odds ratio [OR]) des ECR prépubliés et l'OR des ECR d'articles de revues. Enfin, j'ai estimé le ROR global à travers les méta-analyses en utilisant un modèle de méta-analyse à effets aléatoires. Un ROR < 1 indiquait que les ECR prépubliés donnaient des estimations d'effet plus grandes que les ECR d'articles de revues.

J'ai sélectionné 37 méta-analyses incluant 114 essais (44 preprints, 70 articles de revue) ; 24 méta-analyses évaluant des patients hospitalisés (81 ECR), et 13 évaluant des patients ambulatoires (33 ECR). Le nombre médian d'ECR par méta-analyse était de 2 (IQR, 2–4 ; maximum, 11), la taille médiane des échantillons d'ECR était de 199 (IQR, 99–478) participants. Les caractéristiques des ECR preprint et d'articles de revue étaient comparables pour la plupart des variables. Globalement, il n'y avait pas de différence statistiquement significative dans les estimations des effets globaux entre les essais preprint et les essais d'articles de revue à comité de lecture (ROR, 0.88; 95% CI, 0.71–1.09; I^2 = 17.8%; τ^2= 0.06).

En conclusion, je n'ai pas trouvé de différence importante entre les effets globaux des traitements des preprints et les effets globaux des publications évaluées par les pairs. Ces résultats étaient cohérents dans les analyses de sensibilité post hoc. Cependant, mes résultats doivent être interprétés avec prudence en raison du petit nombre d'études dans la plupart des méta-analyses et de la grande incertitude des ROR respectifs. Dans l'ensemble, dans le contexte d'un paysage de recherche en constante évolution, et en particulier dans le cadre d'une pandémie en évolution rapide, considérer les résultats des essais preprints peut être raisonnable. Bien entendu, les examinateurs systématiques et les développeurs de directives devraient évaluer l'inclusion des preprints individuellement, en tenant compte du risque de biais et de la complétude des rapports.

Dans mon deuxième travail, j'ai évalué la cohérence des estimations des effets entre la preprint et l'article de revue ultérieur des ECR COVID-19. J'ai également utilisé des données issues de la revue systématique dynamique COVID-NMA sur les traitements pharmacologiques pour COVID-19 jusqu'au 20 juillet 2022. J'ai identifié des ECR évaluant des traitements pharmacologiques contre les soins standards/placebo pour les patients atteints

de COVID-19, qui ont été initialement postés sous forme de preprints et publiés par la suite sous forme d'articles de revue. J'ai également pris en compte les résultats critiques définis par COVID-NMA et exclu les essais qui ne rapportaient pas la même analyse dans les deux documents. Les données ont été extraites indépendamment par des paires de chercheurs avec consensus en cas de désaccords. J'ai extrait les estimations des effets de la première preprint et les ai comparé aux estimations des effets de l'article de revue.

Le lien entre la preprint et l'article de revue a été effectué dans le cadre de la revue systématique dynamique COVID-NMA. Le lien entre la preprint et l'article a été développé en collaboration avec une équipe de recherche du Centre National de la Recherche Scientifique (CNRS) en France. L'outil générait une alerte lorsqu'une preprint était mise à jour ou publiée sous forme d'article de revue. Des paires de chercheurs utilisaient l'outil pour identifier ces rapports ultérieurs, puis extrayaient toutes les données supplémentaires et/ou mises à jour de manière indépendante, se réunissant pour parvenir à un consensus en cas de désaccord. Par conséquent, un enregistrement précis des rapports de preprint et de publication correspondants dans la base de données COVID-NMA est disponible pour téléchargement sous forme de paire preprint-publication. Pour identifier les ECR éligibles, j'ai récupéré cet enregistrement dans la base de données COVID-NMA et sélectionné la première preprint postée sur un serveur de preprints et l'article de revue ultérieur. Lorsque cela était disponible, j'ai utilisé la date de publication en ligne afin de calculer le délai entre la preprint et la publication de l'article de revue. Sinon, j'ai utilisé la date de publication imprimée.

La recherche a identifié 135 ECR initialement postés sous forme de preprint et publiés par la suite sous forme d'article de revue. J'ai exclu 26 ECR qui ne répondaient pas aux critères d'éligibilité, dont 13 ECR qui rapportaient une analyse intermédiaire dans la prépublication et une analyse finale dans l'article de revue. Globalement, 109 ECR sous forme de paires preprint-article ont été inclus dans l'analyse. Le délai médian entre la preprint et l'article de revue était de 121 (IQR, 73–187) jours, la taille médiane des échantillons était de 150 (IQR, 71–464) participants, 76 % des ECR avaient été enregistrés prospectivement, 60 % avaient reçu un financement industriel ou mixte, 72 % étaient des essais multicentriques. Le risque global de biais a été évalué comme «quelques préoccupations» (some concern) pour 80 % des ECR. J'ai constaté que 81 paires preprint-article des ECR étaient cohérentes pour tous les résultats rapportés. Il y avait neuf ECR avec au moins un résultat présentant une différence

dans le nombre de participants ayant des événements ou le nombre de participants analysés, ce qui a entraîné un changement mineur dans l'estimation de l'effet. De plus, six ECR avaient au moins un critère de jugement manquant dans l'article de revue et 14 ECR avaient au moins un critère de jugement ajouté dans l'article de revue par rapport à la preprint. Il y a eu un changement dans la direction de l'effet dans un seul ECR. Aucun changement dans la signification statistique et la conclusion n'a été trouvé.

En conclusion, les estimations des effets étaient généralement cohérentes entre les preprints COVID-19 et les articles de revue ultérieurs. Les principaux résultats et interprétations n'ont changé dans aucun essai. Néanmoins, certains résultats ont été ajoutés et supprimés dans certains articles de revue.

Objectif 2 : Évaluer le rôle des évaluations par les pairs après publication dans l'identification des problèmes méthodologiques et de rapport des ECR.

Les limites du processus d'évaluation par les pairs « gold standard » sont bien documentées, notamment le fait que les évaluateurs ne sont pas toujours en mesure d'identifier les défauts et les biais dans les manuscrits. Les évaluateurs systématiques, en particulier les évaluateurs systématiques vivants, et la communauté de recherche en général pourraient aider à détecter d'importants problèmes méthodologiques et de reporting qui pourraient ensuite être transmis aux auteurs des essais pour éventuellement les rectifier. Cependant, il existe actuellement un décalage entre ces groupes et on ne sait pas quel impact ces entités de recherche pourraient avoir sur la qualité du manuscrit. Par conséquent, j'ai mené une étude qualitative pour déterminer dans quelle mesure les évaluateurs systématiques et l'évaluation par post-preprint et PPPR ont identifié des problèmes méthodologiques et de reporting dans les ECR COVID-19 qui pourraient être facilement résolus par les auteurs.

Dans cette étude, j'ai examiné les ECR de la COVID-NMA qui évaluaient les traitements pharmacologiques pour les patients atteints de COVID-19 et j'ai récupéré les évaluations RoB et ORB qui ont été menées par les évaluateurs systématiques. Dans le cadre du processus COVID-NMA, les justifications de chaque évaluation ont également été publiées. Je les ai également récupérées pour mon étude. La connaissance de l'outil RoB et de l'ORB a dicté que ces évaluations pouvaient identifier des problèmes tels que des rapports incomplets, la

sélection des résultats rapportés (preuves manquantes ou ajoutées) et le manque d'accès au plan prédéfini.

De plus, j'ai recherché des données de commentaires sur PubPeer, medRxiv, Research Square et SSRN jusqu'au 6 novembre 2023. J'ai ensuite utilisé l'analyse de contenu pour développer de manière inductive les thèmes et les domaines des problèmes méthodologiques et de rapport identifiés par les commentateurs.

J'ai identifié 500 rapports d'ECR éligibles. Les examinateurs systématiques ont identifié des problèmes méthodologiques et de rapport dans 446 (89 %) rapports d'ECR. Dans 391 (78 %) rapports d'ECR, les problèmes pouvaient être facilement résolus par les auteurs de l'essai, c'est-à-dire des rapports incomplets (49 %), la sélection des résultats rapportés (52 %) et l'absence d'accès au plan prédéfini (25 %). Par ailleurs, 74 (15 %) rapports d'ECR avaient reçu au moins un commentaire sur PubPeer ou les serveurs de préimpression, pour un total de 345 commentaires. Dans 46 (9 %) rapports d'ECR, les problèmes identifiés par les commentaires d'évaluation par les pairs après la prépublication et après la publication ont pu être facilement résolus par les auteurs de l'essai ; les problèmes étaient liés à des rapports incomplets (5 %), à des erreurs (4 %), à une analyse statistique (2 %), à une manipulation (2 %), à la sélection des résultats rapportés (1 %) et à l'absence d'accès aux données brutes/plan prédéfini (1 %).

Certaines limites de l'étude doivent être reconnues. Tout d'abord, je dois à nouveau reconnaître que ces résultats peuvent ne pas être généralisables aux commentaires post-prépublication et PPPR en dehors du contexte de la pandémie puisque je n'ai inclus que les ECR COVID-19 dans l'échantillon. Deuxièmement, cette étude a également été limitée par les décisions de la COVID-NMA dans la mesure où les évaluations RoB et ORB n'étaient disponibles que pour les résultats définis par l'examen. Néanmoins, ces résultats ont été choisis pour leur pertinence clinique et j'ai inclus à la fois des critères d'évaluation de la sécurité et de l'efficacité. Enfin, je n'ai pas pu évaluer l'expertise des commentateurs en matière de méthodologie de recherche ni explorer d'éventuels conflits d'intérêts car la plupart des commentaires post-preprint et PPPR étaient anonymes. Cependant, l'anonymat encourage souvent une plus grande participation au PPPR, et l'objectif de cette étude n'était pas de confirmer la validité des questions soulevées dans ces commentaires.

En conclusion, mon étude a montré que les examinateurs systématiques sont bien placés pour améliorer la qualité de la recherche car ils ont identifié des problèmes dans la plupart des ECR qui pourraient être facilement résolus par les auteurs de l'essai. Je soutiens que l'absence d'un mécanisme de rétroaction des auteurs établi représente une occasion manquée de faciliter de telles améliorations. D'un autre côté, malgré la boucle de rétroaction existante vers les auteurs présents dans PPPR, elle a démontré une efficacité limitée dans l'identification des problèmes méthodologiques et de reporting. Mais je suggère un cadre pour intégrer l'évaluation par les pairs après la preprint dans le flux de travail formel.

Objectif 3 : Comparer la cohérence des rapports entre les registres d'essais cliniques et le rapport final publié.

Les registres d'essais cliniques sont une autre source de données importante à prendre en compte dans l'écosystème des preuves. La recherche a montré que les résultats des registres, en particulier les données de sécurité, peuvent être plus complets que dans les articles de revues. Les problèmes de mauvaise communication des méthodes et des résultats dans les essais sont un problème depuis des décennies. Pour cette raison, la loi américaine de 2007 sur les amendements à la Food and Drug Administration (FDAAA) 801 exigeait que les essais cliniques applicables publient leurs résultats sur ClinicalTrials.gov dans l'année suivant leur achèvement. L'Europe a suivi, avec des mandats similaires en 2014 pour le registre européen des essais cliniques (EU-CTR). Ainsi, examiner si ces réglementations sont respectées et si ces résultats sont systématiquement rapportés à la fois dans le registre et dans l'article de revue publié, ou dans la version finale preprint s'il n'y a pas d'article de revue disponible, peut aider à comprendre comment utiliser au mieux les résultats du registre des essais cliniques dans le plus grand écosystème de preuves.

J'ai inclus uniquement les ECR de traitement pharmacologique COVID-NMA qui étaient enregistrés dans ClinicalTrials.gov ou EU-CTR et qui ont rapporté des résultats jusqu'au 24 avril 2024 à la fois dans le registre et dans un article de revue (ou preprint). J'ai également pris en compte les résultats critiques définis par COVID-NMA et le résultat principal des ECR respectifs et j'ai extrait ces données du registre, en les comparant aux données du rapport final publié ou preprint. Les données ont été extraites indépendamment par des paires de chercheurs avec un consensus pour résoudre les désaccords.

Mon analyse a porté sur 117 ECR dont les résultats ont été publiés sur ClinicalTrials.gov ou EU-CTR et dans une publication en ligne (article de revue ou preprint). Le délai médian entre la date d'achèvement primaire de l'essai et la date de mise en ligne du rapport final (article de revue ou preprint) et la date de publication des résultats sur ClinicalTrials.gov ou EU-CTR était respectivement de 151 (IQR, 108-175) jours et de 295 (IQR, 173-254) jours. La taille médiane de l'échantillon était de 250 (IQR, 82-496) participants, 89 % des ECR étaient uniquement enregistrés sur ClinicalTrials.gov, 98 % des résultats provenaient de ce registre, 84 % des ECR avaient été enregistrés de manière prospective et 71 % avaient reçu un financement industriel ou mixte. Le risque global de biais évalué a été jugé « quelque peu préoccupant » pour 74 % des ECR. La cohérence dans la notification de tous les résultats n'a été constatée que dans 12 % des paires registre-rapport. Au moins un résultat manquait dans le registre de 59 % des ECR, et 47 % des ECR avaient au moins un résultat ajouté au registre par rapport à l'article de la revue ou au rapport préliminaire. Il y avait 37 % d'ECR qui avaient au moins un résultat avec un changement dans le nombre de participants avec des événements de résultat. Les données de résultat principal étaient cohérentes entre le registre et le rapport final dans 68 % des ECR. Les résultats de sécurité, bien que plus fréquemment rapportés dans le registre par rapport aux résultats d'efficacité (82 % contre 63 %), étaient moins systématiquement rapportés entre les paires registre-rapport d'ECR (27 % contre 49 %).

Je reconnais certaines limites à cette étude. Je n'ai pris en compte que ClinicalTrials.gov et EU-CTR, mais ce sont les plus grands registres d'essais cliniques avec des réglementations pour la publication des résultats. Deuxièmement, comme c'est le cas pour toutes les études de cette thèse, je me suis concentré sur les ECR COVID-19, donc mes conclusions sont limitées à ce contexte COVID-19 et à ce type d'étude. De plus, l'analyse est limitée aux résultats définis par la COVID-NMA et non aux résultats rapportés par les essais individuels (à l'exception du résultat principal), de sorte que la cohérence peut être réduite dans ce cas. Cependant, ces résultats de revue ont été choisis pour leur pertinence clinique et comprenaient à la fois des critères d'évaluation de la sécurité et de l'efficacité. Enfin, les modifications du protocole dans la revue en direct, rendues nécessaires par l'évolution du paysage scientifique, pourraient également avoir eu un impact sur la taille et la composition de l'échantillon.

En total, la majorité des ECR présentaient des divergences dans les résultats entre les registres d'essais cliniques et le rapport final, c'est-à-dire l'article de revue ou la version finale préimprimée. Cependant, le résultat principal a été systématiquement rapporté pour la plupart des paires registre-rapport d'ECR. En général, les ECR COVID-19 ont démontré une bonne conformité dans la publication des résultats du registre dans l'année suivant leur achèvement.

En conclusion, cette thèse met en évidence l'importance et l'utilité de différentes sources d'information pour potentiellement améliorer la fiabilité et la robustesse des revues systématiques. Certaines présentent des risques. Les preprints et les registres d'essais cliniques permettent de diffuser rapidement les résultats de la recherche, ce qui permet à la communauté scientifique d'accéder plus rapidement à de nouvelles données. Cependant, des travaux supplémentaires doivent être menés sur les données des registres pour mieux comprendre comment les utiliser au mieux. Les preprints et les PPPR ajoutent un niveau supplémentaire de contrôle pour améliorer la qualité de la recherche, en fournissant des commentaires précieux qui peuvent aborder des problèmes qui ont été manqués lors de l'examen formel par les pairs. Les examinateurs systématiques identifient déjà d'importants problèmes méthodologiques et de reporting qui pourraient être facilement résolus par les auteurs d'essais, mais la boucle de rétroaction fait défaut.

Si quelque chose est devenu clair tout au long de ce travail, c'est que nous devons rationaliser toutes les sources d'information. Pour vraiment améliorer la qualité de la recherche et la prise de décision fondée sur des données probantes, nous devons dépasser un écosystème de synthèse des données probantes et progresser vers un écosystème de données probantes entièrement intégré. Cela nécessite de créer des liens plus solides entre toutes les entreprises de recherche, c'est-à-dire les investigateurs, les examinateurs systématiques et la communauté de recherche au sens large. En favorisant une meilleure collaboration et une meilleure communication entre ces groupes, nous pouvons garantir que les données probantes sont continuellement mises à jour, complètes et reflètent les meilleures données disponibles. Un écosystème de données probantes intégré accélérerait la traduction des résultats des études en impact concret, ce qui profiterait en fin de compte à l'ensemble de la communauté scientifique et à la santé publique.

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I am so incredibly grateful to have your friendship. Love youse!

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List of abbreviations

BMJ	British Medical Journal
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
EU-CTR	European Union Clinical Trials Register
EMA	European Medicines Agency
FDA	Federal Drug Administration
HIV	Human Immunodeficiency Virus
JAMA	Journal of the American Medical Association
LSR	Living Systematic Review
ORB	Outcome Reporting Bias
PICO	Population, Intervention, Comparison, Outcome
PPPR	Post-publication Peer Review
RCT	Randomized Controlled Trial
RoB	Risk of Bias
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
WHO	World Health Organization

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Introduction

1. Research Dissemination

1.1 Peer review and Peer-reviewed Publications

The history of peer review began with the establishment of scholarly societies and the birth of academic journals in the 17th century. The Royal Society of London, founded in 1660, played a pivotal role in this development with the launch of *Philosophical Transactions*, often cited as the world's first scientific journal. Early on, the decision to publish was typically made by the journal editor or the society council, but it was at the American Medical Editors' Association meeting in 1893 that Ernest Hart, then editor of the *British Medical Journal (BMJ)*, discussed the impact of scientific specialization and called for the use of external reviewers to assess the validity and significance of submitted manuscripts.(1) However, it wasn't until the mid-20th century that this practice was truly adopted and peer review became more structured and universally accepted across disciplines. This shift was driven by the increasing volume of scientific research and the need for a more rigorous evaluation process to ensure the integrity and quality of published work. By the 1970s and 1980s, most reputable journals (*Nature* in 1973 and *The Lancet* in 1976) required manuscripts to undergo this scrutiny before publication.(2)

Peer review is used to determine which manuscripts sufficiently meet the journal's standards by ensuring that the work is significant, original and, most importantly, scientifically and ethically sound. In doing so, it aims to improve the quality of manuscripts and identify the most impactful contributions to science.(3) With the implementation of a double-blind and single-blind review process, where the identities of authors and reviewers might be concealed, the potential bias in the evaluation of manuscripts is reduced. Recently, though, there has been a shift towards open peer review with the growth of the Open Science movement, including making reviewer and author identities known and publishing review reports.(4)

Today, peer review is the gold standard of academic publishing, with peer-reviewed journal articles often considered to be the most trusted and reliable source of information.

1.1.1 Limitations of peer review

Peer review is not without its flaws. To draw attention to these limitations and research on peer review, Drummond Rennie, former editor of the *Journal of the American Medical Association (JAMA)*, founded *The First International Congress on Peer Review in Biomedical Publication* in 1989.(5) Richard Smith, former editor of the *BMJ*, said in a popular editorial on peer review,

> *"So we have little evidence on the effectiveness of peer review, but we have considerable evidence on its defects. In addition to being poor at detecting gross defects and almost useless for detecting fraud it is slow, expensive, profligate of academic time, highly subjective, something of a lottery, prone to bias, and easily abused."* (6)

As Smith pointed out, one major issue of peer review is the delay in manuscript publication, how slow the process is, largely due to difficulties in finding willing reviewers. This reluctance stems from various factors, including time constraints in an already competitive academic environment, reviewer fatigue from excessive review requests, especially in highly qualified reviewers, and lack of recognition or compensation for review work.(7,8) The problem is particularly acute in open-access journals, where authors pay to publish, but reviewers remain uncompensated.

These challenges can have far-reaching consequences. The scarcity of expert reviewers often forces editors to rely on less experienced ones, potentially leading to the publication of flawed research or the rejection of quality work due to overly critical reviews. Among 78 preprint-journal article pairs of studies, Kapp et al. showed that peer review failed to improve transparency, completeness and accuracy of reporting.(9) This supports the conclusions of another study finding that peer reviewers often fail to detect important deficiencies in the reporting of the methods and results of RCTs.(10) Spin is another important concern whereby the impact of peer review on removing this in abstract conclusions has proven to be low.(11) Spin, or "*the distortion of study findings is a specific way of reporting, either intentional or unintentional, implying that the beneficial effect of the experimental treatment is greater than that shown by the results."*(11)

The peer review process has also shown limitations in detecting research misconduct, such as plagiarism, data fabrication, or image manipulation.(12) The pressure to publish in academia ("publish or perish") can precipitate unethical practices, including the use of "paper mills" that produce fake papers for sale, or sells authorships for real manuscripts.(13–15)

1.2 Beyond the Gold Standard

The landscape of scientific research is increasingly complex, offering a wealth of information available from various sources. With peer review now taking on monikers like *"a tarnished gold standard"* (16) due to the prevalence of its flaws, it is clear that relying solely on traditional processes and documents is insufficient. The use of additional data sources is warranted. This was particularly emphasized during the COVID-19 pandemic when rapid access to emerging data was vital for informing public health measures and clinical decisions.

Clinical trial registry

As a first step, clinical trial registries are an important source of information, helping to track the progress of studies and offering insights into ongoing research. There are now several registries worldwide, including ClinicalTrials.gov, and the European Clinical Trials Register (EU-CTR). Since 2007, the United States Federal Drug Administration Amendments Act 801 (US FDAAA 801) requires applicable clinical trials to post their results on ClinicalTrials.gov within one year of trial completion. In 2014, the posting of results for any interventional trials registered on the EU-CTR was also mandated. As of August 2024, the results of 65,770 trials are available at ClinicalTrials.gov.(17) However, a study found only 8% of FDAAA 801 applicable clinical trials on pancreatic adenocarcinoma had reported results on Clinicaltrials.gov 12 months after the primary completion date.(18) On the other hand, the FDAAA Trial Tracker shares more promising numbers, stating that 77.4% of 20,855 studies that they are tracking, have reported results, but I did not find factors such as timing of results reporting.(19)

The benefits of clinical trial registries are significant for enriching the evidence base.(20) They often provide results of recent trials before they appear in published literature, and tend to be more comprehensive in their reporting of safety data than what is published in journal articles.(21,22) However, research has shown there to be discrepancies in the general reporting of data in clinical trials registries and published reports.(23) They also typically

provide limited methodological details, vague outcome descriptions, and rarely describe randomization processes.(24) To address these limitations, ClinicalTrials.gov now allows uploading of protocols and statistical analysis plans. Additionally, registries can help identify outcome reporting bias (ORB) i.e., the selective reporting of study results based on their nature or direction, rather than being reported as prespecified (either in a trial registry, protocol or statistical analysis plan).(25,26)

Clinical study reports

Clinical study reports (CSRs) are documents prepared and submitted to regulators when applying for new medical treatments. Regulatory agencies like the European Medicines Agency (EMA) has made clinical study reports (CSRs) routinely accessible since 2015 via an online platform.(27) CSRs provide the most complete and organized account of study methods, efficacy and safety data and bias assessment, which Jefferson and colleagues use to rationalize CSR inclusion in systematic reviews.(28) They argue that, we can really only evaluate reporting biases when comparing multiple reports of the same trial, like journal articles with CSRs. Also, the lack of transparency and detail in journal articles can hinder meta-analyses.

However, there are drawbacks to CSRs.(20) Access to these reports can be limited by some regulatory agencies. Also, the advantage of the completeness of reporting and organized structure of CSRs comes at a cost. The documents are long and extensive, hence time-consuming for researchers during data extraction. Finally, CSRs could be heavily censored with some information removed and hidden.

Preprints

Another critical source of information is preprints. Preprints are preliminary, non-peer-reviewed versions of a manuscript that are uploaded to publicly accessible platforms like medRxiv, bioRxiv, Research Square and SSRN. Preprints offer a significant advantage to journal articles by allowing researchers to disseminate their findings quickly without waiting for the often-lengthy peer review process. This immediacy can also enable prompt responses to new information. For this reason, the COVID-19 pandemic precipitated a surge in the use of preprints to disseminate findings. During the early stages of the pandemic, preprints provided insights into viral transmission, epidemiology, and potential treatments long before

they appeared in published journal articles.(29–31) These early data allowed for faster development of guidelines and interventions, potentially saving lives.(32)

But questions remained: Are preprints reliable? Should we exercise caution when using or interpreting preprint data and establish alerts to track a subsequent journal article? Could a preprint add information that is not reported in a journal article? The primary concern is that the lack of formal peer review can lead to the spread of inaccurate or incomplete data. For example, early in the pandemic, a bioRxiv preprint claimed that the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) had similarities to the human immunodeficiency virus (HIV).(33) This assertion sparked major criticism from the scientific community and the preprint was withdrawn, but Google search interest for terms related to HIV and coronavirus had already increased.(34) But, one can argue that this is similar to how some journal articles can also vary in quality (Figure 1).

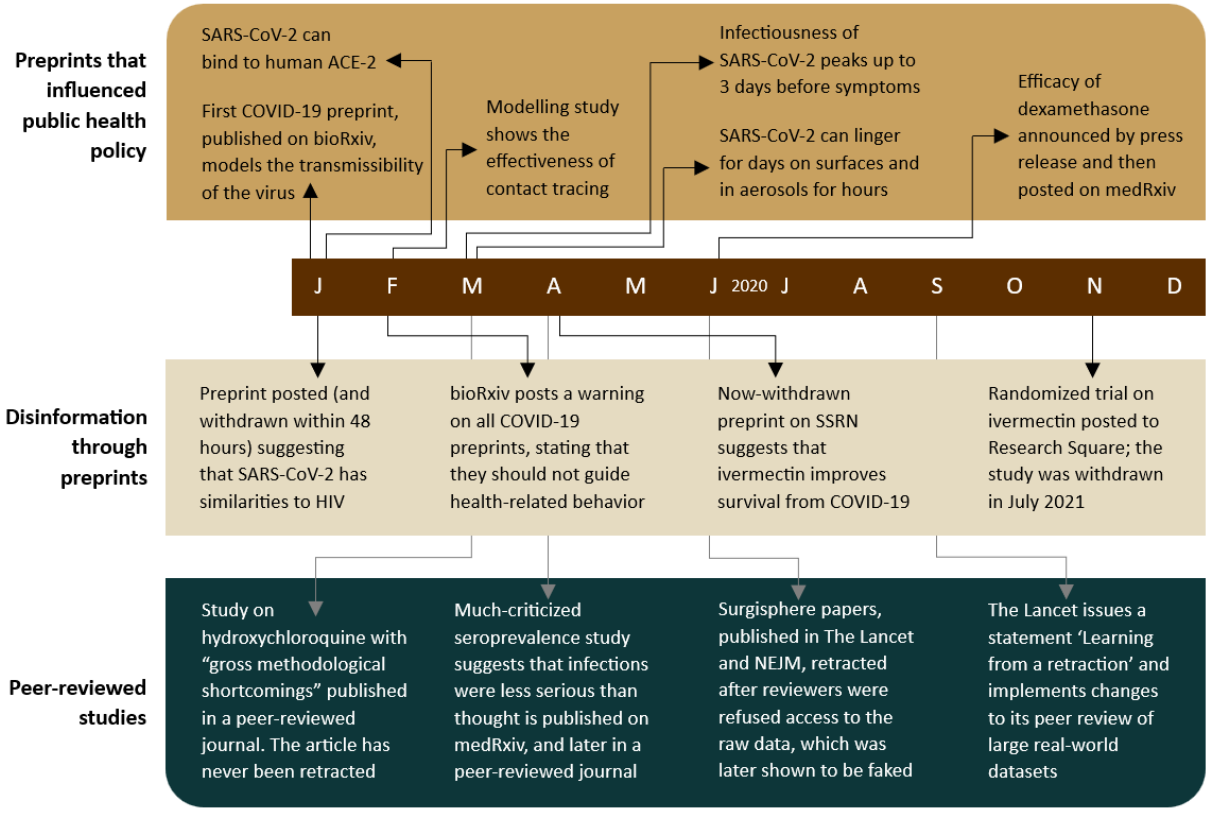

Figure 1: Preprints, press releases, and policy (adapted from Watson, 2022 (35))

In his commentary article, Liam Brierley posed the question of whose responsibility it is to manage the use and interpretation of preprint results. He claims,

> *"…the answer is likely to be universal: that of authors to ensure that their preprint research is rigorous and presented objectively, that of preprint repositories to streamline opportunities for peer commentary, …that of academics to provide such commentary in a timely and constructive manner, and that of the wider public readership to acknowledge the limitations of preprint research."*(34)

Post-preprint and post-publication peer review

As Brierley talked about *"opportunities for peer commentary"*, post-publication peer review is another informal and valuable source of data. As opposed to journal-managed, formal peer review, post-publication peer review (PPPR) involves the scientific community evaluating and commenting on research after it has been published.(36,37) This process can identify areas for improvement that may not have been detected during formal peer review.

The COVID-19 pandemic transformed scientific communication, including increased activity on PPPR platforms like PubPeer. PubPeer and major preprint servers, like medRxiv, allow open commentary on study methods and results from members of the scientific community. This approach facilitates the identification of methodological and reporting issues in publicly available research. Sometimes these important criticisms can cause major editorial actions, like retractions and expressions of concern.(38,39) Even if such actions are not taken, these comments are vital.

For example, Elisabeth Bik, a dedicated research sleuth, criticized the validity of data presented in a hydroxychloroquine-COVID-19 study.(40–42) Despite her detailed analysis and the extensive scrutiny from much of the scientific community including formal calls for retraction, the paper has not yet been retracted.(43–45) Encouragingly, though, it underscores the value of this additional layer of review in raising awareness of biases and flaws in research. Bik has become well-known for her work in identifying manipulated images and other types of research misconduct, with some notices even mentioning her by name.(46) Recently, she was instrumental in the 2024 retraction of a *Nature* paper by Jiang et al., after an investigation was launched due to questions she posted on PubPeer about Jiang's data in

2019.(47–49) The paper, cited nearly 4,500 times, has become the most-cited retracted paper in history. Such cases exemplify how post-preprint and PPPR can uphold scientific integrity and enhance the robustness of evidence-based publishing.

2. Evidence synthesis ecosystem

'Evidence synthesis' refers to *"the process of bringing together information from a range of sources and disciplines to inform debates and decisions on specific issues."*(50) Systematic reviews and meta-analyses are types of evidence synthesis methods.

2.1 What is a systematic review and meta-analysis?

A systematic review is a comprehensive summary of relevant prior studies on a specific topic according to a prespecified and explicit method.(51)

In 1753, James Lind published the work, *"A treatise of the scurvy"*, in which he reviewed all existing published literature on the disease, writing,

> *"As it is no easy matter to root out prejudices…it became requisite to exhibit a full and impartial view of what had hitherto been published on the scurvy, and that in a chronological order, by which the sources of these mistakes may be detected."*

Today, Lind's treatise would be classified as a systematic review (52), but it took two centuries and the publication of Archie Cochrane's book, "*Effectiveness and Efficiency: Random Reflections on Health Services",* in 1972 for the foundation for evidence-based medicine to be truly laid. In his book, Cochrane emphasized the importance of using evidence from well-designed evaluations, particularly RCTs, to inform healthcare decisions. He also advocated for synthesizing evidence to guide resource allocation, and in 1979, called for 'critical summaries' of all relevant RCTs by specialty. This directly inspired the development of evidence synthesis methods. Cochrane then went on to use the term 'systematic review' in the foreword to a 1987 collection of evidence syntheses on perinatal intervention trials, recognizing it as a milestone in the evaluation of care.(53)

Turning to quantitative methods, in 1976, Gene Glass coined the term 'meta-analysis' as *"the statistical analysis of a large collection of analysis results from individual studies for the*

purpose of integrating the findings"(54) into a single quantitative estimate or summary effect size. A systematic review often includes a meta-analysis component to enhance the precision of estimates regarding the efficacy of interventions or the association between risk factors and outcomes. The number of published meta-analyses has grown exponentially over time, with currently more than 10,000 meta-analyses published each year (results from a PubMed search using the publication type 'meta-analysis') (Figure 2).(55) Meta-analyses are heavily cited in academic literature, often serving as a definitive reference in the field.(56)

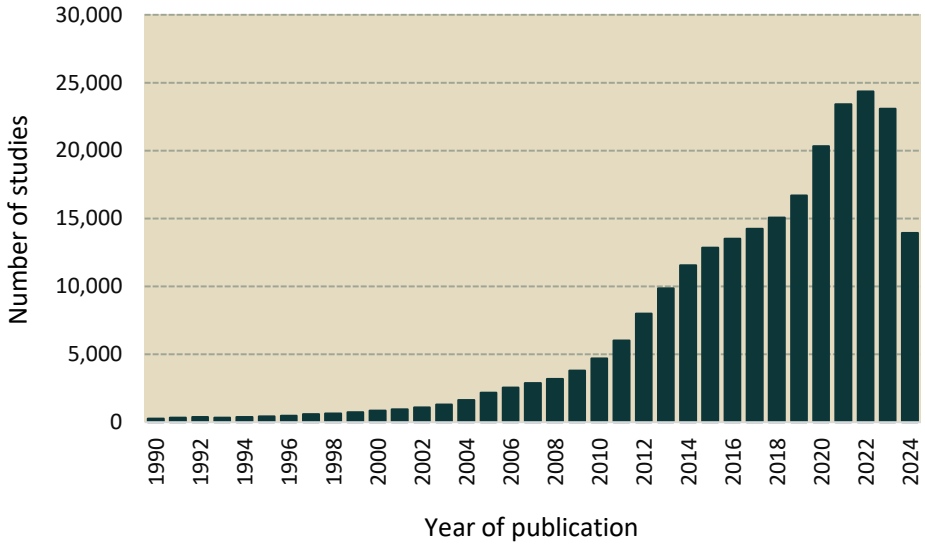

Figure 2: Number of PubMed-indexed articles with the tag 'meta-analysis' for publication type, from 1 January 1990 to 22 August 2024 (adapted from Ioannidis, 2016 (55))

2.2 Why do a systematic review and meta-analysis?

Each year, the results of approximately 30,000 RCTs are published (results from a PubMed search using the publication type 'randomized controlled trial' and terms 'humans', not 'animals'). Stakeholders all struggle to navigate this sea of information when making critical healthcare decisions. Plus, the discrepancies in research findings can lead to confusion and uncertainty. Resolving this issue necessitates a comprehensive and up-to-date synthesis of all available evidence. This synthesis should evaluate not only the efficacy and safety of interventions but also the quality of the evidence itself. Accordingly, evidence synthesis

methods like systematic reviews and meta-analyses of RCTs were developed to address this need.

Beyond synthesizing existing evidence, systematic reviews play a vital role in guiding future research efforts and ensuring efficient use of resources. The Cochrane Handbook explains that a systematic review should be the first step before initiating new research in order to ensure that this research doesn't unnecessarily duplicate existing studies, to get an idea of the research landscape and what is currently being investigated, to highlight knowledge or evidence gaps, and to potentially uncover methodological flaws in the previous studies that can be addressed in the design of the new research.(51,57).

On the hierarchy of evidence pyramid, the volume of information available decreases as you move up the pyramid, but so too does bias, while relevance to the clinical setting increases.(58) Properly conducted systematic reviews and meta-analyses are at the top of the pyramid and thus are considered the pinnacle of evidence-based medicine (Figure 3).

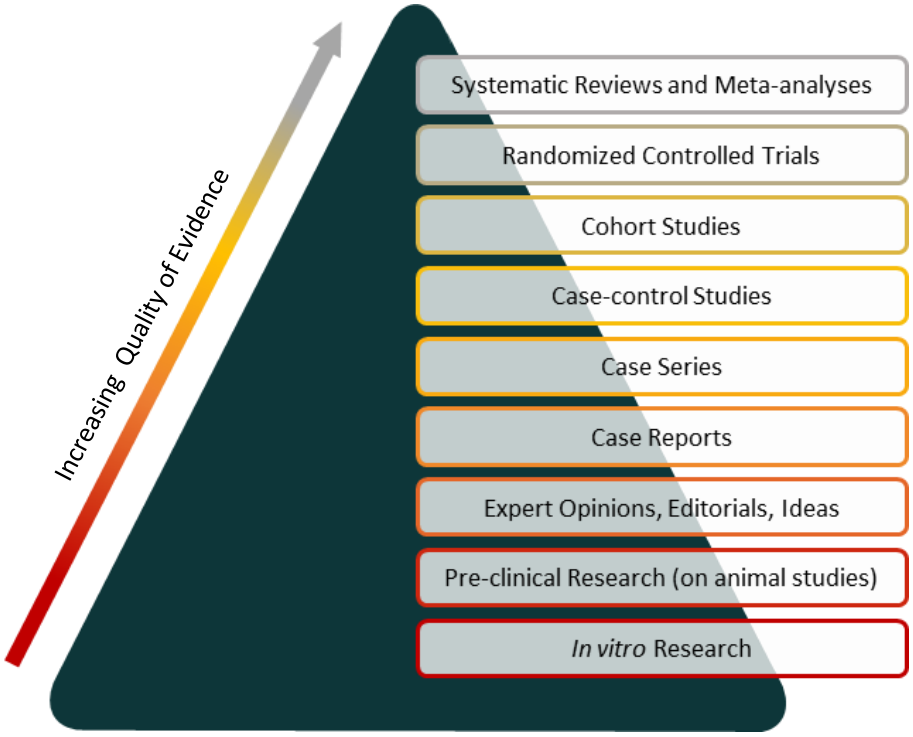

Figure 3: Hierarchy of evidence pyramid (adapted from Jain, 2020 (58))

2.3 Steps to performing a systematic review and meta-analysis

The process of conducting a systematic review begins with a clinical question using the PICO (population, intervention, comparator, outcome). framework. Next, is the development of a protocol that explicitly outlines the review's objectives, eligibility criteria, outcomes of interest and statistical analysis plan, followed by protocol registration on PROSPERO or a similar publicly accessible database.(59) This allows for transparency, increasing accountability and reducing the risk of selective reporting. Next, the literature search should aim to be comprehensive and include multiple sources beyond just bibliographic databases (e.g., MEDLINE/PubMed, Embase) and published journal articles. Grey literature is a valuable source of information to reduce publication bias. This includes conference abstracts, dissertations, clinical trial registries, regulatory reports, and unpublished data (e.g., contacting authors directly). Semiautomated web-based tools like Rayyan use artificial intelligence, machine-learning and natural language processing to assist systematic reviewers during title and abstract screening.(60) Full-text consideration is then performed, followed by data extraction and risk of bias assessment using the Cochrane risk of bias (RoB) 2 tool.(61) Of note, screening, data extraction and risk of bias assessments are all completed independently, in duplicate, with consensus to solve conflicts.

The Cochrane RoB 2 tool is designed to evaluate the risk of bias in the results of RCTs by focusing on specific domains through which bias might be introduced.(62) These domains include the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. The tool uses a set of signaling questions to each domain, from which an algorithm proposes a judgement of 'low', 'some concerns' or 'high' risk of bias. The overall risk of bias is the least favorable assessment across all domains and is supported by written justifications.

Finally, data synthesis is conducted either by a descriptive summary or meta-analysis with results graphically depicted in a forest plot. It is also important to explore heterogeneity in the result via subgroup and sensitivity analyses. The report is then finalized, adhering to PRISMA guidelines.(63,64)

A summary of the stages in the conduct of systematic reviews is provided in Table 1.

Table 1: Steps in the conduct of a systematic review (adapted from Sriganesh, 2016 (65))

Essential steps	
Formulating a research question	• Use the PICO format to frame the question which is neither too broad nor too specific (e.g. does inhalation anesthesia result in higher post-operative cognitive dysfunction compared to intravenous anesthesia in elderly patients undergoing urological surgery?) • Identify team who will be part of this review (content expert, methodologist, experienced librarian, statistician, pairs of reviewers, review coordinator) • Prepare review protocol detailing the planned process and register (PROSPERO) before the review begins
Developing a literature search strategy	• Involve an experienced librarian to select appropriate search words, perform database searches using relevant filters and manage search result • Provide appendix detailing search strategy and results
Selection of relevant studies	• Define inclusion and exclusion criteria for studies based on your PICO format question • Screen title and abstracts independently, guided by an instruction manual, after pre-testing among reviewers • Obtain full-texts of all promising studies identified through title and abstract screening, and evaluate for inclusion independently as per predefined criteria • Maintain record of exclusions with reasons for settling disagreements
Data extraction	• Design and pre-test extraction form among reviewers to evaluate ease of use and extraction of relevant data • Achieve consensus for conflicts
Appraising the quality of selected studies	• Use standard checklists/scale to evaluate quality of all included studies e.g., Cochrane RoB 2.0 tool for RCTs
Data synthesis and meta-analysis	• Tabulate results of individual studies, explain excluded studies • Evaluate and plan suitability for meta-analysis or qualitative synthesis • Examine for and attempt to explain heterogeneity by subgroup or sensitivity analyses
Reporting the findings	• Adhere to the PRISMA guidelines while reporting results • Evaluate, grade and report strength of evidence for each reported outcome • Provide flow diagram depicting the flow of studies in the review

2.4 Limitations of a systematic review and meta-analysis

Despite their importance, traditional systematic reviews and meta-analyses face a significant challenge in that they quickly become outdated. Paul and Barari discuss when to conduct these types of studies, stating that systematic reviews are most appropriate when *"the research topic is evolving to allow a researcher to provide a current view of what is known and define the future direction of the research domain*."(66) But this begs the question, how

current is "current" in rapidly evolving fields? For meta-analyses, they recommend waiting until *"the research topic is mature enough to allow a researcher to provide an overall picture of relationships and the role of moderators in a research domain."*(66) But does "mature enough" really mean that it is up-to-date. Once again, this question must be emphasized for rapidly evolving fields. These criteria highlight a fundamental tension in evidence synthesis i.e., the need to gather enough evidence to draw meaningful conclusions versus the risk of excluding the latest findings. Research has found that significant new evidence is already available for 7% of systematic reviews by the day of publication, while after two years, 23% of reviews are rendered inaccurate if not updated.(67) Cochrane proposes updating reviews within two years to address this issue, but generally few systematic reviews do so since only approximately 6% of systematic reviews are Cochrane reviews (results based on the number of PubMed-indexed articles with the tag 'The Cochrane database of systematic reviews' for journal compared to 'systematic review' for publication type).

The time-intensive nature of conducting these comprehensive literature searches, data extraction, and analysis is a disadvantage. The median time to publication of a Cochrane review is 2.78 years (range 0.96 to 8.05), and almost a quarter remain unpublished after 8 years.(68) This lengthy time gap between planning and publishing a systematic review presents significant challenges for guideline developers and decision-makers who require timely, evidence-based insights to inform their work.

Furthermore, Boutron et al discusses the often chaotic planning of systematic reviews and meta-analyses, which leads to redundancy and leaves critical questions in the field unanswered.(69,70) This redundancy wastes resources and can cause confusion when reviews on the same topic reach conflicting conclusions. Also, systematic review methods are tend to be flawed. Search strategies are often not comprehensive, with many reviews failing to search for unpublished data or consult trial registries.(21,71,72) These omissions can lead to publication bias and skewed results.

Additionally, many systematic reviews and meta-analyses fail to present an overview of all interventions that are available for a given condition.(73) For instance, a study quantified the waste of research of systematic reviews, finding that for the specific topic, at least 40% of available interventions, comparisons and trials were missing from the reviews.(71) Systematic reviews and meta-analyses may struggle to adequately address complex clinical questions

that involve multiple interventions, outcomes, or patient populations, and most systematic reviews and meta-analyses focus primarily on efficacy and neglect safety outcomes.(69) This imbalance can lead to an incomplete understanding of the overall risk-benefit profile of interventions.

Efforts to improve the methodology, reporting, and updating of systematic reviews and meta-analyses are needed.

3. Dynamic approach to evidence synthesis

3.1 Living systematic reviews

> *"In the growing deluge of research the noble science of systematic review resembles archeology: academic teams searching for buried artifacts and working tirelessly to reveal their true meaning."*(74)

This from Julian Elliott and colleagues in a 2014 piece in *PLoS Medicine* where they proposed living systematic reviews (LSRs) as an innovative evolution of traditional systematic reviews, combining *"currency with rigour to enhance the accuracy and utility of health evidence."*(74) They called it *"an emerging opportunity to narrow the evidence-practice gap…[i.e.,] a gap between research findings (what is known) and health care practice (what is done)".*(74)

An LSR is defined as a systematic review that is frequently and consistently updated, synthesizing new evidence as it is identified.(74) The need for this type of review is particularly emphasized in rapidly evolving fields, when the findings are key guides for decision-making, and when there is low or very low certainty in the existing evidence.(75)

The CENTER-TBI project was the first to implement LSR methods in the treatment and management of traumatic brain injuries.(76) The Cochrane Living Evidence Network was launched in 2016, to introduce LSR concepts, showcase completed research on living data synthesis, and provide educational resources.(77) Over the following years, the Cochrane Collaboration published several LSRs, establishing itself as a leader in the field.(78) Initially, from 2014 when LSRs were first proposed to 2019, only a few studies were published. However, the COVID-19 pandemic spurred a significant increase in LSRs, with a study finding 213 articles published across 69 journals, which far surpassed the total number of prior publications.(78)

The ongoing update process in LSRs is facilitated by digital tools and platforms to streamline updates, including automated methods for literature searches and data extraction, as well as regular expert review cycles to verify data. This ensures transparency and efficiency of the evidence synthesis process, and that the review remains a reliable resource for decision-making.

3.1.1 COVID-NMA Initiative

One notable example of an LSR is the COVID-NMA initiative.(79)

The emergence of SARS-CoV-2 in December 2019 that led to the COVID-19 pandemic (declared by the World Health Organization (WHO) on March 11, 2020 (80)) exposed weaknesses in global health preparedness and response. The scientific community was plunged into chaos with numerous clinical trials being conducted and publications racing to meet the urgent demand for information, given the exponential increase in mortality rate. The standard of care changed frequently with the variability in clinical presentation, the advent of promising and discouraging results on certain treatments, as well as the evolving genetic variants of concern. Forgoing the typical narrow scope of systematic reviews (i.e., focusing on one specific treatment or comparison), COVID-NMA combined continuous surveillance of all trials with real-time data analysis to provide a living mapping and a comprehensive living synthesis of all COVID-19 treatments, preventive interventions and vaccines. It relied on a complex process whereby screening, data extraction and RoB assessments were performed daily, by pairs of researchers, independently and in duplicate, with disagreements resolved through consensus and a third reviewer when necessary. Meta-analysis and grading of the evidence were conducted weekly (Figure 4). All results were made available on a publicly accessible platform (covid-nma.com).

The COVID-NMA living systematic review leveraged data from a variety of formal and informal sources, including journal articles, preprints, clinical trial registries, and regulatory reports to provide up-to-date evidence on the efficacy and safety of different therapeutic options. By continually updating the review as new studies emerged, and frequently conducting expert quality control, COVID-NMA was able to offer publicly available and timely insights that informed clinical practice and policy decisions during the pandemic. It was a massive, complex, international research initiative that was supported the WHO and Cochrane. The

COVID-NMA living mapping and synthesis was concluded in August 2023. As of latest record in August 2024, over 775 million cases of COVID-19 have been reported worldwide, of which approximately 7 million resulted in death.(81)

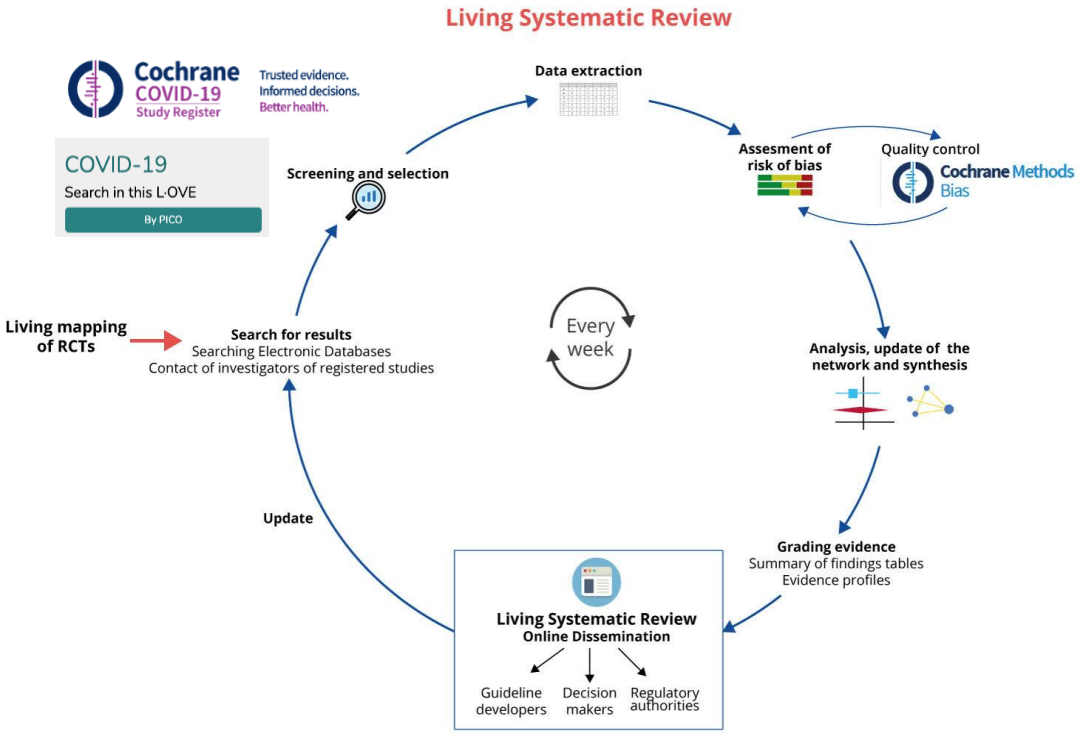

Figure 4: The COVID-NMA living systematic review process

4. Evidence ecosystem

Systematic reviews, particularly living systematic reviews, could serve as a gateway to identifying important flaws. As part of their usual process, systematic reviewers assess risk of bias in trials using the Cochrane RoB 2.0 tool and ORB assessment which identifies issues such as incomplete or selective reporting of results. A link between trialists and systematic reviewers could provide an opportunity for authors to correct these issues, which would ultimately enhance the quality of research dissemination. Of course, the delay between the trial publication and the review publication is a critical factor that warrants consideration. Moreover, community feedback via post-preprint and PPPR is another valuable avenue for detecting specific issues in trial methodology and reporting. Formal peer review was intended to ideally weed out these flaws, but given its limitations, there is a distinct and desperate

need for new and supplementary methods of research evaluation. Some have been suggested or employed.(82–85) PPPR, in conjunction with formal peer review, can enhance the robustness of knowledge dissemination.

Currently, there is limited interaction between research enterprises, but particularly among trialists, systematic reviewers and the general research community.(69) This disconnect persists despite recommendations that trials should begin and end with systematic reviews of relevant evidence.(86) For example, upon trial completion, there's a noticeable lack of proactive sharing of results with systematic reviewers for updating existing reviews.(87,88) Furthermore, trialists often disregard PPPR feedback, sometimes even deleting comments when possible. This disengagement extends to the broader research community who aren't truly incentivized to contribute to peer review in this way, or any way for that matter. Overall, building an interconnected and interactive evidence ecosystem among all research enterprises should be a priority.

5. Aims and Objectives

The central aim of this doctoral thesis was to explore the benefits and risks of integrating various types of information in living systematic reviews. More specifically, the research was conducted using the COVID-NMA living systematic review and guided by three main objectives:

1. To investigate the influence of publication type (preprint vs. journal article) on treatment effect. This involved a meta-epidemiological study of meta-analyses including preprint and journal article RCTs (Study one), as well as a study directly comparing preprints and their subsequent journal article (Study two).
2. To assess the role of post-publication peer reviews in the identification of methodological and reporting issues of RCTs. This was conducted using qualitative content analysis of open commentary data from PubPeer, medRxiv, Research Square and SSRN and systematic reviewer Risk of Bias justifications. (Study three).
3. To compare the consistency of reporting between clinical trial registries and the final published report. This was addressed through a methodological review, searching for results posted to the ClinicalTrials.gov registry and published in a journal article or preprint, if no journal article was available. (Study four).

Part 1: Evaluation of the influence of publication type on treatment effect

Chapter 1: Association between publication type and summary treatment effect

Previously, I presented an overview of the thesis' aims and objectives. I explained the recent surge in preprint use in order to gain quick insights into therapeutic and preventative interventions of COVID-19. However, questions persist about the reliability of these results given that they have not been peer-reviewed and could cause the spread of misinformation. This is particularly concerning when considering incorporating preprint results into evidence syntheses for decision-making.

To answer these questions, I wanted to examine meta-analyses that included RCTs of different publication types, since at the point of evidence synthesis, it is unclear which preprints will eventually be published in peer-reviewed journals. Thus, a meta-epidemiological study was conducted, evaluating whether summary treatment effect estimates differed between preprint and journal article RCTs.

Summary of findings

In this study, I utilized data from the COVID-NMA living systematic review up to July 20, 2022. We identified all meta-analyses evaluating pharmacological treatments vs. standard of care/placebo for COVID-19. Meta-analyses must include at least one preprint and at least one peer-reviewed journal article. I considered the COVID-NMA-defined critical outcomes.

As COVID-NMA is a living systematic review, once the weekly or biweekly updates were executed, the database was saved. Therefore, the database is formatted into multiple time-varying versions of a given meta-analysis. I selected meta-analyses for our study using automated random selection of a meta-analysis, at any given time-point, that included at least one preprint article and at least one journal article. I estimated the difference in effect

estimates between preprint and journal article RCTs as the ratio of odds ratio (ROR). For each meta-analysis, I first estimated the odds ratio (OR) from preprint RCTs and OR from journal article RCTs. Then, I estimated the pooled ROR across meta-analyses. An ROR < 1 indicated that preprint RCTs overestimate treatment effects when compared to journal article RCTs.

In total, I selected 37 meta-analyses of 114 RCTs (44 preprints, 70 journal articles). The median number of RCTs per meta-analysis was 2 (IQR, 2–4) RCTs, and the median sample size of RCTs was 199 (IQR, 99–478) participants. The characteristics of preprint and journal article RCTs were comparable for most variables. There was no statistically significant difference in summary effect estimates between preprint and journal article RCTs (ROR, 0.88; 95% CI, 0.71–1.09; I^2 = 17.8%; τ^2= 0.06).

There were some limitations of our assessment. The findings may not be generalizable to other fields since we focused only on COVID-19 RCTs. Also, there was a small number of RCTs within most meta-analyses, which increased the uncertainty around the estimation. Finally, I considered only meta-analyses of RCTs, and RCTs usually rely on pre-registered protocols. Therefore, other study types like observational studies could yield different results.

To the best of my knowledge, this is the first meta-epidemiological study to assess the association between publication type (preprints vs. journal articles) and treatment effects. With this work, I did not find an important difference between summary treatment effects of preprints and summary treatment effects of peer-reviewed journal articles. These results were consistent in post-hoc sensitivity analyses. Given these findings and especially in the context of a fast-moving pandemic, it may be reasonable to consider preprint results. Of course, caution should be taken to evaluate these preprint RCTs individually, and assess the risk of bias and completeness of reporting.

Article

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"No evidence of important difference in summary treatment effects between COVID-19 preprints and peer-reviewed publications: a meta-epidemiological study"

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The online supplement files of the article are presented in Annex 1 of this thesis.

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ORIGINAL ARTICLE

No evidence of important difference in summary treatment effects between COVID-19 preprints and peer-reviewed publications: a meta-epidemiological study

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Abstract

Objectives: Preprints became a major source of research communication during the COVID-19 pandemic. We aimed to evaluate whether summary treatment effect estimates differ between preprint and peer-reviewed journal trials.

Study Design and Setting: A meta-epidemiological study. Data were derived from the COVID-NMA living systematic review (covid-nma.com) up to July 20, 2022. We identified all meta-analyses evaluating pharmacological treatments vs. standard of care or placebo for patients with COVID-19 that included at least one preprint and one peer-reviewed journal article. Difference in effect estimates between preprint and peer-reviewed journal trials were estimated by the ratio of odds ratio (ROR); ROR <1 indicated larger effects in preprint trials.

Results: Thirty-seven meta-analyses including 114 trials (44 preprints and 70 peer-reviewed publications) were selected. The median number of randomized controlled trials (RCTs) per meta-analysis was 2 (interquartile range [IQR], 2–4; maximum, 11), median sample size of RCTs was 199 (IQR, 99–478). Overall, there was no statistically significant difference in summary effect estimates between preprint and peer-reviewed journal trials (ROR, 0.88; 95% CI, 0.71–1.09; $I^2 = 17.8\%$; $\tau^2 = 0.06$).

Conclusion: We did not find an important difference between summary treatment effects of preprints and summary treatment effects of peer-reviewed publications. Systematic reviewers and guideline developers should assess preprint inclusion individually, accounting for risk of bias and completeness of reporting.

Keywords: Preprint; Peer-review; COVID-19; Meta-epidemiology; Meta-analysis; Randomized controlled trial

1. Introduction

Preprints (i.e., scientific manuscripts uploaded to publicly accessible platforms without formal external peer review) have been widely used as a major source of research dissemination in several disciplines such as physics, computer science, and mathematics [1,2], but their use has been slower to endorse in the medical sciences. However, during the coronavirus disease 2019 (COVID-19) pandemic, preprints have emerged as a major source of research communication due to the demand for faster access to clinical study findings [3,4]. The traditional peer review process often requires several months, which can delay the implementation of effective

Data availability: The datasets, metadata and code used and analyzed during the current study are available from the corresponding author upon reasonable request.

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0895-4356/

What is new?

Key findings

- No strong evidence that preprints, on average, have different summary treatment effect estimates than peer-reviewed journal publications. Results should be interpreted with caution due to imprecision and heterogeneity.
- Results were consistent in post-hoc sensitivity analyses.

What this adds to what was known?

- Inclusion of preprint trials within a meta-analysis is not largely endorsed but this may not have an impact on intervention effect.

What is the implication and what should change now?

- Within the constantly evolving research landscape and especially in the context of a fast-moving pandemic, considering the results of preprint trials may be reasonable.
- Systematic reviewers and meta-analysts should assess preprint inclusion on an individual level, accounting for risk of bias and completeness of reporting.

treatments in clinical practice and cost lives, particularly during pandemics. For example, over 700,000 new COVID-19 cases were confirmed worldwide within a relatively short delay of 1 month between the preprint and journal publication of the RECOVERY-dexamethasone trial [5]. In this regard, preprints offer a solution, especially to patients, as their results can be publicly available in approximately 2–4 days [6].

Additionally, preprint use allows patients and clinicians to keep pace with the volatile research climate and make informed decisions about care, especially in the context of the rapidly evolving COVID-19 pandemic. Decision-makers can also use preprints to develop clinical practice guidelines to optimize patient impact. However, the lack of peer review raises concerns regarding the reliability of the preprint results and their inclusion in systematic reviews and meta-analyses for decision-making [7,8].

Generally, meta-epidemiological studies use collections of meta-analyses to investigate the association between a trial characteristic and treatment effect [9]. In this study, we aimed to evaluate whether summary treatment effect estimates differ on average between preprint and peer-reviewed journal randomized controlled trials (RCTs).

2. Material and methods

2.1. Study design

We conducted a meta-epidemiological study of meta-analyses including preprint and peer-reviewed journal RCTs. Our protocol is available on the Open Science Framework (https://osf.io/hfrp4/?view_only=b06282a8429e4ae1af458f4e372576f7). We report here the results of objective 2 of the protocol, the meta-epidemiological study.

2.2. Changes to the protocol

To increase the size of our sample, we included meta-analyses of RCTs assessing all pharmacological treatments and did not restrict the analysis to specific treatment types. Furthermore, we postponed the last search to July 20, 2022.

2.3. Data source and search

Data were derived from the COVID-NMA living systematic review (covid-nma.com), which aimed to provide decision-makers with a complete, high-quality, and up-to-date synthesis of evidence on interventions for the prevention and treatment of COVID-19 [10].

Our study used the methods of the COVID-NMA initiative. These are described in eMethods 1 [see Supplement]. In brief, the comprehensive search strategy involved searching two validated secondary sources for primary RCTs. We searched the Epistemonikos L-OVE COVID-19 platform (app.iloveevidence.com/covid19) [11] and Cochrane COVID-19 study register (covid-19.cochrane.org/). The Retraction Watch database was also searched to identify retracted studies (retractionwatch.com/retracted-coronavirus-covid-19-papers). Screening and data extraction were performed in duplicate, with disagreements resolved by consensus and a third reviewer when necessary. We then meta-analyzed the results weekly. The COVID-NMA protocol was revised on March 1, 2022, to reduce the scope by including only studies evaluating immunomodulators and antiviral therapies and updating the analysis biweekly instead of weekly.

2.4. Study selection

We identified all eligible COVID-NMA living meta-analyses evaluating pharmacological treatments vs. standard of care or placebo for patients with COVID-19 that included at least one preprint article and one peer-reviewed journal article up to July 20, 2022. We considered the following COVID-NMA-defined critical outcomes.

- Clinical improvement at day 28 (D28) (i.e., a hospital discharge or improvement on the scale used by trialists to evaluate clinical progression and recovery. We recorded the scale and the threshold used by authors to define improvement as appropriate [see eMethods 2 in Supplement]

- WHO clinical progression Score [12] of level 7 or above (i.e., mechanical ventilation +/− additional organ support or death) (D28)
- All-cause mortality (D28)
- Incidence of any adverse events
- Incidence of serious adverse events

We excluded meta-analyses evaluating preventive interventions (e.g., use of personal protective equipment, movement control strategies), vaccines, nonpharmacological treatments, and supportive treatments for patients admitted to the intensive care unit.

As COVID-NMA is a living systematic review, all analyses were updated weekly and then biweekly as new studies were identified and extracted and the database saved. Therefore, the database is formatted into multiple time-varying versions of a given meta-analysis. Meta-analyses were selected for inclusion in the final dataset in two steps. First, we randomly selected a given time point where a meta-analysis included at least one preprint article and at least one peer-reviewed journal article. Selection was automated using R code [13]. Second, if at this given time point a meta-analysis meeting the eligibility criteria (in terms of treatment comparison and outcomes) were available for more than one of the above outcomes, the meta-analysis that included the highest number of trials was selected. Individual RCTs that reported zero events in both the intervention and comparator groups did not contribute to the analysis. We excluded meta-analyses and RCTs that compared two active treatments [14].

2.5. Data extraction

Data were previously extracted in the context of the COVID-NMA living systematic review in duplicate, with consensus to resolve disagreements [15].

The following data were considered: type of publication (preprint/peer-reviewed publication), timing of the publication (first 6 months of the pandemic [up to September 2020], 6–12 months [October 2020 to March 2021], after 12 months), type of funding (industry, mixed, public, none, or not reported or unclear), type of participants (hospitalized patients or outpatients), location (low/middle or high-income country) [16], number of centers (single or multicentric), and intervention details.

For the critical outcome measures under consideration, the number of events, number of participants analyzed, and risk of bias assessment according to the Cochrane Risk of Bias 2.0 tool for RCTs were extracted [17].

2.6. Data synthesis

We generated descriptive statistics for all the trials. We reported frequencies and percentages for categorical characteristics and medians with interquartile ranges (IQRs) for continuous characteristics.

We performed a meta-epidemiological analysis to estimate the difference in summary effect estimates between preprint and peer-reviewed journal RCTs. This was expressed as the ratio of odds ratio (ROR). For each meta-analysis, we first estimated the treatment effect (i.e., odds ratio [OR]) from preprint RCTs and OR from peer-reviewed journal RCTs. All outcomes were transformed such that an OR of <1 demonstrated a beneficial effect of the experimental treatment. To estimate the ROR for each meta-analysis of more than two RCTs, we used a random-effects meta-regression model with the publication status (preprint or peer-reviewed journal) of the RCTs as a covariate. The meta-analysis-specific ROR was the exponent of the regression coefficient. For meta-analyses of only two RCTs (one preprint and one peer-reviewed journal), we calculated the ROR as the ratio of the two study-specific ORs. Finally, we estimated the pooled ROR across meta-analyses and the 95% confidence interval (CI) using a random-effects meta-analysis model. An ROR of <1 indicated that preprint RCTs yielded larger estimates of intervention effects than peer-reviewed journal RCTs. Heterogeneity across RORs was assessed using the I^2 statistic, Cochran Q chi-squared test, and between-meta-analyses variance τ^2.

2.6.1. Subgroup and sensitivity analyses

Due to the small number of studies within each meta-analysis, we could not use a meta-regression model, including pre-specified covariates (sample size, type of funding, number of centers, registration timing, and overall risk of bias). Nevertheless, we performed post-hoc sensitivity analyses, including only meta-analyses, in which the subsets of preprint and peer-reviewed journal RCTs were homogenous with respect to the pre-specified covariates: type of funding (industry or mixed vs. others [i.e., public/no funding/not reported/unclear]), number of centers (single or multicentric trials), registration timing (prospective or retrospective), and overall risk of bias (low/some concerns/high). We did not consider the sample size in the additional analyses because the majority of the RCTs included more than 100 participants.

We also conducted post-hoc sensitivity analyses to examine the impact of early synthesis of preprint and peer-reviewed publication RCTs and synthesis at later stages. For this purpose, we randomly selected two samples of meta-analyses: 1) meta-analyses including only two trials (one preprint and one peer-reviewed journal, i.e., early synthesis); and 2) meta-analyses including at least three trials (ensuring heterogeneity in publication type, i.e., synthesis at later stage). Furthermore, we analyzed whether including data from retracted trials would have impacted the results. Finally, we conducted a post-hoc subgroup analysis with respect to the type of outcome (objective vs. subjective).

We compared effect estimates between preprint and peer-reviewed journal RCTs in these samples.

3. Results

3.1. Characteristics of included meta-analyses

Overall, up to our search date, the COVID-NMA living systematic review had generated 323 meta-analyses of pharmacological treatment comparisons for patients with COVID-19. We selected 37 meta-analyses of pharmacological treatments vs. standard of care/placebo that included at least one preprint article and one peer-reviewed journal publication, for a total of 114 RCTs (44 preprints and 70 peer-reviewed journal articles). The details of the selection process are displayed in Fig. 1. eTable 1 in the Supplement presents the characteristics of the included meta-analyses. Overall, 24 meta-analyses assessed hospitalized patients (81 RCTs), and 13 assessed outpatients (33 RCTs). In eight meta-analyses, preprint RCTs were published first compared to peer-reviewed journal RCTs, whereas in 29 meta-analyses, peer-reviewed publication RCTs were published first. The median number of RCTs per meta-analysis was 2 (IQR, 2–4; maximum, 11).

3.2. Characteristics of preprint and peer-reviewed journal RCTs

Table 1 reports the characteristics of the included RCTs. In total, 114 RCTs were included. There were three three-

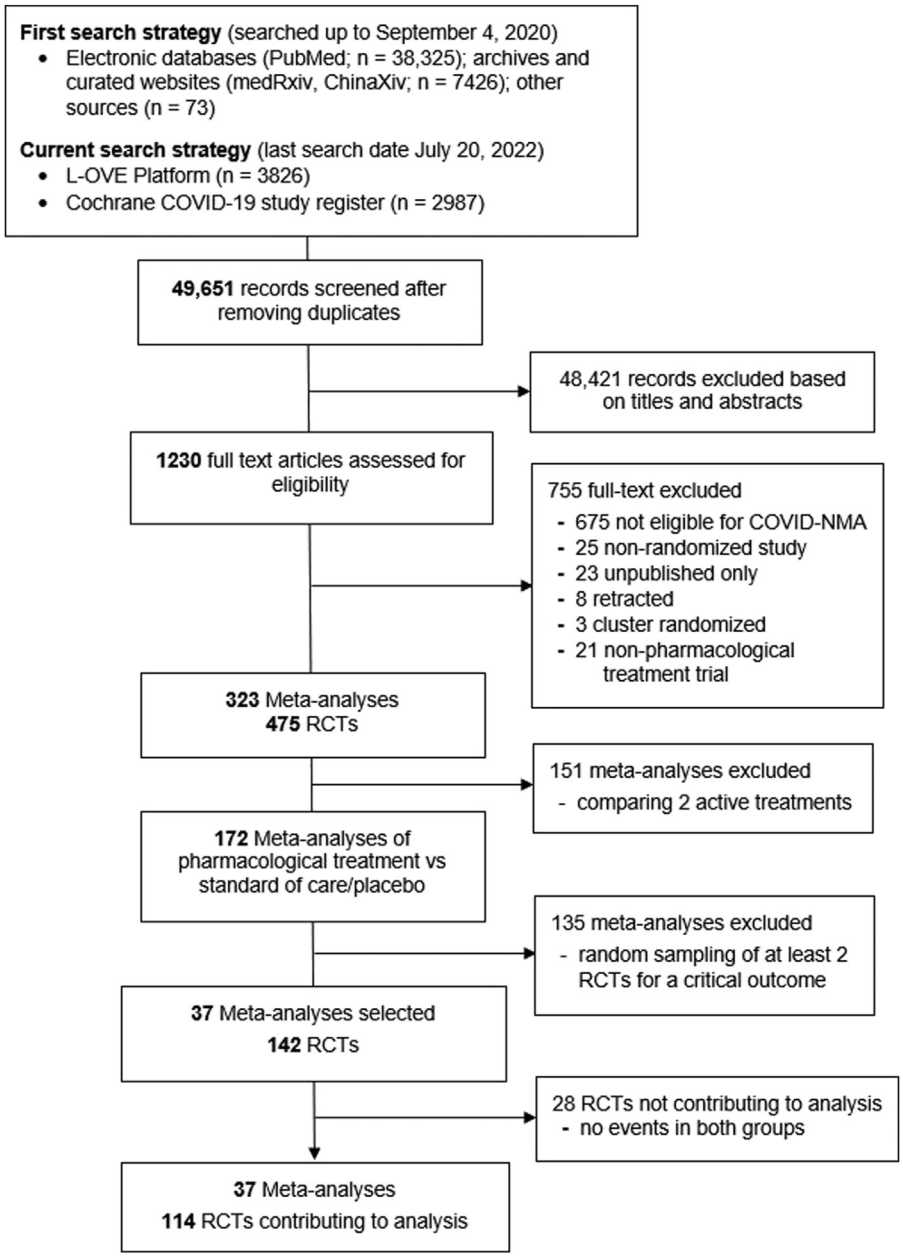

Fig. 1. Flowchart of included randomized controlled trials (last search date July 20, 2022).

Table 1. Characteristics of preprint and peer-reviewed journal RCTs

Characteristics	Total RCTs, *n* = 114 (%)	Preprint RCTs, *n* = 44 (%)	Peer-reviewed journal RCTs, *n* = 70 (%)
Sample size[a] (*n*)	199 (99–478)	201 (98–447)	199 (103–491)
Registration timing			
Prospective	78 (68)	33 (75)	45 (64)
Retrospective	34 (30)	11 (25)	23 (33)
Not reported or unclear	2 (2)	0	2 (3)
Type of funding			
Industry or mixed	76 (67)	31 (70)	45 (64)
Others	38 (33)	13 (30)	25 (36)
Number of centers			
Single	24 (21)	8 (18)	16 (23)
Multicenter	90 (79)	36 (82)	54 (77)
Overall risk of bias			
Low	17 (15)	3 (7)	14 (20)
Some concerns	86 (75)	35 (80)	51 (73)
High	11 (10)	6 (14)	5 (7)
Setting			
Hospitalized	81 (71)	31 (70)	50 (71)
Outpatients	33 (29)	13 (30)	20 (29)
Blinding			
Blinded	59 (52)	27 (61)	32 (46)
Unblinded	55 (48)	17 (39)	38 (54)
Location(s)			
High-income	56 (49)	24 (55)	32 (46)
Low-/middle-income	43 (38)	15 (34)	28 (40)
Mixed	15 (13)	5 (11)	10 (14)
Publication time[b]			
<6 mo	22 (19)	4 (9)	18 (26)
6–12 mo	45 (39)	15 (34)	30 (43)
>12 mo	47 (41)	25 (57)	22 (31)

RCT, randomized controlled trial.
Others, public/no funding/not reported/unclear.
[a] Median (interquartile range).
[b] Reference—start of the pandemic.

arm trials, each contributing to more than one meta-analysis. The characteristics of preprint and peer-reviewed journal RCTs were comparable for most variables. The median sample size of trials was 199 (IQR, 99–478), 68% were prospectively registered, 67% received industry or mixed funding, 79% were multicentric trials, and 75% were assessed to have some concerns of overall risk of bias.

3.3. Differences in treatment effect estimates between preprint and peer-reviewed journal RCTs

The summary ROR of treatment effect estimates between preprint and peer-reviewed journal RCTs was 0.88 (95% CI, 0.71–1.09; 95% PI, 0.51–1.50; I^2 = 17.8%; P = 0.36; τ^2 = 0.06) (Fig. 2), suggesting no evidence of an association between preprint and peer-reviewed journal publications on treatment effect estimates. However, considering the small number of studies within most meta-analyses and the large uncertainty of the respective RORs, strong conclusions could not be drawn. Meta-analysis-specific RORs ranged from 0.08 to 13.99. In total, 21 and 16 meta-analyses estimated RORs of <1 and >1, respectively. We found similar results in post-hoc sensitivity analyses when accounting for type of funding, number of centers, registration timing, and overall risk of bias (eFigures 1–4).

Post-hoc sensitivity analyses exploring the impact of early synthesis and synthesis at later stages found consistent results with ROR = 0.86 (95% CI, 0.51–1.45; 95% PI, 0.31–2.34; I^2 = 22.2%; P = 0.24; τ^2 = 0.19) for early synthesis (i.e., only two RCTs included in the meta-analyses) (eFigure 5) and ROR = 0.98 (95% CI, 0.84–1.14; 95% PI, 0.84–1.14; I^2 = 0.0%; P = 0.94; τ^2 = 0.00) for synthesis at later stages (i.e., at least three RCTs included) (eFigure 6). Posthoc sensitivity analysis including retracted trials also yielded similar results;

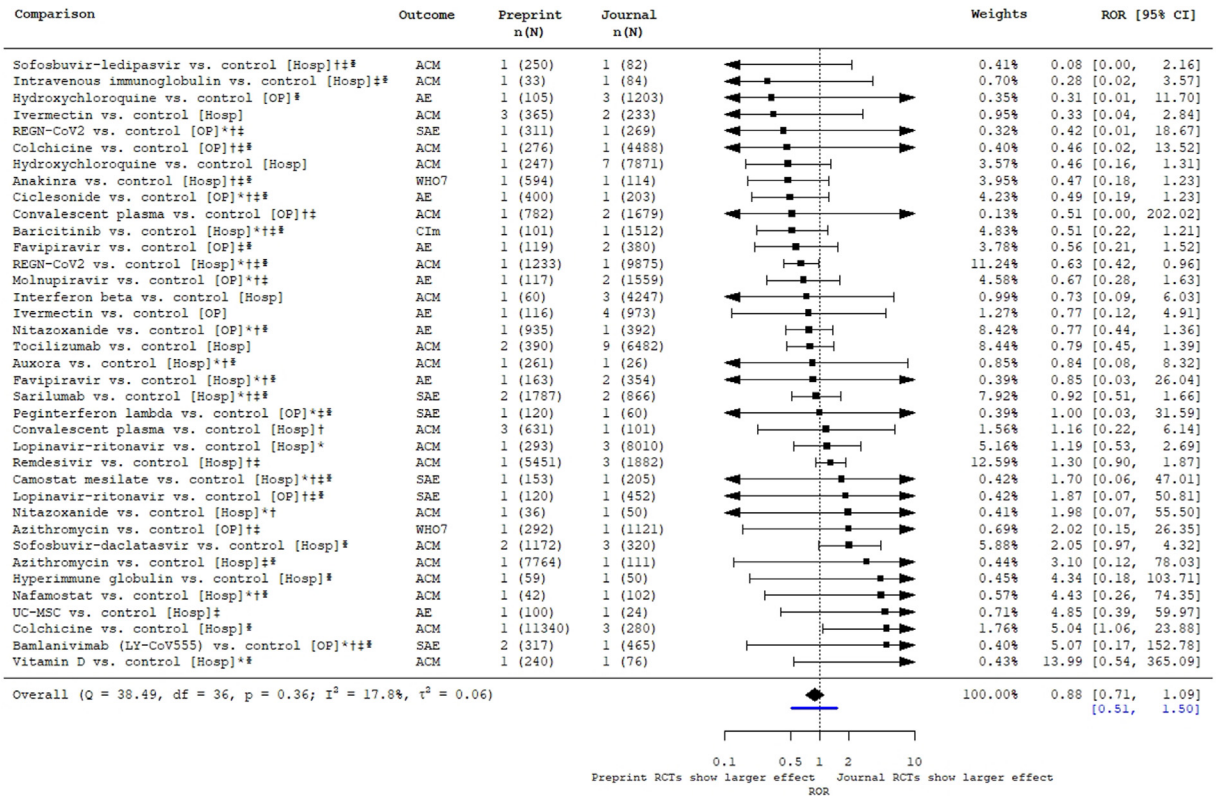

Fig. 2. Difference in treatment effect estimates between preprint and peer-reviewed journal RCTs RCT, randomized controlled trial; *n*, number of RCTs; *N*, number of participants analyzed; journal, peer-reviewed journal; ROR, ratio of odds ratio; CI, confidence interval; control, standard of care or placebo; REGN-CoV2, casirivimab-imdevimab; UC-MSC, umbilical cord mesenchymal stem cell infusion; Vitamin D, calcifediol/cholecalciferol; Hosp, hospitalized patients; OP, outpatients; ACM, all-cause mortality; AE, adverse event; SAE, Serious Adverse Event; WHO7, World Health Organization Clinical Progression Score of level 7 or above; CIm, clinical improvement *Meta-analysis of RCTs with homogeneity in type of funding. †Meta-analysis of RCTs with homogeneity in the number of centers. ‡Meta-analysis of RCTs with homogeneity in registration timing. ǂMeta-analysis of RCTs with homogeneity in overall risk of bias. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

ROR = 0.86 (95% CI, 0.70−1.07; 95% PI, 0.51−1.47; I^2 = 17.5%; P = 0.36; τ^2 = 0.06) (eFigure 7). Finally, posthoc subgroup analysis with respect to the type of outcome (objective or subjective) suggests that differences between preprints and journal publications may be larger when evaluating subjective outcomes ROR = 0.74 (95% CI, 0.55−0.98) but the test for subgroup differences is not significant (P = 0.20) (eFigure 8).

4. Discussion

This study presents a comprehensive analysis of the summary treatment effect estimates from meta-analyses of preprint and peer-reviewed journal RCTs. The trials assessed pharmacological treatments for patients with COVID-19. We did not find an important difference between the summary treatment effects of preprint RCTs and the summary treatment effects of peer-reviewed journal RCTs. The results should be interpreted with caution, though, considering the small number of trials within most meta-analyses and the large uncertainty of the respective RORs.

To the best of our knowledge, this is the first meta-epidemiological study to assess the association between publication type (preprints vs. peer-reviewed journals) and treatment effects.

Other studies have investigated preprint-peer-reviewed publication pairs of RCTs and found no major discrepancies between the first preprint and related peer-reviewed journal reports of trials extracted from the living systematic review and network meta-analysis [18−20] and COVID-NMA [10,21]. Zeraatkar et al. [18] also found mostly consistent results when comparing meta-analyses that included and excluded preprint reports. Other studies have also investigated preprint-peer-reviewed publication pairs of RCTs based on transparency, completeness, and accuracy of reporting, as well as results reporting and spin, and found that the peer review process had a negligible impact on the respective study endpoints [22,23].

4.1. Strengths and limitations

We conducted a meta-epidemiological study to estimate the bias associated with publication type (preprints vs. peer-reviewed journals). At the point of evidence synthesis, it is

unclear which preprints will eventually be published in peer-reviewed journals. Therefore, by examining meta-analyses themselves via this type of study, focusing on those that include different trials of different publication types, and estimating whether there is a statistical difference, we can better assess the reliability of preprint results. Furthermore, our study utilized data from a large living systematic review and meta-analysis (COVID-NMA). COVID-NMA relies on an extensive process, from screening to analysis. All data were extracted in duplicate, and disagreements were resolved by consensus and a third reviewer when necessary. Finally, our study assessed a software-generated random sample of meta-analyses available over time within a living review.

Our study has some limitations. First, we focused on COVID-19 trials, which may not be representative of preprints and peer-reviewed journal publications in other fields outside of the pandemic. Peer review was majorly affected by COVID-19, with significant expedition of the peer review process and difficulties accessing highly skilled peer reviewers. Second, the number of RCTs per meta-analysis was small, with a median of 2 (IQR, 2−4), which increased the uncertainty around the estimation. We could not account for pre-specified covariates in a meta-regression analysis and could only rely on subgroup analyses due to the small number of RCTs per meta-analysis. Finally, we considered only meta-analyses of RCTs. RCTs usually rely on pre-registered protocols; thus, results could be different for other study types, such as observational studies.

5. Conclusions

Overall, we did not find strong evidence to suggest that the summary treatment effect estimates would be larger, on average, in preprints than in peer-reviewed journal publications. Such analyses should be replicated in larger samples, including a greater number of RCTs in different fields. For systematic reviewers and guideline developers, preprint inclusion allows for rapid decision-making and should be assessed at the individual level, considering the risk of bias and the completeness of reporting.

CRediT authorship contribution statement

Mauricia Davidson: Conceptualization, Methodology, Data curation, Investigation, Formal analysis, Visualization, Writing − original draft, Writing − review & editing. **Theodoros Evrenoglou:** Formal analysis, Writing − review & editing. **Carolina Graña:** Investigation, Writing − review & editing. **Anna Chaimani:** Conceptualization, Methodology, Formal analysis, Writing − review & editing, Supervision. **Isabelle Boutron:** Conceptualization, Methodology, Writing − review & editing, Supervision.

Declaration of competing interest

MD received a PhD fellowship from the Université Paris Cité. No other competing interests were reported.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2023.08.011.

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Chapter 2: Comparison of effect estimates between preprints and subsequent journal articles

In Chapter 1, I investigated the difference in summary treatment effects between preprints and journal articles. This perspective was at the meta-analysis level. I am particularly interested in evaluating the potential discrepancies at the trial level via an in-depth one-on-one comparison between different publication types. Anticipating some changes in the content across different documents and sources for the same RCT is reasonable, as these changes may be due to updated analyses or reporting. This is particularly emphasized between a preprint and a subsequent journal article as peer review often impacts the content of a manuscript before it is published. Therefore, I conducted a study aimed at assessing the consistency in effect estimates between preprint and subsequent journal article of COVID-19 RCTs.

Summary of findings

Again, I derived data from the COVID-NMA living systematic review of pharmacological treatments for COVID-19 up to July 20, 2022. I identified RCTs evaluating pharmacological treatments vs. standard of care/placebo for COVID-19 patients that were originally posted as preprints and subsequently published as journal articles. I also considered the COVID-NMA-defined critical outcomes and excluded trials that did not report the same analysis in both documents. Data were extracted independently by pairs of researchers with consensus to resolve disagreements. We extracted the number of patients analyzed and the number of outcome events from the first preprint and compared them to those from the journal article.

As part of the process, COVID-NMA incorporated a preprint-article linker tool that was developed in collaboration with a research team from the French National Centre for Scientific Research. The tool alerted systematic reviewers when a preprint was updated or published as a journal article so that extraction of any new or modified data could be performed. As standard practice, this was done independently, in duplicate with meetings for consensus to reconcile any disagreements. As a result, the COVID-NMA database contained a

downloadable record of the corresponding preprint and journal article reports. For this study, I used this record to select the first preprint posted on a preprint server and the subsequent journal article. When available, I used the online publication date to calculate the time between preprint post and journal article publication. If this date was not available, I used the print publication date.

I included 109 preprint–article RCTs in the analysis. The median delay between preprint and journal article was 121 (IQR, 73–187) days, the median sample size was 150 (IQR, 71–464) participants, 76% of RCTs had been prospectively registered, 60% received industry or mixed funding, 72% were multicentric trials. The overall risk of bias was rated as 'some concern' for 80% of RCTs. I found consistent reporting for all outcomes in 81 preprint–article pairs of RCTs. There were discrepancies in 18 RCTs; nine RCTs had a minor change in the effect estimate; six and 14 RCTs had at least one outcome missing and added in the journal article, respectively, compared to the preprint. There was a change in the direction of effect in one RCT. I did not find changes in statistical significance and conclusion in any RCT.

This study had some limitations. Similar to the first work, my research was conducted on COVID-19 RCTs, so the results may not be representative of preprints and peer-reviewed journal articles in other fields and study types. Also, I could not determine whether the preprints that remained unpublished were hindered by the peer review process due to unsupported conclusions. However, in post-hoc analysis, I found that trial characteristics were generally similar between published and unpublished preprints. Finally, the decisions of the living review, such as protocol revisions, potentially impacted the sample size and composition of my study.

Overall, effect estimates were generally consistent between preprints and subsequent journal articles of COVID-19 RCTs. The main results and interpretation did not change in any RCT.

This work and the previous make an argument for integrating preprint results into evidence synthesis, given the general consistency of results reporting and no evidence of a difference in summary effect between the two publication types.

Article

Mauricia Davidson, Theodoros Evrenoglou, Carolina Graña, Anna Chaimani, Isabelle Boutron

"Comparison of effect estimates between preprints and peer-reviewed journal articles of COVID-19 trials"

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The online supplement files of the article are presented in Annex 2 of this thesis.

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RESEARCH

Open Access

Comparison of effect estimates between preprints and peer-reviewed journal articles of COVID-19 trials

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Abstract

Background Preprints are increasingly used to disseminate research results, providing multiple sources of information for the same study. We assessed the consistency in effect estimates between preprint and subsequent journal article of COVID-19 randomized controlled trials.

Methods The study utilized data from the COVID-NMA living systematic review of pharmacological treatments for COVID-19 (covid-nma.com) up to July 20, 2022. We identified randomized controlled trials (RCTs) evaluating pharmacological treatments vs. standard of care/placebo for patients with COVID-19 that were originally posted as preprints and subsequently published as journal articles. Trials that did not report the same analysis in both documents were excluded. Data were extracted independently by pairs of researchers with consensus to resolve disagreements. Effect estimates extracted from the first preprint were compared to effect estimates from the journal article.

Results The search identified 135 RCTs originally posted as a preprint and subsequently published as a journal article. We excluded 26 RCTs that did not meet the eligibility criteria, of which 13 RCTs reported an interim analysis in the preprint and a final analysis in the journal article. Overall, 109 preprint–article RCTs were included in the analysis. The median (interquartile range) delay between preprint and journal article was 121 (73–187) days, the median sample size was 150 (71–464) participants, 76% of RCTs had been prospectively registered, 60% received industry or mixed funding, 72% were multicentric trials. The overall risk of bias was rated as 'some concern' for 80% of RCTs. We found that 81 preprint–article pairs of RCTs were consistent for all outcomes reported. There were nine RCTs with at least one outcome with a discrepancy in the number of participants with outcome events or the number of participants analyzed, which yielded a minor change in the estimate of the effect. Furthermore, six RCTs had at least one outcome missing in the journal article and 14 RCTs had at least one outcome added in the journal article compared to the preprint. There was a change in the direction of effect in one RCT. No changes in statistical significance or conclusions were found.

†Anna Chaimani and Isabelle Boutron contributed equally to this work.

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Conclusions Effect estimates were generally consistent between COVID-19 preprints and subsequent journal articles. The main results and interpretation did not change in any trial. Nevertheless, some outcomes were added and deleted in some journal articles.

Keywords Preprint, Peer-review, Discrepancy, COVID-19, Randomized controlled trial

Background

The scientific community has witnessed a significant shift in the way research findings are disseminated due to the COVID-19 pandemic and the subsequent rise of preprints [1, 2]. Preprints are early versions of scientific research papers that are made publicly available before they have undergone formal peer review and publication. By circumventing the lengthy peer review process, preprints allow for rapid communication on new evidence to inform public health responses. This is particularly crucial during pandemics. Notably, results of the world's largest COVID-19 platform trial, RECOVERY [3], were first reported as preprints, enabling swift, real-time evaluation of the interventions and potential harms. While discussing the benefits of preprints in patient care, lead RECOVERY author, Peter Horby, emphasized that peer review delays could have life-threatening consequences [4].

Without formal peer review and rigorous quality control, preprints can amplify misleading information stemming from biases, methodological limitations, incomplete analyses, and even fraud [5]. Preprint use has been scrutinized both from a public understanding perspective and in regards to scientific principles. Firstly, there is a concerning lack of understanding of preprint data among the general public. For example, widespread media attention given to two small, biased preprints that erroneously claimed smoking to be protective against COVID-19 impacted public health as it resulted in a surge in nicotine purchases and smoking uptake in certain countries [6].

Secondly, it is reasonable to expect some discrepancies between the content of various documents and sources for the same randomized controlled trial (RCT), particularly between the preprint and the subsequent journal article, as peer review often impacts the content of a manuscript before it is published. A meta-research study of 139 studies reported in preprint and subsequent journal article or in different versions of the preprint found a change in the abstract's conclusion in 24% of studies [7]. In contrast, a study of 78 preprint–article pairs of RCTs showed consistency in terms of the completeness of reporting [8]. Another analysis of 67 interventional and observational studies found that preprints and their subsequent journal articles were similar in terms of reporting and spin (i.e., distorted interpretation of results) [9]. Similarly, a study of 74 preprint–article pairs of RCTs showed few important differences in treatment effect estimates between the two documents [10].

To further explore the consistency between various documents reporting the results of trials, we assessed the consistency in effect estimates between preprints and subsequent journal articles of COVID-19 RCTs included in a large living systematic review of COVID-19 pharmacological treatments.

Methods

The protocol is available on Open Science Framework (https://osf.io/hfrp4/?view_only=b06282a8429e4ae1af458f4e372576f7). Here, we report the results of objective one - to assess the consistency in the estimates of treatment effects between preprints and the subsequently published articles. We expanded our sample size by including RCTs assessing all pharmacological treatments instead of limiting our analysis to specific treatment types as planned in the protocol. Additionally, we updated the final search to July 20, 2022.

Data source and search

Our study used the data and methods of the COVID-NMA living systematic review (covid-nma.com) [11] [see Methods S1 in the Additional file]. Briefly, COVID-NMA is a living evidence synthesis and living mapping of RCTs on interventions for the prevention and treatment of COVID-19. The search strategy was modified over time to involve searching only two bibliographic databases: the Epistemonikos L-OVE COVID-19 platform [12] and Cochrane COVID-19 Study Register [13]. The Retraction Watch database [14] was also searched to identify retracted trials and directly remove them from the COVID-NMA review (Additional file Table S1). Screening and data extraction were performed by pairs of researchers, independently and in duplicate, with disagreements resolved by consensus and a third researcher, when necessary.

Eligibility criteria

We selected eligible RCTs in the COVID-NMA living systematic review that evaluated pharmacological treatments for patients with COVID-19 and that were originally posted as preprints and subsequently published in a peer-reviewed journal. The last search date was July 20, 2022. We considered the following COVID-NMA-defined critical outcomes:

- Clinical improvement at day 28 (D28) defined as a hospital discharge or improvement on the scale used by trialists to evaluate clinical progression and recovery.
- WHO Clinical Progression Score of level 7 or above (i.e., mechanical ventilation +/− additional organ support or death) (D28).
- All-cause mortality (D28).
- Incidence of any adverse events.
- Incidence of serious adverse events.

We excluded RCTs evaluating preventive interventions (e.g., use of personal protective equipment, movement control strategies), vaccines, non-pharmacological treatments, and supportive treatments for patients admitted to the intensive care unit. We also excluded RCTs that did not report any critical outcome and that reported different analyses in both documents (e.g., interim analysis reported in the preprint and final analysis reported in the journal article).

Linking preprint and subsequent journal article

The linkage between the preprint and journal article was performed as part of the COVID-NMA living systematic review. The preprint–article linker was developed in collaboration with a research team from the French National Centre for Scientific Research. The tool automatically generated an alert when a preprint was updated or published as a journal article. Pairs of researchers used the tool to identify these subsequent reports and then extracted any additional and/or updated data independently, meeting for consensus to reconcile any disagreements. Consequently, an accurate record of the corresponding preprint and journal publication reports in the COVID-NMA database is available for download as a preprint-publication pair. To identify eligible RCTs, one researcher (MD) retrieved this record from the COVID-NMA database and selected the first preprint posted on a preprint server and the subsequent journal article. When available, we used the online publication date in order to calculate the delay between preprint post and journal article publication. Otherwise, we used the print publication date.

Data extraction

We retrieved data that were previously extracted in duplicate independently by pairs of researchers, with consensus to resolve disagreements for the COVID-NMA living systematic review: publication type (preprint, journal article), publication date (date that the report was published online, when available), trial registration (prospective, retrospective relative to the start date of the trial), funding type (industry, mixed, public, none, not reported/unclear), study centers (single, multicentric), setting (hospital, outpatient clinic), geographical RCT location according to the World Bank Country Income Classification [15], and intervention details.

For the critical outcome measures under consideration, the number of participants with outcome events and the number of participants analyzed were retrieved. Risk of bias was assessed according to the Cochrane Risk of Bias 2 tool [16] and each outcome result was rated as 'Low', or 'Some concerns', or 'High' risk of bias. Particularly, we considered the overall risk of bias assessments i.e., the highest risk of bias found in any domain for any critical outcome in the trial. The previously extracted data were split into two parts and two researchers (MD, CG) verified these data, meeting for consensus if a discrepancy was found.

Data synthesis

For the descriptive analysis, frequencies and percentages were calculated for categorical variables, while medians with interquartile ranges (IQRs) were calculated for continuous variables.

We systematically explored whether the number of participants with outcome events, number of participants analyzed, and treatment effect estimates were consistent between preprints and subsequent journal articles for all critical outcomes. The discrepancies between results reported in a preprint and subsequent journal article were classified as (1) change in the estimate of the effect of at least one outcome, (2) change in the direction of the effect, (3) change in statistical significance, and (4) change in the overall conclusion. We also investigated whether the outcomes were deleted or added in the journal articles compared to the preprints. We used R software, [17] with the *metafor* [18] and *forestplot* [19] packages, for all analyses.

Results

Of the 49,651 records screened, 1230 were assessed for eligibility and we identified 135 treatment RCTs that were originally posted as a preprint and subsequently published as a journal article. We excluded 26 RCTs because they did not conform to eligibility criteria; one preprint was removed from the preprint server, three RCTs were excluded because there was an error in data retrieval (i.e., they were incorrectly labelled in the COVID-NMA database as a preprint but the data were from trial registry results (n=2) and from the journal article (n=1)), three RCTs evaluated non-pharmacological treatments, six RCTs did not report any critical outcomes and 13 RCTs reported interim analysis in the preprint and final analysis in the journal article. Increased sample sizes and longer follow-up and enrolment periods were observed in the final analyses of the subsequent journal articles

compared to the interim analyses of the preprints. Overall, 109 RCTs were included in the analysis (Fig. 1).

Characteristics of preprints that were subsequently published in a journal article are presented in Table 1. The median delay between preprint and peer-reviewed journal article was 121 (IQR, 73–187) days. The median sample size was 150 (IQR, 71–464) participants, 76% of RCTs had been prospectively registered, 60% received industry or mixed funding, 72% were multicentric trials.

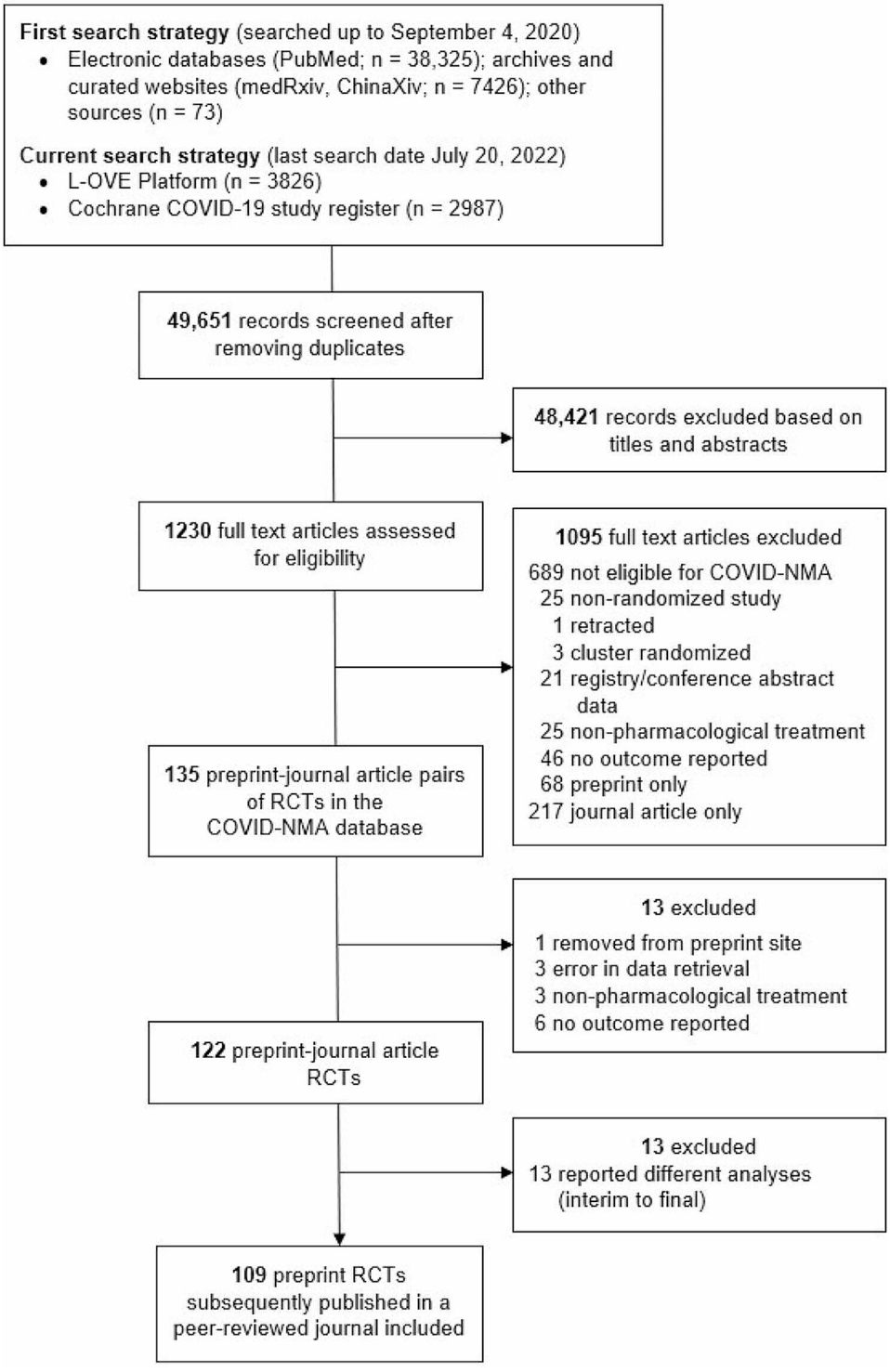

Fig. 1 Flowchart of included randomized controlled trials (last search date July 20, 2022)

Table 1 Characteristics of preprint–article RCTs

Characteristics		Preprint–Article RCTs n = 109 (%)	RCTs with consistent data n = 81 (%)	RCTs with added/deleted outcomes n = 20* (%)	RCTs with change in effect estimate n = 9* (%)
Sample size, median (IQR)		150 (71–464)	149 (66–420)	129 (85–663)	606 (240–1225)
Delay†, median (IQR)		121 (73–187)	128 (79–187)	91 (27–153)	127 (99–210)
Registration timing, n (%)	Prospective	83 (76)	62 (77)	14 (70)	8 (89)
	Retrospective	25 (23)	18 (22)	6 (30)	1 (11)
	Not reported/unclear	1 (1)	1 (1)	0	0
Funding type, n (%)	Industry/mixed	65 (60)	45 (56)	16 (80)	5 (56)
	Public	34 (31)	28 (35)	1 (5)	4 (44)
	Others	10 (9)	8 (10)	3 (15)	0
Study centers, n (%)	Single	30 (28)	28 (35)	2 (10)	0
	Multicenter	79 (72)	53 (65)	18 (90)	9 (100)
Overall risk of bias‡, n (%)	Low	13 (12)	7 (9)	6 (30)	1 (11)
	Some concerns	87 (80)	66 (81)	13 (65)	8 (89)
	High	9 (8)	8 (10)	1 (5)	0
Setting, n (%)	Hospital	93 (85)	67 (83)	18 (90)	8 (89)
	Outpatient clinic	16 (15)	14 (17)	2 (10)	1 (11)
Geographical location‡, n (%)	High-income countries	42 (39)	30 (37)	8 (40)	5 (56)
	Low-/middle-income countries	49 (45)	39 (48)	7 (35)	3 (33)
	Countries of different income levels	18 (17)	12 (15)	5 (25)	1 (11)
Preprint post§, n (%)	< 6 months	21 (19)	14 (17)	6 (30)	1 (11)
	6–12 months	45 (41)	32 (40)	10 (50)	3 (33)
	> 12 months	43 (39)	35 (43)	4 (20)	5 (56)

RCT, randomized controlled trial; mixed, industry and public funding; others, no funding/not reported/unclear

* One RCT had an outcome added in the journal article and outcomes with changes in the effect estimate

† Number of days between preprint post and journal article publication online

‡ Highest risk of bias assessed for any outcome in any domain

‡ World Bank Country Income Classifications [15]

§ Relative to March 2020 i.e., start of the pandemic

The overall risk of bias assessed was rated as 'some concern' for 80% of RCTs.

Of the 109 preprint–article pairs of RCTs, 81 were consistent for all outcomes. We found six RCTs with at least one outcome missing in the journal article, and 14 RCTs with at least one outcome added in the journal article compared to the preprint. There were nine RCTs that had at least one outcome with a change in the number of participants with outcome events or the number of participants analyzed, which yielded a minor change in the estimate of the effect (Fig. 2) [20–37]. There was one RCT with a change in the direction of the effect. No changes in the statistical significance or overall conclusions between preprint and journal article were observed for any RCT.

Characteristics of the preprints that were never published in a peer-reviewed journal are compared to those that were published (Additional file Table S2). Generally, we found that basic characteristics of RCTs initially posted as preprints were similar between those that were subsequently published and those that were not.

Discussion

In this study, we analyzed the consistency in treatment effect estimates between RCTs first available as a preprint and subsequently published in a peer-reviewed journal. We found only trivial discrepancies between COVID-19 preprints and subsequent journal articles in most pharmacological treatment RCTs. Nevertheless, some outcomes were added and deleted in the journal articles compared with the preprints and one trial showed a change in the direction of effect between preprint and subsequent journal article.

Our study findings demonstrate substantial agreement with the conclusions of other COVID-19 studies. In a retrospective review of 74 RCTs included in a living network meta-analysis [38, 39] up to August 2021, Zeraatkar et al. did not observe important discordance between the first preprint and subsequent journal article [10]. The cross-sectional study by Bero et al. found only marginal changes to outcomes reporting and spin between 67 preprint–article pairs of studies published between March and October 2020 [9]. In contrast, in a meta-research

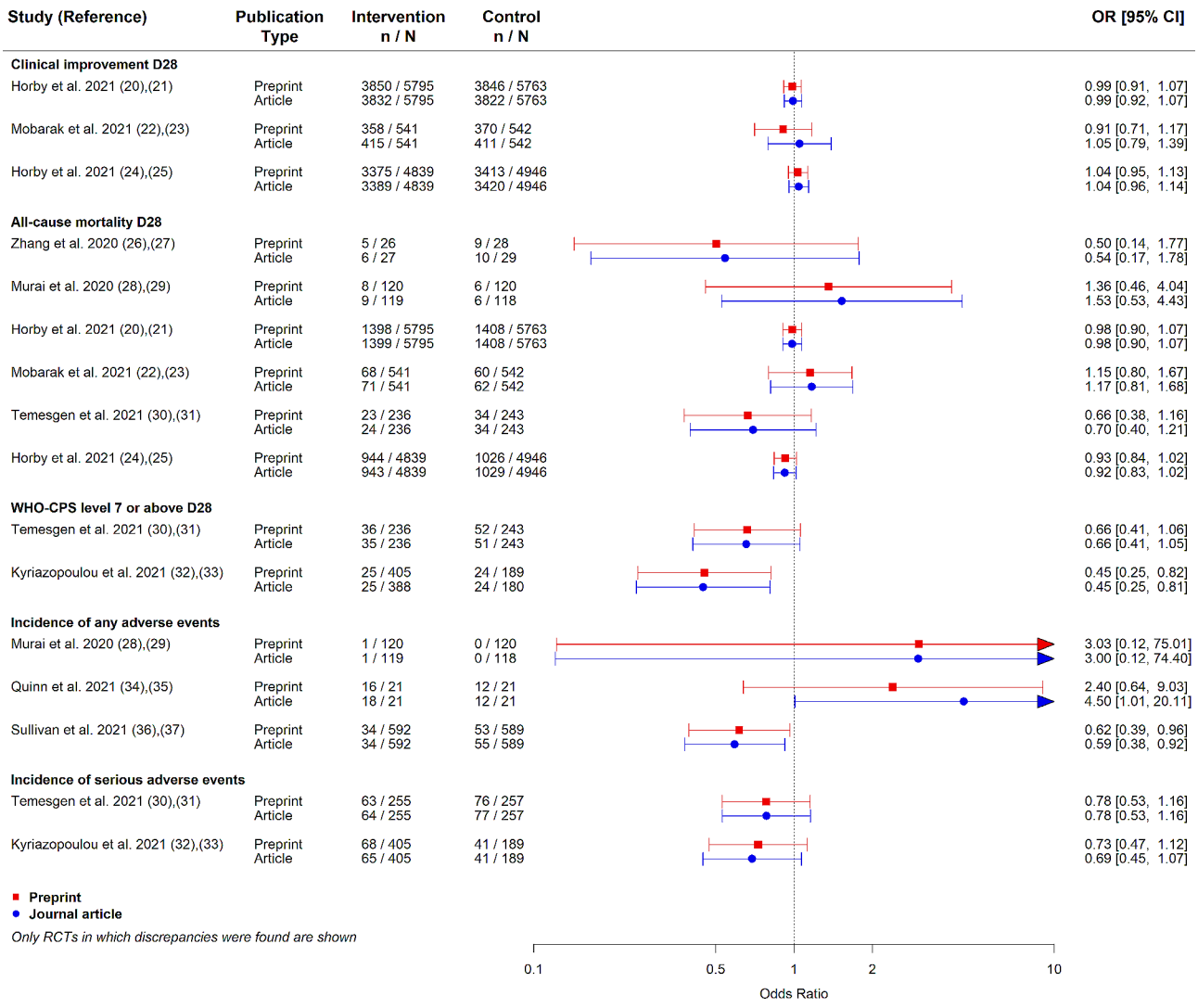

Fig. 2 Discrepancy in effect estimates between preprint and subsequent journal article of COVID-19 RCTs. RCT, randomized controlled trial; n, number of participants with outcome events; N, number of participants analyzed; CI, confidence interval; D28, day 28; article, peer-reviewed journal; WHO-CPS, World Health Organization Clinical Progression Score

study of preventive, therapeutic, or post-acute care interventions for COVID-19, Oikonomidi et al. found significant changes in results and abstract's conclusions in 55% of the sample of 66 preprint–article studies published up to August 2020 [7].

While over half (58%) of preprints are subsequently published in a peer-reviewed journal [40], the fact is that some will remain unpublished, due to journal rejection because of poor methodological and statistical quality or, in rare cases, lack of submission. Based on this, some suggest that preprints should be excluded from meta-analyses [41]. Thus, as part of objective two of our protocol, we conducted a meta-epidemiological study, selecting 37 meta-analyses at different timepoints that included both preprint and journal article RCTs [42].

Strengths and limitations

We assessed the consistency of results between preprint and journal article pairs of RCTs, as significant changes found in the subsequent journal article bring the reliability of preprint data into question. Furthermore, our data were retrieved from a large living systematic review (COVID-NMA). COVID-NMA employed a validated, comprehensive search strategy to identify all relevant evidence.

There are some limitations of our assessment. Firstly, this research was conducted on COVID-19 RCTs, so results may not be generalizable to other fields and study types. In non-COVID-19-related studies, Carneiro et al. [43] determined that preprints were lacking in reporting quality but, on average, the quality of reporting between preprints and subsequent journal articles was

comparable. Another study found small differences in journal article conclusions of 7.2% of non-COVID-19–related and 17.2% of COVID-19–related abstracts compared to the preprint [44]. Secondly, for those preprints that were never published in a journal, we could not evaluate whether peer review prevented journal publication due to unsupported conclusions. Nevertheless, we found that trial characteristics were generally similar between preprints that were subsequently published in peer-reviewed journals and those that remained unpublished. Finally, our study is limited to the decisions of the living review. For example, protocol revisions could affect the sample composition.

Conclusion

We identified changes in effect estimates in 8% of COVID-19 randomized controlled trials between preprint and subsequent journal article. Some outcomes were deleted or added in the journal articles; therefore, it is important to retrieve both documents and explore reasons for discrepancies. Certainly, a critical approach should be adopted when using results from preprints due to the lack of peer review.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12874-023-02136-8.

Supplementary Material 1: Definitions of trial characteristics; Methods S1; Table S1; Table S2; Figure S1

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Author contributions

MD, AC, and IB conceived and designed the study. MD, TE and AC conducted the statistical analyses. MD and CG were involved in the acquisition of the data. All authors were involved in the interpretation of the data. MD drafted the manuscript. All authors critically reviewed the manuscript. All authors read and approved the final manuscript. AC and IB supervised the work.

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Data availability

The data and code used during the current study are available at https://github.com/MDavids0n/Preprint_Journal.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Publisher's Note

Part 2: Analysis of post-publication peer review and systematic review assessments

In the Introduction, I presented the weaknesses of the 'gold standard' peer review process, mentioning that peer reviewers are not always able to identify flaws and biases in manuscripts. For this reason, I am especially motivated to find ways to supplement this traditional process. Systematic reviewers, particularly living systematic reviewers, and the general research community could aid in detecting important methodological and reporting issues which could then be fed back to trial authors to possibly rectify. However, presently, there is a disconnect between these groups and it is unclear how much of an impact these research entities could have on the manuscript quality. Therefore, I conducted a qualitative study to determine to what extent systematic reviewers and post-preprint and post-publication peer review identified methodological and reporting issues in COVID-19 RCTs that could be easily resolved by the authors.

Summary of findings

In this study, I considered RCTs in COVID-NMA that evaluated pharmacological treatments for patients with COVID-19 and retrieved the RoB and ORB assessments that were conducted by systematic reviewers. As part of the COVID-NMA process, justifications for each assessment were also published. I also retrieved these for my study. Knowledge of the RoB tool and ORB dictated that these assessments could pinpoint issues like incomplete reporting, selection of the reported results (either missing or added evidence), and lack of access to the pre-specified plan.

Additionally, I searched for commentary data on PubPeer, medRxiv, Research Square and SSRN up to 6 November 2023. I then employed content analysis to inductively develop themes and domains of methodological and reporting issues identified by commenters.

I identified 500 eligible RCT reports. Systematic reviewers identified methodological and reporting issues in 446 (89%) RCT reports. In 391 (78%) RCT reports, the issues could be easily resolved by the trial authors i.e., incomplete reporting (49%), selection of the reported results

(52%), and no access to the pre-specified plan (25%). Alternatively, 74 (15%) RCT reports had received at least one comment on PubPeer or preprint servers, totaling 345 comments. In 46 (9%) RCT reports, the issues identified by post-preprint and post-publication peer review comments could be easily resolved by the trial authors; the issues were related to incomplete reporting (5%), errors (4%), statistical analysis (2%), spin (2%), selection of the reported results (1%), and no access to the raw data/pre-specified plan (1%).

Some study limitations should be recognized. First, I must again acknowledge that these findings may not be generalizable to post-preprint and PPPR comments outside the context of the pandemic since I only included COVID-19 RCTs in the sample. Second, this study was also constrained by decisions of COVID-NMA in that RoB and ORB assessments were only available for review-defined outcomes. Nevertheless, these outcomes were chosen for their clinical relevance and I included both safety and efficacy endpoints. Finally, I could not evaluate the commenters' expertise in research methodology or explore any potential conflicts of interest because most post-preprint and PPPR comments were anonymous. However, anonymity often encourages greater participation in PPPR, plus the objective of this study was not to confirm the validity of the issues raised in these comments.

In conclusion, my study showed that systematic reviewers are well placed to improve research quality as they identified issues in most RCTs that could be easily resolved by the trial authors. I argue that the lack of an established author feedback mechanism represents a wasted opportunity for facilitating such improvements. On the other hand, despite the existing feedback loop to authors present in PPPR, it demonstrated limited effectiveness in identifying methodological and reporting issues. But, I suggest a framework for incorporating post-preprint peer review into the formal workflow.

Article

Mauricia Davidson, Christoffer Bruun Korfitsen, Carolina Riveros, Anna Chaimani, Isabelle Boutron

"Post-publication peer review and the identification of methodological and reporting issues of COVID-19 trials"

BMJ Evidence-Based Medicine (under review)

The online supplement files of the article are presented in Annex 3 of this thesis.

Post-publication peer review and the identification of methodological and reporting issues in COVID-19 trials: a qualitative study

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Abstract

Objectives: We aimed to determine to what extent systematic reviewers and post-preprint and post-publication peer review identified methodological and reporting issues in COVID-19 trials that could be easily resolved by the authors.

Design: Qualitative study.

Data sources: COVID-NMA living systematic review (covid-nma.com), PubPeer, medRxiv, Research Square, SSRN.

Methods: We considered randomized controlled trials (RCTs) in COVID-NMA that evaluated pharmacological treatments for COVID-19 and retrieved systematic reviewers' assessments of the risk of bias and outcome reporting bias. We also searched for commentary data on PubPeer and preprint servers up to 6 November 2023. We employed qualitative content analysis to develop themes and domains of methodological and reporting issues identified by commenters.

Results: We identified 500 eligible RCT reports. Systematic reviewers identified methodological and reporting issues in 446 (89%) RCT reports. In 391 (78%) RCT reports, the issues could be easily resolved by the trial authors; issues included incomplete reporting (49%), selection of the reported results (52%), and no access to the pre-specified plan (25%). Alternatively, 74 (15%) RCT reports had received at least one comment on PubPeer or preprint servers, totaling 345 comments. In 46 (9%) RCT reports, the issues identified by post-preprint and post-publication peer review comments could be easily resolved by the trial authors; the issues were related to incomplete reporting (5%), errors (4%), statistical analysis (2%), spin (2%), selection of the reported results (1%), and no access to the raw data/pre-specified plan (1%).

Conclusions: Without changing their process, systematic reviewers identified issues in most RCTs that could be easily resolved by the trial authors; however, the lack of an established author feedback mechanism represents a wasted opportunity for facilitating improvement and enhancing the overall manuscript quality. On the other hand, despite the existing feedback loop to authors present in post-publication peer review, it demonstrated limited effectiveness in identifying methodological and reporting issues.

Key messages

What is already known on this topic

- Despite its central role in ensuring rigorous research dissemination, a typical peer review process has limitations; however systematic reviewer assessments and post-publication peer review can identify key issues in trials, even facilitating potential editorial action.

What this study adds

- Through risk of bias and outcome reporting bias assessments, systematic reviewers identified methodological and reporting issues in the majority of trials that could be easily resolved by trial authors.
- Post-publication peer review is underutilized and poorly identified key issues in research quality.

How this study might affect research, practice or policy

- Direct engagement between systematic reviewers and trial authors is a missed opportunity that should be addressed to supplement formal peer review.
- Encouraging a culture within the research community that values post-publication peer review is essential for maximizing its effectiveness.

Background

Peer review is regarded as the cornerstone of rigorous research. The usual peer-review process begins when a manuscript is submitted to an academic journal for publication.(1) A journal editor then assigns independent researchers to assess the quality of the manuscript. In turn, the independent researchers produce a report that aids the editor in deciding whether to publish or reject the submission, or request further revisions prior to acceptance or rejection.(2,3) While individual journal policies vary, acknowledging that the peer-review process has a few limitations is important. The process is generally slow and is often compounded by difficulties in identifying reviewers, who may not thoroughly address issues, such as incomplete or biased reporting.(4–7)

Recognizing the need for new methodologies in research evaluation in contrast to the formal journal-managed pre-publication peer review process, alternative approaches have been implemented or proposed.(8–11) Systematic reviews, particularly living systematic reviews, could provide a valuable avenue for detecting important methodological and reporting issues, such as incomplete or selective reporting of results; however, the time that lapsed between the trial publication and the review is a critical factor that warrants consideration.(12) Establishing a feedback loop between authors and systematic reviewers could facilitate timely alerts to authors, provide an opportunity to correct these issues, and ultimately, enhance the quality of research dissemination.

Furthermore, in the dynamic landscape of scientific communication, post-publication peer review (PPPR) platforms, such as PubPeer, have been developed. PPPR allows a wider audience to provide feedback on published work with ongoing assessments and improvements to study findings.(13,14) Researchers utilizing these platforms can raise community awareness of flaws in published research, prompt critical discussions, and, in some cases, cause major editorial actions, like retractions and expressions of concern.(15,16) The COVID-19 pandemic reshaped scientific communication and triggered an exponential increase in the number of published articles, driven by the urgency to communicate research findings. This surge in articles shortened the peer review process and resulted in the widespread use of preprints for rapid dissemination. PubPeer and similar platforms experienced increased activity during this period, and major preprint servers, such as

medRxiv, facilitated open commentary on study methods and results, which made it possible to improve the manuscripts prior to their formal peer review and publication in an academic journal. Large-scale living systematic reviews, such as the COVID-NMA living systematic review, were implemented and enabled systematic reviewers to highlight and identify specific issues.

Therefore, using a sample of trials included in the COVID-NMA living systematic review, we aimed to determine 1) to what extent systematic reviewers identified methodological and reporting issues in COVID-19 trials that could be easily resolved by authors, and 2) to what extent post-preprint and post-publication peer-review identified methodological and reporting issues in COVID-19 trials and to describe whether these issues could be easily resolved by authors.

Methods

We conducted a qualitative study of COVID-19 preprints and peer-reviewed journal articles in the COVID-NMA living systematic review.

Data source and search

We used data from the COVID-NMA living systematic review (www.covid-nma.com), hereafter referred to as COVID-NMA.(17) COVID-NMA was a living systematic review of interventions for the prevention and treatment of COVID-19. It was built from a comprehensive search of two validated secondary sources to identify eligible randomized controlled trials (RCTs): the Epistemonikos L-OVE COVID-19 platform (18) and the Cochrane COVID-19 Study Register.(19) The Retraction Watch database (20) was also searched to identify and remove retracted trials from the review. Screening and data extraction were performed by pairs of researchers, independently and in duplicate, with disagreements resolved through consensus and a third reviewer, when necessary. Data were extracted from preprints, all preprint updates, peer-reviewed journal articles, and all available documentation (e.g., supplementary material).(21) See Methods S1 in Annex 3 for more details on the study's methodology, search strategy, and the scope of the COVID-NMA. As of August 2023, the COVID-NMA living mapping and synthesis has concluded.

Study selection

We included all RCTs that evaluated pharmacological treatments for patients with COVID-19 and were available as preprints or journal articles. The last search date for any treatment RCT was 14 December 2022. Dates for individual treatment comparisons are detailed in Annex 3.

We excluded RCTs that evaluated non-pharmacological treatments, preventive interventions (e.g., personal protective equipment and movement control strategies), vaccines, and supportive treatments for patients admitted to intensive care units. We also excluded cluster RCTs and RCT results only reported in their trial registry or in a conference abstract.

Identification of issues by systematic reviewers

As part of the COVID-NMA protocol, two systematic reviewers, independently and with consensus, assessed each RCT included in the review for risk of bias (RoB) using the Cochrane RoB 2 tool (22) and outcome reporting bias (ORB) (23,24) in 14 pre-specified outcomes (such as clinical improvement, incidence of viral negative conversion, World Health Organization (WHO) clinical progression score of level 7 or above, all-cause mortality, hospitalization or death (in an outpatient setting), incidence of any adverse events, and incidence of serious adverse events). Systematic reviewers provided detailed justification for each RoB assessment. If an RCT did not report such outcomes, RoB could not be assessed. Details of the review outcomes, as well as RoB and ORB assessment rules are provided in Additional File 1. One researcher (MD) retrieved all the RoB justifications reported by COVID-NMA systematic reviewers for all domains and rated as 'some concerns' or 'high' RoB for the pre-specified outcomes; they also identified methodological and reporting issues that could be easily resolved by the trial authors. Additionally, MD retrieved ORB assessments for all the pre-specified outcomes.

The issues that were identified through the living systematic review and that could be easily resolved by the trial authors included:

- Incomplete reporting – considered when there was no or little information on the allocation sequence generation; allocation concealment; blinding status of participants, care providers, and outcome assessors; participant crossover and/or administration of co-interventions of interest (antivirals, corticosteroids, biologics) per arm during the trial (assessed only in unblinded studies); number of participants randomized per arm;

number of participants analyzed per arm for the review pre-specified outcomes; and the reasons for, or proportions of, missing data per arm. Information on this issue of incomplete reporting was retrieved from RoB assessments.

- Selection of the reported results – considered in cases of missing or added evidence.
    - Missing evidence i.e., the outcomes were planned in the clinical trial protocol, statistical analysis plan, or trial registry; however, the results were not available for inclusion in the synthesis, (probably) because the *P*-value, magnitude, or direction of the results were considered unfavorable by the study investigators. Information on this issue was retrieved from the ORB assessments.
    - Added evidence i.e., the study results were available for inclusion in the synthesis but not planned to be analyzed in the clinical trial protocol, statistical analysis plan, or trial registry. Information on this issue was retrieved from RoB and ORB assessments.
- No access to the pre-specified plan – considered when there was no pre-specified clinical trial protocol, statistical analysis plan, or trial registry available for assessment, regardless of whether study results were available for inclusion in the synthesis. Information on this issue was retrieved from RoB and ORB assessments.

MD also retrieved the general trial data reported by COVID-NMA systematic reviewers: first author, publication source (preprint or journal name), publication date, and full-text links.

Identification of issues by post-preprint and post-publication peer review

One researcher (MD) systematically searched PubPeer using the digital object identifiers (DOIs) of eligible RCTs to aggregate all available comments. Commentary data published from 2020 onwards were retrieved from medRxiv using the Disqus application programming interface (API) (disqus.com/api/docs/) and R code (25,26); these were then cross-referenced with the DOIs of the eligible RCTs. A manual commentary data search was conducted on the Research Square and Social Science Research Network (SSRN) preprint platforms using trial DOIs. Reports that received at least one comment were included. For preprints, only the first version was considered. The last search date for the commentary data was 6 November 2023. We collected post-preprint and PPPR commentary data using qualitative content analysis to inductively develop themes and domains. Two researchers (MD, CBK) used 20 PubPeer

comments to identify themes/domains of the issues addressed by the commenters. The two researchers (MD, CBK) then met to reach consensus on the domains to be included in a data extraction form, along with a senior researcher (IB). The researchers used this initial set of domains to extract data, independently and in duplicate, in groups of 20 comments with consensus in the case of disagreements. Two researchers (MD, CR) extracted the commentary data from the preprint servers in the same manner. Finally, one researcher (MD) identified subdomains for the 'study design' domain. During the data extraction process, newly identified domains were documented and discussed with IB for continuous fine-tuning. All researchers had a minimum of 3 years of training in clinical epidemiology, particularly trial methodology. Of note, we did not independently confirm the validity of the issues raised in the comments. Information was collected on all the comments, such as the comment source (PubPeer, preprint server [medRxiv, Research Square, SSRN]) and the publication date of the comment. Information on whether any changes had been made to the original report (i.e. erratum or retraction) was also retrieved. When available, data on the commenters' name, affiliation, specific requests (i.e. erratum or retraction), actions (i.e. conducted a specific check or reanalysis, commented the erratum/retraction notice, or published a commentary), and whether the trial author addressed the comment, were collected. Finally, whether the issues identified could be easily resolved by the trial authors were assessed.

Data synthesis

Frequencies and percentages were calculated for the categorical variables, while medians with interquartile ranges (IQRs) were calculated for the continuous variables. The extracted qualitative data were coded using thematic analysis and grouped to develop domains. We used R software (27) with the *tidyverse* (28) package for all analyses.

Results

Characteristics of the eligible RCTs

Of the 575 pharmacological treatment RCTs identified in the database search, 500 met the eligibility criteria (Figure 5). Overall, the median sample size of the RCTs was 120 (IQR, 62–353) participants; 65% of were prospectively registered, and 47% received industry or mixed funding (Table 2).

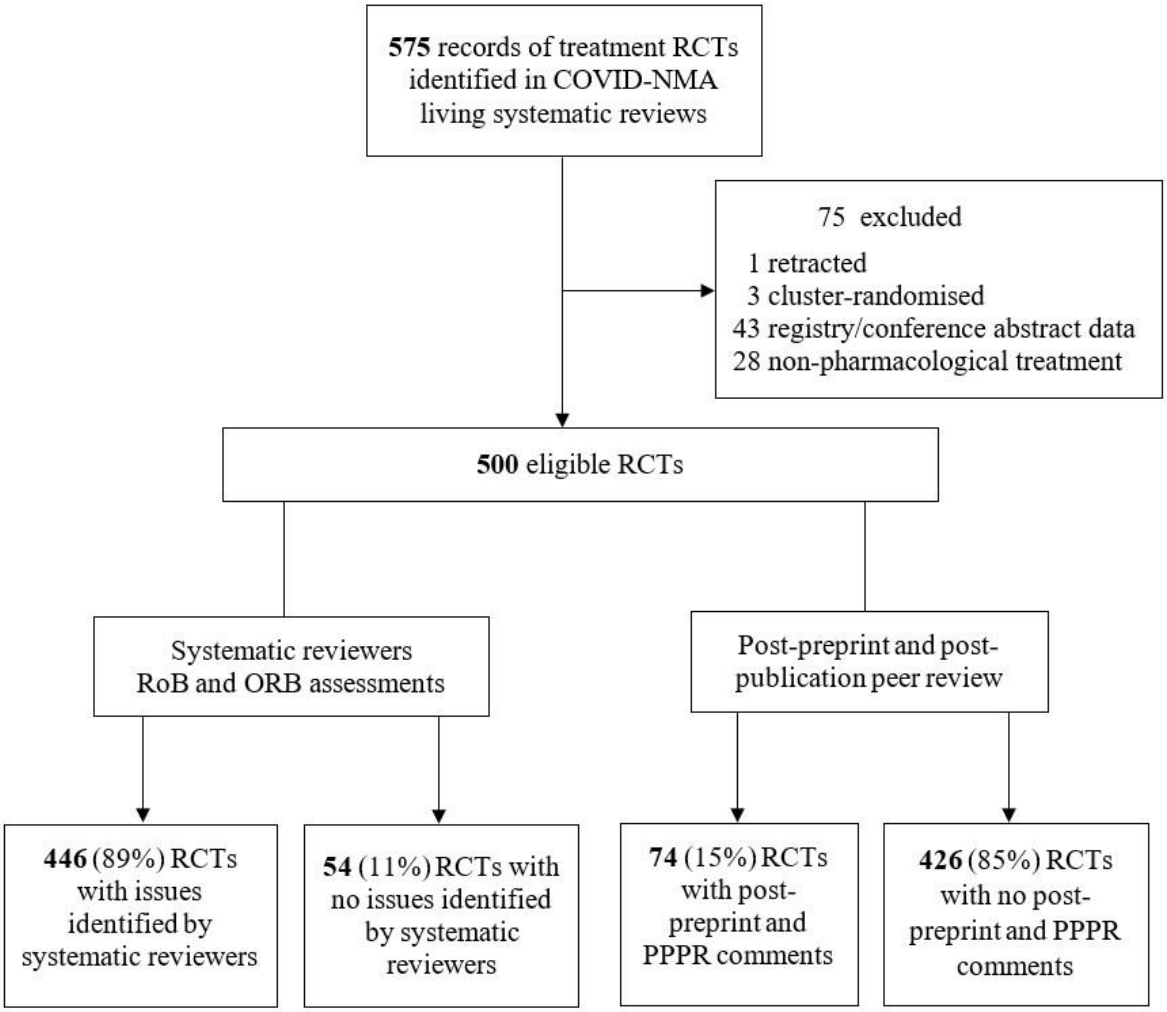

Figure 5: Flowchart of included RCTs for systematic reviewer and PPPR assessment

RCTs: randomized controlled trials; RoB: risk of bias; ORB: outcome reporting bias; PPPR: post-publication peer review

Table 2: Characteristics of eligible RCTs

Characteristics		**Total RCTs** n = 500 (%)
Sample size, median (IQR)		120 (62–353)
Publication type	Preprint	69 (14)
	Preprint and subsequent journal article	150 (30)
	Journal article	281 (56)
Registration timing	Prospective	326 (65)
	Retrospective	142 (28)
	Not reported/unclear	32 (6)
Funding type	Industry/mixed	235 (47)
	Other	265 (53)
Preprint post/Article publication[†]	< 6 months	70 (14)
	6–12 months	101 (20)
	> 12 months	329 (66)
Major editorial action	Retraction	1 (<1)
	Erratum	7 (1)

RCT: randomized controlled trial; IQR: interquartile range; Mixed: industry and public funding; Other: public/no funding/not reported/unclear. [†]Relative to March 2020 (i.e., start of the pandemic). Percentages may not add up due to rounding or shared characteristics.

Systematic reviewer assessments

Of the 500 RCTs, systematic reviewers identified methodological and reporting issues in 446 (89%) RCT reports; in 391 (78%) RCT reports, issues could be easily resolved by the trial authors (Figure 6). In 247 (49%) RCT reports, these issues were attributed to incomplete reporting, that is, they included no or not enough information on allocation sequence generation (2%), allocation concealment (25%), blinding details (6%), participant cross-over and/or balance in the administration of co-interventions of interest per arm (30%), number of trial participants randomized or analyzed per arm (1%), and the reasons for and/or proportions of missing data per arm, if any (8%). Systematic reviewers also identified issues in the selection of reported results in 260 (52%) RCT reports due to missing evidence (9%) or added evidence (48%). In 97 (25%) RCT reports, systematic reviewers identified that there was no access to the pre-specified plan (i.e. protocol, statistical analysis plan, and/or registry).

Notably, systematic reviewers rated 27 (5%) RCTs as 'low' RoB; therefore, we considered that no issues were identified in those RCTs. RoB assessments were not conducted for 27 (5%) RCTs due to lack of review pre-specified outcomes reported in these RCTs.

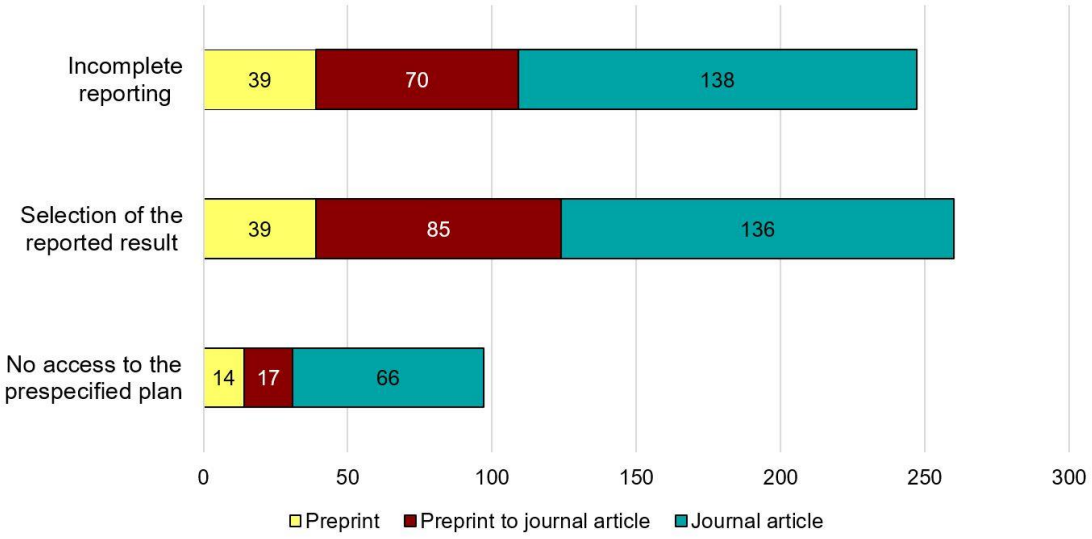

Figure 6: RCTs with resolvable issues identified by systematic reviewers (78%)

RCTs: randomized controlled trials

Post-preprint and PPPR

Among the 500 RCTs, 74 (15%) received at least one comment on either preprint servers or PubPeer for 345 retrieved comments in total (Table 3). Three RCTs had both post-preprint and PPPR comments, that is, comments on the preprint and the subsequent published journal article. The median number of comments per RCT report was 1.5 (IQR, 1–3; max, 26), the median word count was 64 (IQR, 28–136; max, 3569), and the median delay between preprint post or journal article publication and comment post was 11 (IQR, 2–65) days: 10 (IQR, 2–65) days for preprints and 27 (IQR, 0–66) days for journal articles. Of the 74 RCT reports with at least one comment, 28 (38%) had commentary data posted to PubPeer, and 54 (73%) had commentary data posted on preprint servers, mainly medRxiv (40 RCTs, 54%). Twenty-five comments from 20 (27%) RCT reports were structured as a traditional peer review report. Trial authors responded directly to 12 original comments on seven (9%) RCT reports, and most satisfied the issues raised in the original comment.

Table 3: Characteristics of post-preprint and PPPR comments

Characteristics		**N = 74[§] (%)**
Number of comments (comments)		345
Number of comments per RCT[*] (comments)		1.5 (1–3)
Word count[*] (words)		64 (28–136)
Delay[*†] (days)		11 (2–65)
Publication type[⁑] (n)	Preprint	50 (68)
	Journal article	24 (32)
Comment source (n)	PubPeer	28[‡] (38)
	medRxiv	40[‡] (54)
	Research Square	11 (15)
	SSRN	3[‡] (4)
Methodological or reporting issues identified (n)	Study design	27 (36)
	Incomplete reporting	26 (35)
	Error	21 (28)
	Sample size	14 (19)
	Statistical analysis	12 (16)
	Result applicability	11 (15)
	Spin	11 (15)
	Selection of the reported result	5 (7)
	No access to raw data/pre-specified plan	5 (7)
	Ethics	5 (7)
	Fraud	3 (4)
	Conflict of interest	3 (4)
	Other	25 (34)
Commenter actions (n)	Conducted a specific check	19 (26)
	Conducted a reanalysis	4 (5)
	Commented the erratum/retraction note	3 (4)
	Published a commentary	1 (1)
Commenter requests (n)	Response from author	15 (20)
	Erratum	4 (5)
	Retraction	0
Response received (n)	From author	7 (9)
	• Satisfied needs of the original comment	5 (7)

N: number of RCTs; PPPR: post-publication peer review; RCT: randomized controlled trial; SSRN: Social Science Research Network. [§]3 RCTs had both post-preprint and PPPR comments. [*]Median (interquartile range). [†]Delay between preprint post or journal article publication and comment post. [⁑]At time of comment retrieval. [‡]8 RCTs had comments on 2 platforms.

Feasibility of issue resolution

We coded the following methodological and reporting issues identified by the commenters: incomplete reporting, selection of the reported result, result applicability, statistical analysis, error, sample size, spin, study design, conflicts of interest, ethics, fraud, and no access to the raw data/pre-specified plan. Next, we determined whether these issues could be easily resolved by trial authors using the classification detailed in Box 1.

Of the 500 RCTs, 46 (9%) with post-preprint and PPPR comments identified methodological and reporting issues that could be easily resolved by the trial authors (Figure 7). These issues involved incomplete reporting (26 RCTs, 58 comments), errors (21 RCTs, 31 comments), statistical analysis (12 RCTs, 24 comments), spin (11 RCTs, 13 comments), selection of the reported results (5 RCTs, 8 comments), and no access to the raw data/pre-specified plan (5 RCTs, 5 comments). Seven (1%) RCT reports had an erratum to the final publication. At least one of the reasons provided by the editors for the errata of 3 RCT reports was addressed in post-preprint and PPPR comments. Further, one RCT report was retracted.

Issues that could be easily resolved by authors	Resolution	Issues that could not be easily resolved by the authors	Resolution
• Incomplete reporting • Selection of the reported results • No access to the raw data/pre-specified plan • Statistical analysis • Error • Spin	- Clearer or further explanations of the study's methods or better reporting of the study's findings - Reporting all outcomes pre-specified in the clinical trial protocol, statistical analysis plan, and/or trial register - Providing access to the raw data, protocol, and/or statistical analysis plan - Rerunning the appropriate analyses - Correcting typographical errors or miscalculations - Ensuring consistent reporting between the abstract and/or conclusions and the study's results	• Study design • Sample size • Results applicability • Conflict of interest • Ethics • Fraud	Not feasible during the peer review stage but should be presented as a limitation in the discussion section of the manuscript, with a sufficient explanation.

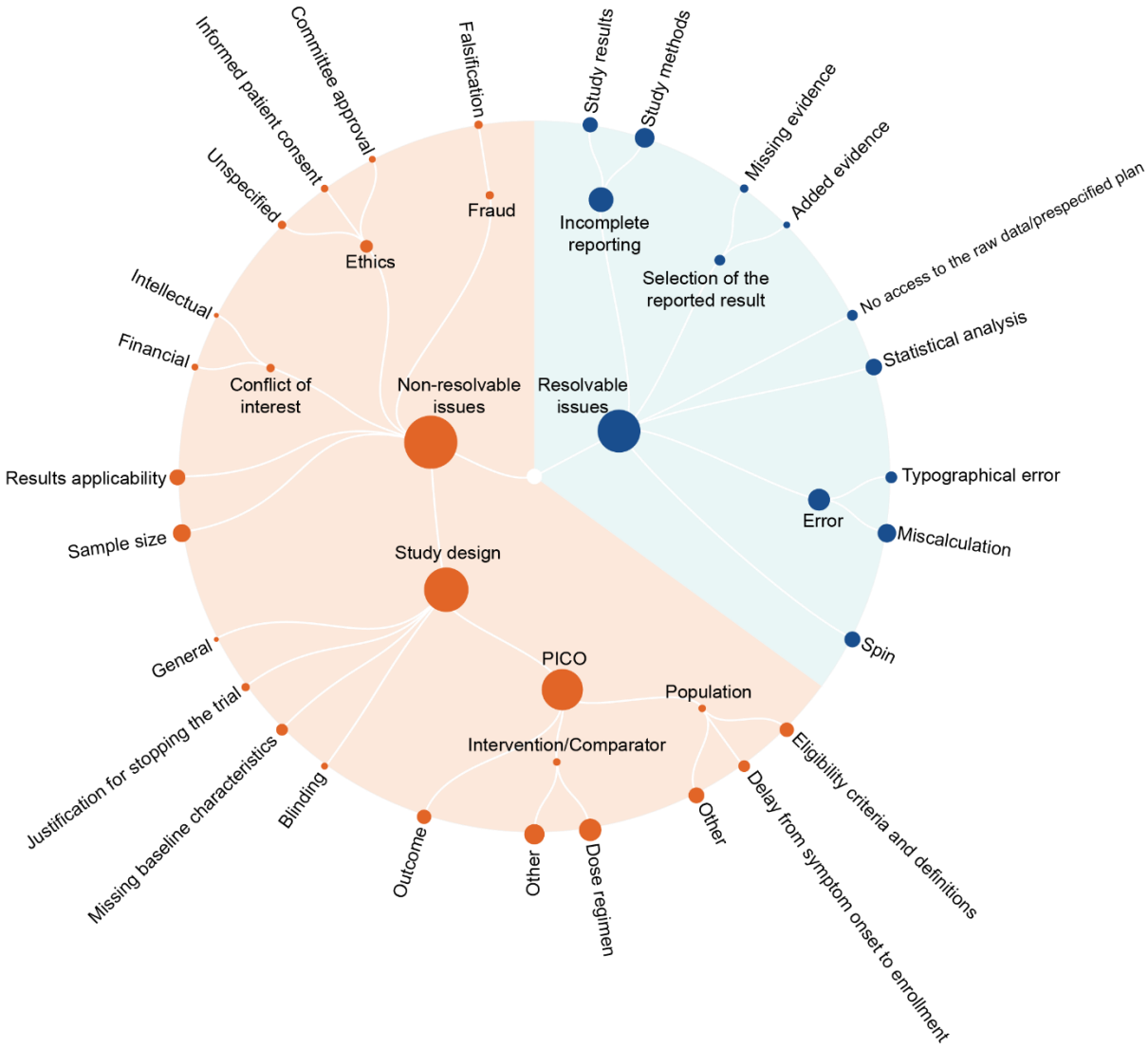

Figure 7: RCTs with issues identified by post-preprint and post-publication peer review

RCTs: randomized controlled trials, PICO: Population, Intervention, Control, Outcome

Discussion

Our study describes the methodological and reporting issues in COVID-19 trials identified by systematic reviewers and in post-preprint and PPPR. We analyzed 500 RCTs and found that the issues identified in systematic reviewer assessments in 391 (78%) RCTs could be easily resolved by the trial authors. Alternatively, post-preprint and PPPR comments identified issues in 46 (9%) RCTs that could be easily resolved by the trial authors.

Earlier studies have analyzed post-preprint and PPPR. Carneiro et al. studied 1,921 comments on 1,037 preprints and observed that critical comments addressed interpretation, methodological design, analysis, reporting, data sharing, and ethics.(25) They concluded that comments posted on preprint servers evaluate content comparable to that examined in formal peer review. Ortega et al. analyzed a sample of 39,985 PubPeer comments in 24,779 publications in 2019 and 2020 and found that 72% reported an element of fraud, with these comments sparking the most discussion and having a longer delay in posting.(29) They also found issues related to a lack of information (2%), honest errors (2%), and methodological flaws (8%). Additionally, in a cross-sectional study of 1,983 preprints that received single comments on the bioRxiv platform before September 2019, Malički et al. noted that over two-thirds of the comments did not originate from the preprint authors, with some comments being categorized as 'issue detected' (10%) and 'asking for raw data or code' (3%).(30) Notably, they found that 11% of author comments explicitly encouraged others to provide feedback, with one comment expressing a preference for revising the preprint rather than making changes to the journal article.(30) To our knowledge, no other study has identified methodological and reporting issues that could be easily resolved by trial authors nor related these issues to those identified in systematic reviewer assessments.

Implications for research

Our findings have several important implications. Incorporating feedback from alternative and informal peer review sources, when duly acknowledged by the authors, can serve as a valuable supplement to formal peer review processes and enhance a manuscript's overall quality. First, by following the usual iterative process of living systematic reviews, which involves continuous evidence synthesis with a detailed assessment of RoB and ORB for each new RCT, systematic reviewers can identify key issues that could be communicated back to the authors to be resolved. In our sample, these issues were identified in 78% of the RCTs. Therefore, the absence of a direct link between reviewers and authors is a missed opportunity, because systematic reviewers should play a role in peer review.

Second, proponents of PPPR stress that it plays a role in identifying methodological and reporting issues and in improving scholarly publishing. However, given that our study showed that post-preprint and PPPR comments identified issues in only 9% of RCTs, further development of these platforms is warranted to maximize their effectiveness. Incentivizing

and fostering a culture within the research community that values PPPR is essential. For example, editors and reviewers could consult post-preprint and PPPR comments, or journals could consider employing a grace period after publication wherein important comments prompt additional revisions by the authors. Furthermore, PPPR, which actively identify irregularities in published data or expose potential research fraud, are often seen as lacking accountability and are labelled as engaging in vigilantism when performed anonymously without formal discourse.(31) A centralized mechanism for coordination and oversight is, therefore, necessary to avoid discriminative and unethical behavior.

Strengths and limitations

RoB and ORB assessment data were retrieved from a large living systematic review (COVID-NMA), which implemented a robust assessment strategy, whereby assessments were performed independently and in duplicate by pairs of researchers, and disagreements were resolved by consensus. The researchers participated in a comprehensive training program with a team of experts, and quality control of the data was performed regularly by an external group. Furthermore, both post-preprint and PubPeer comments were considered for a diverse exploration of the landscape, and rigorous methodological coding procedures were incorporated to enrich the data via thematic analysis.

However, some limitations of our study must be acknowledged. First, we focused solely on COVID-19 trials, so our results may not be generalizable to post-preprint and PPPR comments outside the context of the pandemic. One study found that COVID-19 preprints had higher levels of engagement and received more comments than non-COVID-19 preprints.(26) Second, our study was constrained by decisions related to living reviews; systematic reviewer assessments were only available for review-defined outcomes. However, these outcomes were chosen because of their clinical relevance and included both safety and efficacy endpoints. Finally, most post-preprint and PPPR comments were anonymous; therefore, we could not assess the commenters' expertise in research methodology or investigate their potential conflicts of interest. However, our aim was not to exhaustively verify the validity of the issues highlighted in the comments. Furthermore, anonymity has been linked to increased participation in PPPR, with Lapinski finding that PubPeer, a platform that allows anonymous contributions, received over 37,000 comments on 3,300 publications from 2012 to 2015.(32)

This exceeded PubMed Commons' 4,000 mandatory onymous contributions on the same publications during the same period.

Conclusions

The majority of COVID-19 RCTs had easily resolvable issues identified through RoB and ORB assessments. Systematic reviewers are well placed to improve the quality of manuscripts; however, it is a wasted opportunity, considering that a feedback loop with the trial authors has not been established and acted upon. Alternatively, the impact of post-preprint and PPPR in identifying methodological and reporting issues remains limited. Expanding its reach and leveraging the existing feedback loop to authors is imperative to optimize its effectiveness.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Data availability statement: The datasets generated and/or analyzed during the current study will be made available on https://zenodo.org upon publication of the report.

Competing interests: None declared.

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Author contributions: MD, CBK, AC, and IB conceived and designed the study. MD, CBK, and CR were involved in the acquisition of the data. MD conducted the analyses. All the authors were involved in data interpretation. MD drafted the manuscript. All the authors critically reviewed the manuscript. All the authors read and approved the final version of the manuscript.

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List of abbreviations

API - Application programming interface

DOIs - Digital object identifiers

IQRs - Interquartile ranges

ORB - Outcome reporting bias

PPPR - Post-publication peer review

RCTs - Randomized controlled trials

RoB - Risk of bias

SSRN - Social Science Research Network

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Part 3: Consistency of reporting in clinical trial registries and published reports

In Part 1, I presented my investigations into preprint data and their reliability and integration into evidence synthesis. Clinical trial registries are another data source that I am keen to explore, given that research has shown that registry results, especially safety data, the reporting may be more complete than in journal articles.(20,22) The issues of poor reporting of methods and outcomes in trials has been a problem for decades. For this reason, the 2007 US Food and Drug Administration Amendments Act (FDAAA) 801 required applicable clinical trials to post results on ClinicalTrials.gov within a year of completion. Europe followed suit, with similar mandates in 2014 for the European Clinical Trial Register (EU-CTR). As such, exploring whether these regulations are complied with and whether these outcomes are consistently reported in both registry and the published journal article, or final preprint version if there is no journal article available, can aid in understanding how best to use clinical trial registry results in the greater evidence ecosystem.

Summary of preliminary findings

I included only those COVID-NMA pharmacological treatment RCTs that were registered in either ClinicalTrials.gov or EU-CTR and that reported results up to April 24, 2024 in both the registry and a journal article (or preprint). I also considered the COVID-NMA-defined critical outcomes and the primary outcome of the respective RCTs and extracted these data from the registry, comparing them to the data in final published or preprint report. Data were extracted independently by pairs of researchers with consensus to resolve disagreements.

My analysis included 117 RCTs with results posted on ClinicalTrials.gov or EU-CTR and in an online publication (journal article or preprint). The median delay between primary completion date of the trial and the date of online availability of the final report (journal article or preprint), and the date results were posted to ClinicalTrials.gov or EU-CTR was 151 (IQR, 108–175) days and 295 (IQR, 173–254) days, respectively. The median sample size was 250 (IQR, 82–496) participants, 89% of RCTs were only registered on ClinicalTrials.gov, 98% of results sourced from this registry, 84% of RCTs had been prospectively registered, and 71% received

industry or mixed funding. The overall risk of bias assessed was rated as 'some concern' for 74% of RCTs. Consistency in reporting of all outcomes was found in only 12% of registry-report pairs. At least one outcome was missing in the registry of 59% of RCTs, and 47% of RCTs had at least one outcome added to the registry compared to the journal article or preprint report. There were 37% RCTs that had at least one outcome with a change in the number of participants with outcome events. The primary outcome data was consistent between registry and final report in 68% of RCTs. Safety outcomes, though more frequently reported in the registry versus efficacy outcomes (82% vs. 63%)) were less consistently reported between registry-report pairs of RCTs (27% vs. 49%).

I acknowledge some limitations to this study. I only considered ClinicalTrials.gov and EU-CTR but these are the largest clinical trial registries with regulations for posting results.(87) Secondly, as is the case for all studies in this thesis, I focused on COVID-19 RCTs so my findings are limited to this COVID-19 context and study type. Furthermore, the analysis is limited to COVID-NMA-defined outcomes and not the individual trial reported outcomes (except the primary outcome), so coherence may be reduced in this case. However, these review outcomes were chosen for the clinical relevance and included both safety and efficacy endpoints. Finally, protocol changes in the living review that were necessitated by the changing scientific landscape, could have also impacted sample size and composition.

In conclusion, the majority of RCTs had discrepancies in outcomes between clinical trial registries and the final report i.e., journal article or final preprint version. However, the primary outcome was consistently reported for most registry-report pairs of RCTs. Generally, COVID-19 RCTs demonstrated good compliance in posting of registry results within one year of completion.

Future research is to determine factors associated with posting of registry results are planned and undergoing.

Article

Mauricia Davidson, Anna Chaimani, Isabelle Boutron

"Consistency of reporting of COVID-19 outcomes: a comparison of trial registries and the final published reports"

***(manuscript in progress*)**

Consistency of reporting of COVID-19 outcomes: a comparison of trial registries and the final published reports

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Abstract

Objectives: We aimed to describe trials whose results were publicly posted on ClinicalTrials.gov and EU-CTR and determine factors associated with posting, and to compare the timing and consistency of reporting of COVID-19 trial results in clinical trial registries and their final report, either journal article or preprint.

Data sources: COVID-NMA living systematic review (covid-nma.com), ClinicalTrials.gov, European Clinical Trials Register (EU-CTR)

Methods: We considered randomized controlled trials (RCTs) in COVID-NMA that evaluated pharmacological treatments for COVID-19. RCTs with results available in the eligible clinical trial registries and in journal articles (or final preprint version, if journal articles were not available) were included. COVID-NMA critical outcome data and the primary outcome of the respective RCTs were extracted from the registry and compared to the final published report.

Results: We identified 117 RCTs with results posted on ClinicalTrials.gov or EU-CTR and in an online publication (journal article or preprint). The median delay between primary completion date of the trial and the date of online availability of the final report (journal article or preprint), and the date results were posted to ClinicalTrials.gov or EU-CTR was 151 (IQR, 108–175) days and 295 (IQR, 173–254) days, respectively. The median sample size was 250 (IQR, 82–496) participants, 89% of RCTs were only registered on ClinicalTrials.gov, 98% of results sourced from this registry, 84% of RCTs had been prospectively registered, and 71% received industry or mixed funding. The overall risk of bias assessed was rated as 'some concern' for 74% of RCTs. We found that 14 registry-report pairs of RCTs were consistent for all outcomes. There were 69 RCTs with at least one outcome missing in the registry, and 55 RCTs with at least one outcome added to the registry compared to the preprint or journal article report. There were 43 RCTs that had at least one outcome with a change in the number of participants with outcome events. The primary outcome data was consistent between registry and final report in two-thirds of RCTs (n=79).

Conclusions: The majority of RCTs had discrepancies in outcome data between clinical trial registries and the final online report (journal article or preprint). The primary outcome was consistently reported for most registry-report pairs of RCTs.

Introduction

Systematic reviews of randomized controlled trials (RCTs) are pivotal for assessing intervention efficacy and safety. As most reviews are made up of solely peer-reviewed journal articles, the non-publication of many RCTs compromises review validity due to reduced power and potential publication bias.(1,2) Journal articles can also lack transparency or omit crucial trial information. Some results may be inadequately reported in journal articles, preventing inclusion in meta-analyses. Clinical trial registries play an important role in increasing transparency and accountability in the reporting of trial results. The 2007 US Federal Drug Administration Amendments Act 801 (FDAAA 801) and the European Medicines Agency (EMA) require that results for applicable clinical trials be posted to the ClinicalTrials.gov and the European Clinical Trials Register (EU-CTR), respectively, within one year of trial completion.(3,4) Published and unpublished results should be consistent with the initial trial registration information and any deviations should be noted. While studies have found more complete outcome reporting in trial registries compared to journal articles (5,6), questions persist for those outcomes specified for a systematic review and the consistency registry and journal outcome reporting.

Notably, the COVID-NMA living systematic review, leveraged data from multiple formal and informal data sources to inform evidence synthesis and decision-making in the treatment of COVID-19.(7) Therefore, we aimed to 1) describe trials whose results are publicly posted on ClinicalTrials.gov and EU-CTR and determine factors associated with posting, and 2) compare the timing and consistency of reporting of COVID-19 trial results in clinical trial registries and their final report, either journal article or preprint.

Methods

Data source and search

We used data from the COVID-NMA living systematic review (www.covid-nma.com)(7) – a living mapping and synthesis of RCTs for the treatment and prevention of COVID-19. Detailed methods are provided in the Supplementary file, but in summary, COVID-NMA was built on a comprehensive search of the Epistemonikos L·OVE COVID-19 platform (www.app.iloveevidence.com/covid19) and the Cochrane COVID-19 Study Register (www.covid-19.cochrane.org/). The Retraction Watch Database

(www.retractionwatch.com/retracted-coronavirus-covid-19-papers) was also searched for retracted studies. Screening and data extraction were conducted by pairs of researchers, in duplicate, with disagreements resolved through consensus and a third researcher, when necessary. Data sources included journal articles, preprints, trial registries and supplementary materials.(8)

Identification of RCTs

We included RCTs of the COVID-NMA living systematic review that evaluated pharmacological treatments (last search date – December 14, 2022). We included only those RCTs that were registered in either ClinicalTrials.gov or EUCTR, with results reported up to April 24, 2024, and that was published in journal article or preprint. We excluded all RCTs in the COVID-NMA living systematic review that evaluated non-pharmacological treatments, preventive interventions (e.g., use of personal protective equipment movement control strategies such as self-isolation), vaccines and supportive treatments for patients admitted to the ICU (e.g., high-flow nasal cannula). Cluster RCTs were also excluded.

Data extraction

We used the previously collected data on individual pharmacological treatment RCTs from the COVID-NMA database. We focused on the following: first author, timing of registration, blinding, source of funding, number of centers, setting, intervention assessed and overall risk of bias assessed using the Cochrane Risk of Bias 2 tool.(9)

We extracted data from the clinical trial registry and the final published report. Since RCTs in COVID-NMA were updated as soon as a new report was identified, to ensure data source accuracy, we manually searched the respective registry websites (ClinicalTrials.gov, EU-CTR etc.) to retrieve all registry results for COVID-19 treatments. We also collected data from the journal articles of the included RCTs. If there was no available journal article for the trial, we collected data from the final preprint version of the trial report. Where possible, we extracted data on the source of data (clinical trial registry, journal article/preprint version), date of online publication, number of participants randomized, number of participants analyzed and the critical outcomes defined for the COVID-NMA review.

These included:

- Clinical improvement (D28) defined as a hospital discharge or improvement on the scale used by trialists to evaluate clinical progression and recovery.
- WHO Clinical Progression Score of level 7 or above (i.e., mechanical ventilation +/- additional organ support (extra corporeal membrane oxygenation (ECMO), vasopressors or dialysis) or death (D28)
- All-cause mortality (D28)
- Hospitalization or death (outpatient setting)
- Incidence of any adverse events (AEs)
- Incidence of serious AEs (SAEs)

We also extracted data on the primary outcome of each RCT.

Data synthesis

We generated descriptive statistics for study and population characteristics of RCTs whose results were posted on ClinicalTrials.gov or EU-CTR. We calculated frequencies and percentages for categorical variables, and medians with interquartile ranges (IQRs) for continuous variables. We compared the outcomes reported in the clinical trial registry to its journal article or final preprint, where available. We noted whether the outcome events and number analyzed were reported consistently between the two reports or not. We identified outcomes that were added to the clinical trial registry report versus its journal article or final preprint. If more than one registry, journal article or preprint provide results for a given RCT, we prioritized data from the first available registry results report and from the final published report (journal article or preprint version) to assess consistency.

We conducted Kaplan-Meier analysis to estimate the delay from the primary trial completion date to the date of posting of results in a trial registry, and to the date of final online publication (journal article or final preprint version).

Results

Of the 575 records of treatment RCTs identified in the COVID-NMA database, we identified 376 pharmacological treatment RCTs that were registered on Clinicaltrials.gov or EU-CTR. We excluded RCTs that did not have registry results (n=229), and that only had registry results

(n=30). Overall, 117 RCTs with results posted on ClinicalTrials.gov or EU-CTR and in an online publication (journal article or preprint) were included in the analysis (Figure 8).

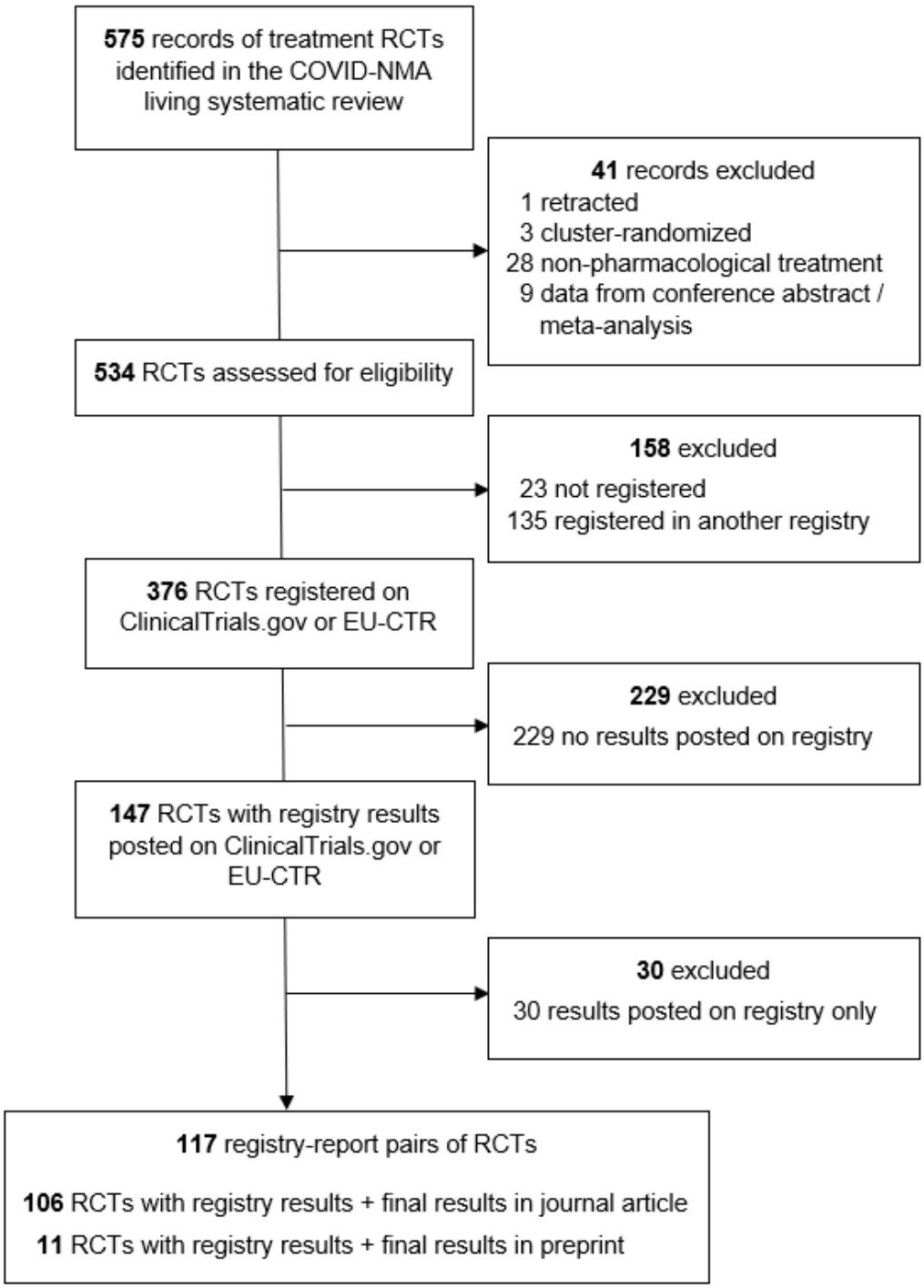

Figure 8: Flowchart of included RCTs

RCT, randomized controlled trial; EU-CTR, European Clinical Trials Register

Characteristics of RCTs with registry results and journal article or preprint data (hereafter registry-report pairs) are presented in Table 4.

Table 4: Characteristics of registry-report RCTs

Characteristics		**Registry-Report RCTs** n = 117 (%)	**RCTs with consistent data** n = 14 (%)	**RCTs with inconsistent data** n = 103 (%)
Sample size, median (IQR)		250 (I82–496)	109 (61–323)	260 (109–518)
Delay* to publication in journal article/preprint, median (IQR)		151 (108–295)	188 (143–227)	146 (104–305)
Delay† to results posting in registry, median (IQR)		295 (173–357)	290 (236–337)	295 (161–370)
Registration platform, n (%)	Clinicaltrials.gov only	104 (89)	12 (86)	92 (89)
	EU-CTR only	2 (2)	1 (7)	1 (1)
	Both	11 (9)	1 (7)	10 (10)
Source of registry results, n (%)	Clinicaltrials.gov	115 (98)	13 (93)	102 (99)
	EU-CTR	2 (2)	1 (7)	1 (1)
Registration timing, n (%)	Prospective	98 (84)	10 (71)	88 (85)
	Retrospective	17 (15)	4 (29)	13 (13)
	Not reported/unclear	2 (2)	0	2 (2)
Final publication, n (%)	Journal article	106 (91)	9 (64)	97 (94)
	Preprint	11 (9)	5 (36)	6 (6)
Funding type, n (%)	Industry/mixed	83 (71)	8 (57)	75 (73)
	Public	31 (26)	6 (43)	25 (24)
	Others	3 (3)	0	3 (3)
At least one US site, n (%)	Yes	93 (80)	12 (86)	81 (79)
	No	24 (21)	2 (14)	22 (21)
At least one European site, n (%)	Yes	37 (32)	4 (29)	33 (32)
	No	80 (68)	10 (71)	70 (68)
Setting, n (%)	Hospital	74 (63)	9 (64)	65 (63)
	Outpatient clinic	43 (37)	5 (36)	38 (37)
Overall risk of bias‡, n (%)	Low	21 (18)	4 (29)	17 (17)
	Some concerns	87 (74)	9 (64)	78 (76)
	High	9 (8)	1 (7)	8 (8)

RCT, randomized controlled trial; EU-CTR, European Clinical Trial Register; Mixed, industry and public funding; Others, no funding/not reported/unclear;

**Number of days between primary trial completion date and date of journal article publication online/preprint post*

†Number of days between primary trial completion date and date of registry results posting

‡Highest risk of bias assessed for any outcome in any domain

The median delay between primary completion date of the trial and the date of online availability of the final report (journal article or preprint) was 151 (IQR, 108–295) days. The median delay between primary completion date of the trial and posting of results on ClinicalTrials.gov or EU-CTR was 295 (IQR, 173–357) days. Of note, 89 RCTs had results available on the registry within one year of the primary completion date and 6 RCTs had registry results available before this date. The median sample size was 250 (IQR, 82–496) participants, 89% of RCTs were only registered on ClinicalTrials.gov, with 98% of results sourced from this registry, 84% of RCTs had been prospectively registered, and 71% received industry or mixed funding. The overall risk of bias assessed was rated as 'some concern' for 74% of RCTs.

Of the 117 registry-report pairs of RCTs, 14 were consistent for all outcomes. We found 69 RCTs with at least one outcome missing in the registry, and 55 RCTs with at least one outcome added to the registry compared to the preprint or journal article report. There were 43 RCTs that had at least one outcome with a change in the number of participants with outcome events. The primary outcome data was consistent between registry and final report in two-thirds of RCTs (n=79).

Safety outcomes were more frequently reported in the registry versus efficacy outcomes (82% vs. 63%). Safety outcomes were less consistently reported between registry-report pairs of RCTs compared to efficacy outcomes (27% vs. 49%).

Discussion

We conducted a preliminary analysis of the consistency of outcome reporting between RCTs with results posted on ClinicalTrials.gov or EU-CTR and in an online publication (journal article or preprint). There were important discrepancies between registry results and the final report (journal article or preprint) in the majority of RCTs. However, the primary outcome was more consistently reported between the two sources.

Other studies have found conflicting information. In a retrospective review, Wieseler et al. compared the quality of reporting among registry reports, clinical study reports, and journal publications.(6) The authors found that registries more poorly reported overall methods ($P<0.001$), but better reported study outcomes ($P=0.005$) when compared with journal articles. They recommended that clinical trial registries be incorporated into systematic

reviews. A 2013 study by Riveros et al. also found that reporting of results was more complete on ClinicalTrials.gov than in journal articles, though they observed that overall reporting still fell short of best practices and improvements are necessary.(5) Of note, these previous studies were mainly focused on completeness rather than consistency of reporting.

Our work demonstrates a marked improvement in compliance with mandatory reporting of results on ClinicalTrials.gov as per the 2007 FDAAA 801 (median 10 (IQR, 6-12) months vs 19 (14-30) in the 2013 study by Riveros et al.)(5) On the other hand, the submission of results to the EU-CTR was alarmingly suboptimal. The use of the platform in general was significantly lower than ClinicalTrials.gov in our sample, even after accounting for the fewer trials conducted in at least one European site.

Moreover, this preliminary work highlights the need for a standardized reporting scheme. Many discrepancies in safety outcomes were due to unreported 'total adverse events'. Registries report 'serious adverse events' and 'other (not including serious) adverse events' yet most authors report 'any adverse events' or 'treatment-emergent adverse events' in their articles. Also, our study found that safety data were less consistently reported between registry-report pairs of RCTs compared to efficacy data, though they were more frequently reported overall. We plan to explore reasons for this inconsistency in future work. Notably, journal articles routinely do not report serious adverse events. Moving forward, we will also complete all analyses, separately exploring timing and consistency of reporting between registries and journal articles, and registries and preprints. We will also investigate characteristics of the 30 RCTs whose results are only available in a clinical trial register. Finally, we will conduct a logistic regression model to determine factors associated with posting of results in clinical trial registries or not. We will consider as potential explanatory variables the type of funding (industry, other), primary study location (USA, Europe), timing of registration (prospective, retrospective), number of centers (multiple, single), sample size, blinding (blinded, unblinded), overall risk of bias (low/some concerns, high), source of final report (journal article, preprint), publication time (with respect to the start of the pandemic) and novelty (i.e., first publication on a treatment comparison).

There are some limitations to this study. Firstly, we focused on COVID-19 RCTs so our results may not be generalizable to other fields and study types. Secondly, we only considered ClinicalTrials.gov and EU-CTR but these are the largest clinical trial registries with regulations for posting results.(10) Furthermore, our study is limited to COVID-NMA-defined outcomes

and not the individual trial reported outcomes, so coherence may be reduced in this case. However, these review outcomes were chosen for the clinical relevance and included both safety and efficacy endpoints. Protocol changes in the living review that were necessitated by the changing scientific landscape, could have also impacted sample size and composition.

Conclusion

In the majority of RCTs there were discrepancies in outcomes between clinical trial registries and the final report i.e., journal article or final preprint version. The primary outcome was consistently reported for most registry-report pairs of RCTs. Generally, COVID-19 RCTs demonstrated good compliance in posting of registry results within one year of completion.

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Discussion

The COVID-19 pandemic caused major disruptions worldwide, exposing significant vulnerabilities in global health preparedness and response and the importance of incorporating diverse data sources into scientific research. My work showed that, among a sample of 37 meta-analyses including 114 RCTs (44 preprints and 70 journal articles), meta-epidemiological analysis yielded no evidence of important difference in summary treatment effects between COVID-19 preprints and journal articles. Also, comparing 109 preprint RCTs to their subsequent journal article, I found that effect estimates were mostly consistent between the pairs of reports. Then, when investigating post-preprint and PPPR comments on 500 RCTs, I found that commenters identified issues that could be easily resolved by the trial authors in only 9% of RCTs, while systematic reviewer assessments identified such types of issues in 78% of RCTs. Finally, initial findings showed poor consistency in outcome reporting between 117 RCTs with clinical trial registry results and journal article or preprint data. However, the primary outcome was mostly consistent between the two documents.

Implications of my results

Integrating Preprints in Evidence Synthesis

Scientific research is increasingly complex, with a wealth of information available from various sources e.g., preprints, clinical trial registries, CSRs, and peer-reviewed journal articles. My research underscores the value of integrating preprints into LSRs. Despite the longstanding recommendation to incorporate grey literature into systematic reviews, most reviews still primarily focus on journal articles, missing out on the comprehensive insights offered by these other sources. It has been the school of thought that preprints are not reliable but, this research showed that the inclusion of preprints within a meta-analysis might not impact the mean intervention effect. In general, effect estimates were mostly consistent between preprints and subsequent journal articles of COVID-19 RCTs. There were no changes to the main results and interpretation of findings in any trial. With the scientific field continuously changing and striving for improvement through updated processes and new information to benefit stakeholders, it might be reasonable to consider preprint data. Particular consideration should be given during a volatile pandemic like COVID-19, with inclusion of

these data on a one-on-one basis, taking care to assess risk of bias and completeness of reporting. In doing so, valuable early data is utilized without compromising the integrity of the analysis.

Streamlining Data in Living Systematic Reviews

Furthermore, due to the vast and growing body of information available today, the key challenge is that information is dispersed across multiple platforms which makes it difficult to be aware of the evolution of a study and its results. An organized system that links various data sources is essential to follow a study from inception through publication and even beyond, to ensure efficient synthesis and analysis. For instance, the preprint-article linker tool developed by Guillaume Cabanac and colleagues for the COVID-NMA living systematic review exemplifies how automation can help track the life cycle of a trial. In this case, there were automatic alerts to researchers when a preprint was updated or published in a peer-reviewed journal. Moreover, we must consider that even published journal articles are 'living' documents, subject to changes like errata or retractions. Thus, there needs to be a comprehensive and dynamic system to streamline all data and updates related to a given study, investigate discrepancies, and integrate this information into LSRs. This approach would ensure that the most up-to-date and accurate information is always available for decision-making.

Enhancing the Role of Systematic Reviewers in Primary Research

My research indicates that systematic reviewers are well-placed to improve how studies are reported and conducted, yet their valuable assessments often remain siloed within individual papers. By following the usual iterative process of LSRs, involving continuous evidence synthesis with detailed assessment of RoB and ORB for each new RCT, in my sample, issues that could be easily resolved by trial authors were identified in 78% of the RCTs. The absence of a direct feedback loop between systematic reviewers and trialists is a significant missed opportunity for enhancing research quality, both in primary research and subsequent evidence synthesis.

A piece in the *Journal of Clinical Epidemiology* discusses the separation between the research enterprises of evidence generation and synthesis.(69) The authors argue that the current relationship between trialists and systematic reviewers is often limited to specific data requests, with reviewers seeking individual participant data, unreported outcomes, or

methodological details to assess risk of bias. However, this interaction rarely extends to providing constructive feedback that could enhance ongoing or future trials, whereas on the part of trialists, they seldom utilize existing systematic reviews to inform decisions like the selection of a comparator, calculation of sample size, or choice of outcomes. Doing so would facilitate better inclusion in future meta-analyses and influence decision-making. Furthermore, after completing their trials, these trial authors typically do not share their results with systematic reviewers so that existing reviews could be updated.

A reinforced link between trialists and systematic reviewers should be a major objective in implementing this cycle of improvement.

Integrating Post-Publication Peer Review into the Research Workflow

While the results on post-preprint and PPPR were not nearly convincing enough as commenters in the study sample identified resolvable issues in only 9% of RCTs, there is potential to significantly enhance its role in the research process. What we know is that incorporating feedback from alternative and informal sources can improve a manuscript's overall quality, but it can also serve as a valuable supplement to formal peer review processes. However, in order to maximize the effectiveness of post-preprint and PPPR, there needs to be incentives for use and further development of these platforms through the evidence linkage that I talked about.

One approach could be to incorporate it into the research workflow. With the widespread adoption of preprints, journals could consider requiring authors to post the preprint at the same time that they submit their manuscript to the journal for publication consideration. Just as formal peer review comments need to be carefully and thoroughly addressed, within the delay for formal peer review, authors could be required to fully acknowledge and respond to all post-preprint peer review comments, including addressing any issues highlighted by commenters that could be easily resolved by authors. Given that in my study, we found the median time from article post to comment post to be 11 days (IQR, 2–65), this aligns well with the delay for formal peer review. Before accepting a manuscript for publication, journal editors should evaluate whether the authors have adequately addressed both formal peer review and post-preprint peer review comments. This multi-layered consideration, i.e., integrating preprints and post-preprint peer review into the formal peer review and

publication workflow, could improve the quality of published research and foster greater engagement from the scientific community.

Limitations of my results

Of course, caution is warranted when interpreting my results as there are some limitations to consider. Firstly, all studies in this thesis relied solely on COVID-19 trials, so results may not be generalizable to other fields, especially outside of a pandemic. Thousands of trials were initiated during this period, with authors rushing to disseminate their findings, potentially at the expense of methodological and reporting quality. Plus, as we know, peer review was majorly affected in the pandemic context, with reviewers under unique pressure to fast-track their evaluations in order to quickly publish key information. This may have negatively impacted the robustness of review, and coupled with the difficulties of accessing highly skilled peer reviewers, the differences between preprints and journal articles may have been minimized. Brierley and colleagues, however, observed small differences between preprint and journal article abstract conclusions more frequently in COVID-19-related studies than in non-COVID-19 studies.(89) There is also the matter of increased engagement and volume of open commentary on COVID-19 research than on other topics.(90) Not only could this have improved our post-preprint and PPPR sample, but it could indicate that COVID-19 preprints may have benefited from more thorough informal review. However, this potential benefit could not be quantified as my aim was not to investigate the consistency of results between preprint versions.

Additionally, all studies in this thesis were limited to the decisions of the COVID-NMA living systematic review. For example, in early 2022, COVID-NMA revised its protocol to include only trials evaluating immunomodulators and antiviral therapies. Then, at the end of 2022, the protocol was revised again to stop including pharmacological intervention trials altogether. These revisions may have affected the sample sizes and composition. Furthermore, systematic reviewer assessments were only available for COVID-NMA-defined outcomes and not for all outcomes reported in the preprints and journal articles. However, all these interventions and outcomes were chosen because of their clinical relevance and both safety and efficacy endpoints were included.

Also, only considered RCTs in my samples, and RCTs usually rely on pre-registered protocols, clearly stating the outcomes to be investigated and reported, reducing the probability of selective reporting. Therefore, consistency of results between preprints and journal articles or meta-epidemiological analysis on other study types, such as observational studies, could be different.

Additionally, there was a median of 2 (IQR, 2-4) RCTs per meta-analysis when estimating the difference in summary treatment effect between preprints and journal articles. This increased the uncertainty around the estimation. Also, as part of the protocol, I had planned to perform a meta-regression to account for potential study or meta-analysis characteristics that might have an impact on the differences in treatment effect estimates between preprints and journal articles. But, due to the small number of RCTs per meta-analysis, I could not account for these pre-specified covariates (sample size, type of funding, number of centers, registration timing, overall risk of bias) and instead relied on subgroup analyses.

Besides this, because one of my goals was to explore the consistency of results between preprints and their subsequent journal article, preprints that were never published in a journal were excluded and I could not evaluate whether peer review prevented journal publication due to unsupported conclusions. Nevertheless, I acknowledged that the results should be put in the context of a broader question and attempted to characterize these preprints, ultimately finding that trial characteristics were generally similar between unpublished and published preprints.

Finally, most post-preprint and PPPR comments were anonymous; therefore, I could not assess the commenters' expertise in research methodology or investigate their potential conflicts of interest. However, I did not seek to exhaustively verify the validity of the issues highlighted in the comments, plus anonymity tends to encourage greater participation in PPPR. A study investigated this phenomenon and found that PubPeer, a platform that allows anonymous contributions, received over 37,000 comments while PubMed Commons, which required commenters to properly identify themselves, received only 4,000 comments on the same studies.(91)

Future work

Looking ahead, I wish to continue contributing to the research, exploring new ways to create an evidence ecosystem and incorporate diverse data sources into living systematic reviews.

Firstly, I plan to continue the work started on clinical trial registries. I aim to determine factors associated with posting of results in clinical trial registries. I will conduct a logistic regression model with potential explanatory variables the type of funding (industry, other), primary study location (USA, Europe), timing of registration (prospective, retrospective), number of centers (multiple, single), sample size, blinding (blinded, unblinded), overall risk of bias (low/some concerns, high), source of final report (preprint, journal article), publication time (with respect to the start of the pandemic) and novelty (i.e., first publication on a treatment comparison).

Also, future work could focus on another non-gold standard source of information, observational studies. These studies often provide initial insights into research questions and can be vital in the early stages of investigating new interventions. I plan to examine the consistency of results between early-stage observational studies and meta-analyses of RCTs and look at how far in advance of the first influential RCT on a particular drug was information from observational studies already publicly available. By comparing these early-stage findings with later meta-analyses of RCTs, we can better understand the reliability and validity of observational data and its role in evidence synthesis.

Research could also focus on CSRs and their impact on evidence synthesis. Reporting consistency between CSRs and published reports could also be investigated, as CSRs may offer a more complete reporting of study methods and efficacy and safety data compared to traditional published articles.

Finally, application of my findings to a broader context outside of COVID-19 is certainly a priority.

Conclusion

This thesis showcases the importance and utility of different sources of information to potentially enhance the reliability and robustness of systematic reviews. Some present risks. Preprints and clinical trial registries allow research findings to be rapidly disseminated, enabling the scientific community to access new data more quickly. However, more work needs to be conducted on registry data to better understand how best they can be utilized. Post-preprint and PPPR add an additional layer of scrutiny to improve research quality, providing valuable feedback that can address issues that were missed during formal peer review. Systematic reviewers already identify important methodological and reporting issues that could be easily resolved by trial authors, but the feedback loop is missing.

If anything has become clear throughout this work, it is that we need to streamline all sources of information. To truly improve the quality of research and evidence-based decision-making, we must move past an evidence synthesis ecosystem and advance to a fully integrated evidence ecosystem. This requires creating stronger links between all research enterprises i.e., trialists, systematic reviewers, and the broader research community. By fostering greater collaboration and communication across these groups, we can ensure that evidence is continuously updated, comprehensive, and reflective of the best available data. An integrated evidence ecosystem would speed up the translation of study results into real-world impact, ultimately benefiting the entire scientific community, and public health.

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eMethods 1

Search strategy

The initial search strategy was developed with Robin Featherstone, Information Specialist, at the Cochrane Editorial & Methods Department and evolved following assessment of secondary sources. The search was updated on September 4, 2020 following an evaluation of the sensitivity of the L-OVE platform and Cochrane COVID-19 Study Register by Pierre et al[1], which identified all RCTs identified through the initial extensive search strategy.

Electronic searches

- The L-OVE platform (https://app.iloveevidence.com/covid19), searched every working day since 4 September 2020. Complete data sources and search methods are available at https://app.iloveevidence.com/covid19/methods.
- The Cochrane COVID-19 Study Register (https://covid-19.cochrane.org/), searched every working day since 4 September 2020. Complete data sources and search methods are available at https://community.cochrane.org/about-covid-19-study-register.

References were not checked as the living search process identified COVID-19 trial records prospectively from the point of trial registration.

The Retraction Watch Database was also searched for retracted studies (https://retractionwatch.com/retracted-coronavirus-covid-19-papers/).

Below we describe our initial search strategy and secondary sources.

First Period of search

Up to September 2020, we relied on the following sources:

PubMed (MEDLINE)	(2019 nCoV[tiab] OR 2019nCoV[tiab] OR corona virus[tiab] OR corona viruses[tiab] OR coronavirus[tiab] OR coronaviruses[tiab] OR COVID[tiab] OR COVID19[tiab] OR nCov 2019[tiab] OR SARSCoV2[tiab] OR SARS CoV-2[tiab] OR SARSCoV2[tiab] OR SARSCoV-2[tiab] OR "COVID-19"[Mesh] OR "COVID-19 Testing"[Mesh] OR "COVID-19 Vaccines"[Mesh] OR "Coronavirus"[Mesh:NoExp] OR "SARS-CoV-2"[Mesh] OR "COVID-19"[nm] OR "COVID-19 drug treatment"[nm] OR "COVID-19 diagnostic testing"[nm] OR "COVID-19 serotherapy"[nm] OR "COVID-19 vaccine"[nm] OR "LAMP assay"[nm] OR "severe acute respiratory syndrome coronavirus 2"[nm] OR "spike protein, SARSCoV-2"[nm]) NOT ("animals"[mh] NOT "humans"[mh]) NOT (editorial[pt] OR newspaper article[pt])

Embase.com	((('coronaviridae'/de OR 'coronavirinae'/de OR 'coronaviridae infection'/de OR 'coronavirus disease 2019'/exp OR 'coronavirus infection'/de OR 'SARS-related coronavirus'/de OR 'Severe acute respiratory syndrome coronavirus 2'/exp OR '2019 nCoV':ti,ab,kw OR 2019nCoV:ti,ab,kw OR ((corona* OR corono*) NEAR/1 (virus* OR viral* OR virinae*)):ti,ab,kw OR coronavir*:ti,ab,kw OR coronovir*:ti,ab,kw OR COVID:ti,ab,kw OR COVID19:ti,ab,kw OR HCoV*:ti,ab,kw OR 'nCov 2019':ti,ab,kw OR 'SARS CoV2':ti,ab,kw OR 'SARS CoV 2':ti,ab,kw OR SARSCoV2:ti,ab,kw OR 'SARSCoV 2':ti,ab,kw) NOT (('animal experiment'/de OR 'animal'/exp) NOT ('human'/exp OR 'human experiment'/de))) NOT 'editorial'/it) NOT ([medline]/lim OR [pubmed-not-medline]/lim) AND [1-12-2019]/sd
Cochrane Central Register of Controlled trials (CENTRAL)	1 ("2019 nCoV" OR 2019nCoV OR "corona virus*" OR coronavirus* OR COVID OR COVID19 OR "nCov 2019" OR "SARS-CoV2" OR "SARS CoV-2" OR SARSCoV2 OR "SARSCoV-2"):TI,AB AND CENTRAL:TARGET 2 Coronavirus:MH AND CENTRAL:TARGET 3 Coronavirus:EH AND CENTRAL:TARGET 4 #1 OR #2 OR #3 5 2019 TO 2021:YR AND CENTRAL:TARGET 6 #5 AND #4 7 INSEGMENT 8 #6 NOT #7
ClinicalTrials.gov	COVID-19 OR 2019-nCoV OR SARS-CoV-2 OR coronavirus
WHO ICTRP	COVID OR 2019-nCoV OR SARS-CoV-2 OR coronavirus OR corona virus
MedRχiv	A curated list of records for COVID-19 and SARS-CoV-2 is available at https://connect.biorxiv.org/relate/content/181. Note that this list also includes sources listed in bioRχiv, but we only screened the sources published on MedRχiv.
Chinaχiv	**Searched** up to 7 April 2020

- We also searched The Cochrane Covid-19 Study Register used as quality control and Epistemonikos L·OVE COVID-19 platform from June 2020.

Second Period (from September 2020)
Since September 2020, we relied on the following sources:

1) The Living OVerview of Evidence (*L-OVE) platform*
Details related to the search performed by this platform and the process is available here https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?population=5e7fce7e3d05156b5f5e032a&intervention_variable=603b9fe03d05151f35cf13dc&section=methods&classification=all.

In brief, the Living OVerview of Evidence (L·OVE) was built, and is maintained, by systematic searches in multiple databases, trial registries and preprint servers. The following sources are regularly searched:

- Pubmed/medline (updated several times a day)
- EMBASE (updated weekly)
- CINAHL (updated weekly)
- PsycINFO (updated weekly)
- LILACS (Latin American & Caribbean Health Sciences Literature) (updated weekly)
- Wanfang Database (updated every 2 weeks)
- CBM - Chinese Biomedical Literature Database (updated every 2 weeks)
- CNKI - Chinese National Knowledge Infrastructure (updated every 2 weeks)
- VIP - Chinese Scientific Journal Database (updated every 2 weeks)
- IRIS (WHO Institutional Repository for Information Sharing) (updated weekly)
- IRIS PAHO (PAHO Institutional Repository for Information Sharing)) (updated weekly)
- IBECS - Índice Bibliográfico Español en Ciencias de la Salud (Spanish Bibliographic Index on Health Sciences) (updated weekly)
- Microsoft Academic (last searched: 23 August 2021)
- ICTRP Search Portal (updated daily)
- Clinicaltrials.gov (updated daily)
- ISRCTN registry (updated daily)
- Chinese Clinical Trial Registry (updated daily)
- IRCT - Iranian Registry of Clinical Trials (updated daily)
- EU Clinical Trials Register: Clinical trials for covid-19 (updated daily)
- NIPH Clinical Trials Search (Japan) - Japan Primary Registries Network (JPRN) (JapicCTI, JMACCT CTR, jRCT, UMIN CTR) (updated daily, via ICTRP search portal)
- UMIN-CTR - UMIN Clinical Trials Registry (updated daily, via ICTRP search portal)
- JRCT - Japan Registry of Clinical Trials (updated daily, via ICTRP search portal)
- JAPIC Clinical Trials Information (updated daily, via ICTRP search portal)
- Clinical Research Information Service (CRiS), Republic of Korea (updated daily, via ICTRP search portal)
- ANZCTR - Australian New Zealand Clinical Trials Registry (updated daily, via ICTRP search portal)
- ReBec - Brazilian Clinical Trials Registry (updated daily, via ICTRP search portal)
- CTRI - Clinical Trials Registry - India (updated daily, via ICTRP search portal)
- RPCEC - Cuban Public Registry of Clinical Trials (updated daily, via ICTRP search portal)
- DRKS - German Clinical Trials Register (updated daily, via ICTRP search portal)
- LBCTR - Lebanese Clinical Trials Registry (updated daily, via ICTRP search portal)
- TCTR - Thai Clinical Trials Registry (updated daily, via ICTRP search portal)
- NTR - The Netherlands National Trial Register (updated daily, via ICTRP search portal)
- PACTR - Pan African Clinical Trial Registry (updated daily, via ICTRP search portal)
- REPEC - Peruvian Clinical Trial Registry (updated daily, via ICTRP search portal)
- SLCTR - Sri Lanka Clinical Trials Registry (updated daily, via ICTRP search portal)
- medRxiv (updated several times a day)
- bioRxiv (updated several times a day)
- SSRN Preprints (updated several times a day)
- ChinaXiv (updated every 2 weeks)
- SciELO Preprints (updated weekly)

- Research Square (updated daily)

2) The Cochrane Covid-19 Study Register

Details related to the search performed by this register and the process are described here: https://community.cochrane.org/about-covid-19-study-register. It is a specialised register built within the Cochrane Register of Studies (CRS) and is maintained by Cochrane Information Specialists. The register contains study reports from several sources, including:

- daily searches of PubMed
- daily searches of ClinicalTrials.gov
- weekly searches of Embase.com
- weekly searches of the WHO International Clinical Trials Registry Platform (ICTRP)
- weekly searches of medRxiv
- monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)

3) Retraction Watch
We also searched the Retraction Watch Database for retracted studies (retractionwatch.com/retracted-coronavirus-covid-19-papers/).

eMethods 2

COVID-NMA-defined critical outcomes

- Clinical improvement at day 28 (D28) *(extracted in priority below)*
  1) at least 2-point improvement in the WHO Clinical Progression Scale[2] or hospital discharge
  2) hospital discharge alone
  3) at least 1-point improvement in the WHO Clinical Progression Scale[2] or hospital discharge

- WHO Clinical Progression Score[2] of level 7 or above (i.e., mechanical ventilation +/– additional organ support or death) (D28)

- All-cause mortality (D28)

- Incidence of any adverse events (includes author definitions such as treatment emergent adverse events (TEAE), solicited adverse events)

- Incidence of serious adverse events (includes author definitions such as serious TEAE)

Meta-analysis	**Setting**	**Database date**	**RCTs** Total (preprints vs. peer-reviewed journals), n	**Sample size** Total (preprints vs. peer-reviewed journals), n	**Type of funding** [industry vs. mixed] Total (preprints vs. peer-reviewed journals), n	**Number of centers** [multicenter] Total (preprints vs. peer-reviewed journals), n	**Registration timing** [prospective] Total (preprints vs. peer-reviewed journals), n	**Overall risk of bias** Total (preprints vs. peer-reviewed journals), n
Anakinra vs. control	Hospitalized patients	07/01/2021	2 (1 vs. 1)	708 (594 vs. 114)	1 (1 vs. 0)	2 (1 vs. 1)	2 (1 vs. 1)	Low – 0 (0 vs. 0) SC – 2 (1 vs. 1) High – 0 (0 vs. 0)
Auxora vs. control	Hospitalized patients	02/17/2022	2 (1 vs. 1)	287 (261 vs. 26)	2 (1 vs. 1)	2 (1 vs. 1)	1 (1 vs. 0)	Low – 0 (0 vs. 0) SC – 2 (1 vs. 1) High – 0 (0 vs. 0)
Azithromycin vs. control	Hospitalized patients	07/08/2021	2 (1 vs. 1)	7875 (7764 vs. 111)	1 (1 vs. 0)	1 (1 vs. 0)	2 (1 vs. 1)	Low – 0 (0 vs. 0) SC – 2 (1 vs. 1) High – 0 (0 vs. 0)
	Outpatients	07/08/2021	2 (1 vs. 1)	1413 (292 vs. 1121)	1 (1 vs. 0)	2 (1 vs. 1)	2 (1 vs. 1)	Low – 0 (0 vs. 0) SC – 1 (1 vs. 0) High – 1 (0 vs. 1)
Baricitinib vs. control	Hospitalized patients	02/03/2022	2 (1 vs. 1)	1613 (101 vs. 1512)	2 (1 vs. 1)	2 (1 vs. 1)	2 (1 vs. 1)	Low – 0 (0 vs. 0) SC – 2 (1 vs. 1) High – 0 (0 vs. 0)
Camostat mesilate vs. control	Hospitalized patients	07/20/2022	2 (1 vs. 1)	358 (153 vs. 205)	2 (1 vs. 1)	2 (1 vs. 1)	2 (1 vs. 1)	Low – 0 (0 vs. 0) SC – 2 (1 vs. 1) High – 0 (0 vs. 0)
Ciclesonide vs. control	Outpatients	12/06/2021	2 (1 vs. 1)	603 (400 vs. 203)	2 (1 vs. 1)	2 (1 vs. 1)	2 (1 vs. 1)	Low – 0 (0 vs. 0) SC – 2 (1 vs. 1) High – 0 (0 vs. 0)

Colchicine vs. control	Hospitalized patients	11/22/2021	4 (1 vs. 3)	11620 (11340 vs. 280)	2 (1 vs. 1)	3 (1 vs. 2)	3 (1 vs. 2)	Low – 0 (0 vs. 0) SC – 3 (1 vs. 2) High – 1 (0 vs. 1)
	Outpatients	07/20/2022	2 (1 vs. 1)	4764 (276 vs. 4488)	1 (0 vs. 1)	2 (1 vs. 1)	2 (1 vs. 1)	Low – 0 (0 vs. 0) SC – 2 (1 vs. 1) High – 0 (0 vs. 0)
Convalescent plasma vs. control	Hospitalized patients	10/23/2020	4 (3 vs. 1)	732 (631 vs. 101)	1 (1 vs. 0)	4 (3 vs. 1)	2 (1 vs. 1)	Low – 0 (0 vs. 0) SC – 2 (1 vs. 1) High – 2 (2 vs. 0)
	Outpatients	05/17/2022	3 (1 vs. 2)	2461 (782 vs. 1679)	2 (1 vs. 1)	3 (1 vs. 2)	3 (1 vs. 2)	Low – 2 (0 vs. 2) SC – 1 (1 vs. 0) High – 0 (0 vs. 0)
Favipiravir vs. control	Hospitalized patients	03/25/2021	3 (1 vs. 2)	517 (163 vs. 354)	3 (1 vs. 2)	3 (1 vs. 2)	1 (0 vs. 1)	Low – 0 (0 vs. 0) SC – 3 (1 vs. 2) High – 0 (0 vs. 0)
	Outpatients	07/20/2022	3 (1 vs. 2)	499 (119 vs. 380)	1 (1 vs. 0)	2 (1 vs. 1)	3 (1 vs. 2)	Low – 0 (0 vs. 0) SC – 3 (1 vs. 2) High – 0 (0 vs. 0)
Hydroxychloroquine vs. control	Hospitalized patients	01/07/2021	8 (1 vs. 7)	8118 (247 vs. 7871)	4 (0 vs. 4)	7 (1 vs. 6)	4 (1 vs. 3)	Low – 3 (1 vs. 2) SC – 3 (0 vs. 3) High – 2 (0 vs. 2)
	Outpatients	07/08/2021	4 (1 vs. 3)	1308 (105 vs. 1203)	2 (0 vs. 2)	3 (0 vs. 3)	3 (0 vs. 3)	Low – 0 (0 vs. 0) SC – 4 (1 vs. 3) High – 0 (0 vs. 0)
Hyperimmune globulin vs. control	Hospitalized patients	02/03/2022	2 (1 vs. 1)	109 (59 vs. 50)	1 (1 vs. 0)	1 (1 vs. 0)	1 (1 vs. 0)	Low – 0 (0 vs. 0) SC – 2 (1 vs. 1) High – 0 (0 vs. 0)
Interferon beta vs. control	Hospitalized patients	03/25/2021	4 (1 vs. 3)	4307 (60 vs. 4247)	2 (0 vs. 2)	1 (0 vs. 1)	2 (0 vs. 2)	Low – 1 (0 vs. 1) SC – 2 (1 vs. 1) High – 1 (0 vs. 1)

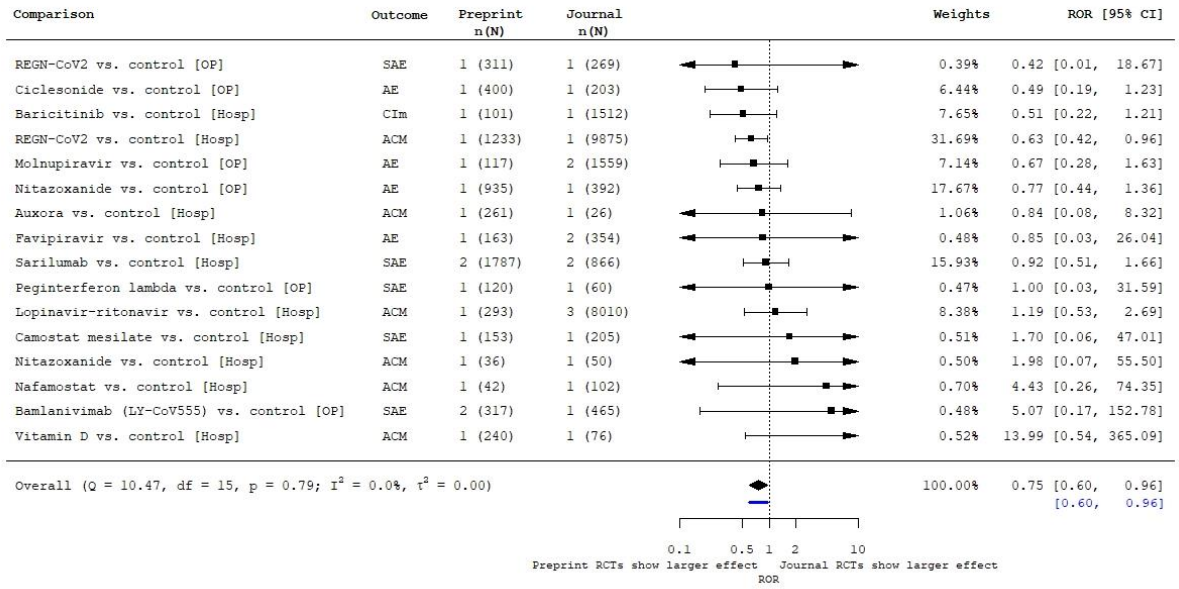
IV immunoglobulin vs. control	Hospitalized patients	11/19/2020	2 (1 vs. 1)	117 (33 vs. 84)	1 (1 vs. 0)	1 (1 vs. 0)	0 (0 vs. 0)	Low – 0 (0 vs. 0) SC – 2 (1 vs. 1) High – 0 (0 vs. 0)
Ivermectin vs. control	Hospitalized patients	06/25/2021	5 (3 vs. 2)	598 (365 vs. 233)	2 (2 vs. 0)	3 (1 vs. 2)	2 (2 vs. 0)	Low – 0 (0 vs. 0) SC – 4 (2 vs. 2) High – 1 (1 vs. 0)
	Outpatients	08/02/2021	4 (1 vs. 3)	1039 (116 vs. 923)	2 (0 vs. 2)	1 (1 vs. 0)	2 (0 vs. 2)	Low – 2 (0 vs. 2) SC – 2 (1 vs. 1) High – 0 (0 vs. 0)
Lopinavir-ritonavir vs. control	Hospitalized patients	03/02/2021	4 (1 vs. 3)	8303 (293 vs. 8010)	4 (1 vs. 3)	3 (1 vs. 2)	2 (1 vs. 1)	Low – 1 (0 vs. 1) SC – 3 (1 vs. 2) High – 0 (0 vs. 0)
	Outpatients	07/20/2022	2 (1 vs. 1)	572 (120 vs. 452)	1 (1 vs. 0)	2 (1 vs. 1)	2 (1 vs. 1)	Low – 0 (0 vs. 0) SC – 2 (1 vs. 1) High – 0 (0 vs. 0)
Bamlanivimab (LY-CoV555) vs. control	Outpatients	05/17/2022	3 (2 vs. 1)	782 (317 vs. 465)	3 (2 vs. 1)	3 (2 vs. 1)	3 (2 vs. 1)	Low – 0 (0 vs. 0) SC – 3 (2 vs. 1) High – 0 (0 vs. 0)
Molnupiravir vs. control	Outpatients	02/03/2022	3 (1 vs. 2)	1676 (117 vs. 1559)	3 (2 vs. 1)	3 (2 vs. 1)	3 (2 vs. 1)	Low – 2 (0 vs. 2) SC – 0 (0 vs. 0) High – 1 (1 vs. 0)
Nafamostat vs. control	Hospitalized patients	02/17/2022	2 (1 vs. 1)	144 (42 vs. 102)	2 (1 vs. 1)	2 (1 vs. 1)	1 (1 vs. 0)	Low – 0 (0 vs. 0) SC – 2 (1 vs. 1) High – 0 (0 vs. 0)
Nitazoxanide vs. control	Hospitalized patients	08/26/2021	2 (1 vs. 1)	86 (36 vs. 50)	2 (1 vs. 1)	2 (1 vs. 1)	1 (0 vs. 1)	Low – 0 (0 vs. 0) SC – 1 (0 vs. 1) High – 1 (1 vs. 0)
	Outpatients	08/26/2021	2 (1 vs. 1)	1327 (935 vs. 392)	2 (1 vs. 1)	2 (1 vs. 1)	1 (1 vs. 0)	Low – 0 (0 vs. 0) SC – 2 (1 vs. 1) High – 0 (0 vs. 0)

Peginterferon lambda vs. control	Outpatients	03/29/2021	2 (1 vs. 1)	180 (120 vs. 60)	2 (1 vs. 1)	1 (0 vs. 1)	2 (1 vs. 1)	Low – 0 (0 vs. 0) SC – 2 (1 vs. 1) High – 0 (0 vs. 0)
Casirivimab-imdevimab (REGN-CoV2) vs. control	Hospitalized patients	07/20/2022	2 (1 vs. 1)	11108 (1233 vs. 9875)	2 (1 vs. 1)	2 (1 vs. 1)	2 (1 vs. 1)	Low – 0 (0 vs. 0) SC – 2 (1 vs. 1) High – 0 (0 vs. 0)
	Outpatients	09/21/2021	2 (1 vs. 1)	580 (311 vs. 269)	2 (1 vs. 1)	2 (1 vs. 1)	2 (1 vs. 1)	Low – 1 (0 vs. 1) SC – 1 (1 vs. 0) High – 0 (0 vs. 0)
Remdesivir vs. control	Hospitalized patients	11/05/2020	4 (1 vs. 3)	7333 (5451 vs. 1882)	3 (1 vs. 2)	4 (1 vs. 3)	4 (1 vs. 3)	Low – 2 (1 vs. 1) SC – 2 (0 vs. 2) High – 0 (0 vs. 0)
Sarilumab vs. control	Hospitalized patients	07/01/2021	4 (2 vs. 2)	2645 (1787 vs. 858)	4 (2 vs. 2)	4 (2 vs. 2)	4 (2 vs. 2)	Low – 0 (0 vs. 0) SC – 4 (2 vs. 2) High – 0 (0 vs. 0)
Sofosbuvir-daclatasvir vs. control	Hospitalized patients	09/21/2021	5 (2 vs. 3)	1492 (1172 vs. 320)	3 (1 vs. 2)	4 (1 vs. 3)	3 (2 vs. 1)	Low – 0 (0 vs. 0) SC – 5 (2 vs. 3) High – 0 (0 vs. 0)
Sofosbuvir-ledipasvir vs. control	Hospitalized patients	10/20/2021	2 (1 vs. 1)	332 (250 vs. 82)	1 (0 vs. 1)	0 (0 vs. 0)	0 (0 vs. 0)	Low – 0 (0 vs. 0) SC – 2 (1 vs. 1) High – 0 (0 vs. 0)
Tocilizumab vs. control	Hospitalized patients	10/07/2021	11 (2 vs. 9)	6872 (390 vs. 6482)	8 (1 vs. 7)	10 (1 vs. 9)	7 (2 vs. 5)	Low – 2 (0 vs. 2) SC – 8 (1 vs. 7) High – 1 (1 vs. 0)
Umbilical cord mesenchymal stem cell infusion vs. control	Hospitalized patients	03/04/2021	2 (1 vs. 1)	124 (100 vs. 24)	1 (0 vs. 1)	1 (1 vs. 0)	2 (1 vs. 1)	Low – 1 (1 vs. 0) SC – 1 (0 vs. 1) High – 0 (0 vs. 0)
Vitamin D vs. control	Hospitalized patients	02/15/2021	2 (1 vs. 1)	316 (240 vs. 76)	0 (0 vs. 0)	1 (1 vs. 0)	1 (0 vs. 1)	Low – 0 (0 vs. 0) SC – 2 (1 vs. 1) High – 0 (0 vs. 0)

eTable 1: Characteristics of included meta-analyses

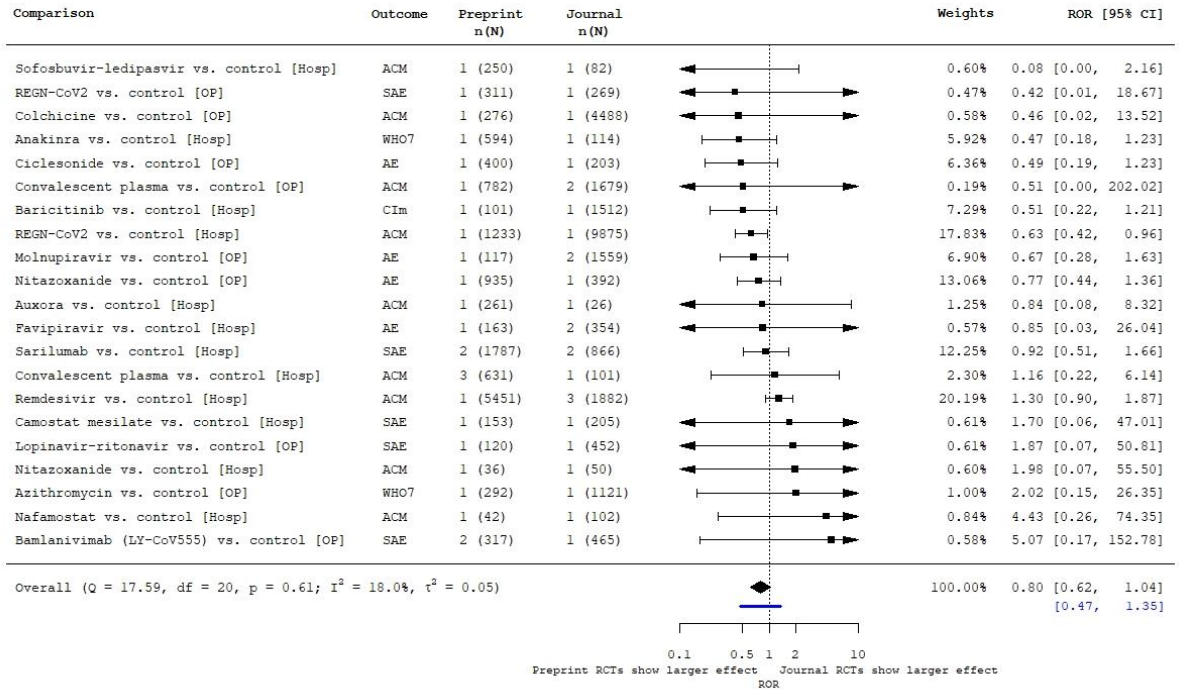
RCT, randomized controlled trial; control, standard of care or placebo; IV, intravenous; vitamin D, calcifediol/cholecalciferol; SC, some concerns

eFigure 1: Post-hoc sensitivity analysis – Homogenous Funding Type. Difference in treatment effect estimates between preprint and peer-reviewed journal RCTs



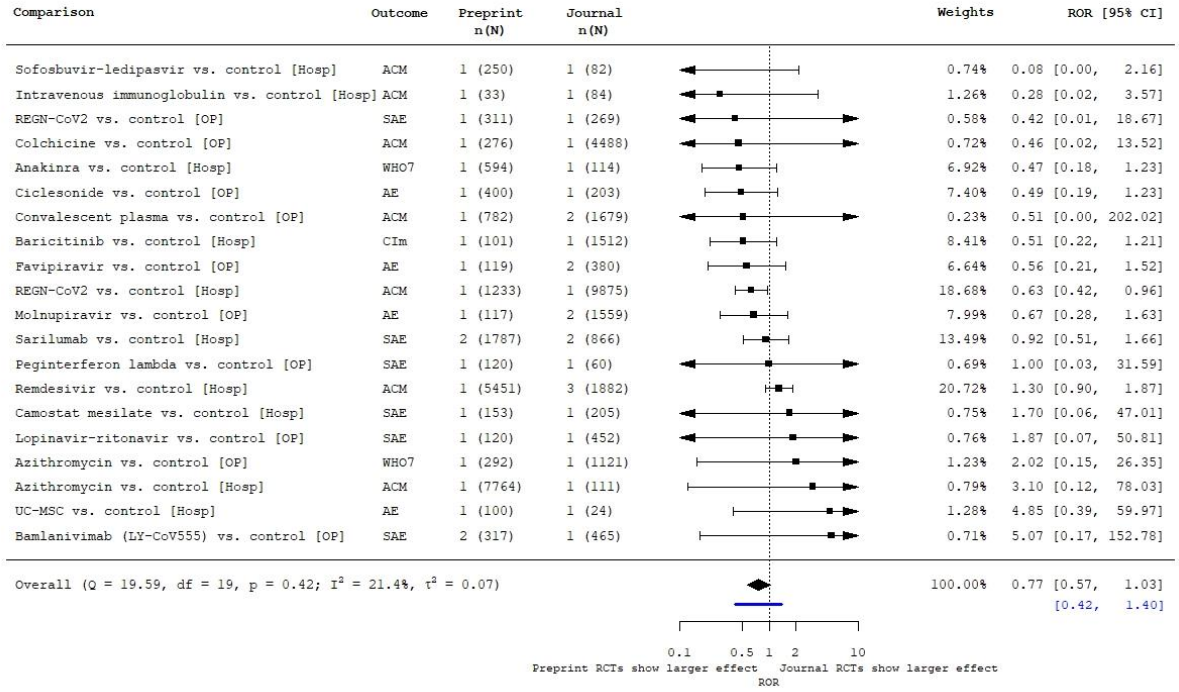
RCT, randomized controlled trial; n, number of RCTs; N, number of participants analyzed; journal, peer-reviewed journal; ROR, ratio of odds ratio; CI, confidence interval; control, standard of care or placebo; REGN-CoV2, casirivimab-imdevimab; Vitamin D, calcifediol/cholecalciferol; Hosp, hospitalized patients; OP, outpatients; ACM, all-cause mortality; AE, adverse event; SAE, Serious Adverse Event; CIm, Clinical Improvement

eFigure 2: Post-hoc sensitivity analysis – Homogenous Number of Centers. Difference in treatment effect estimates between preprint and peer-reviewed journal RCTs



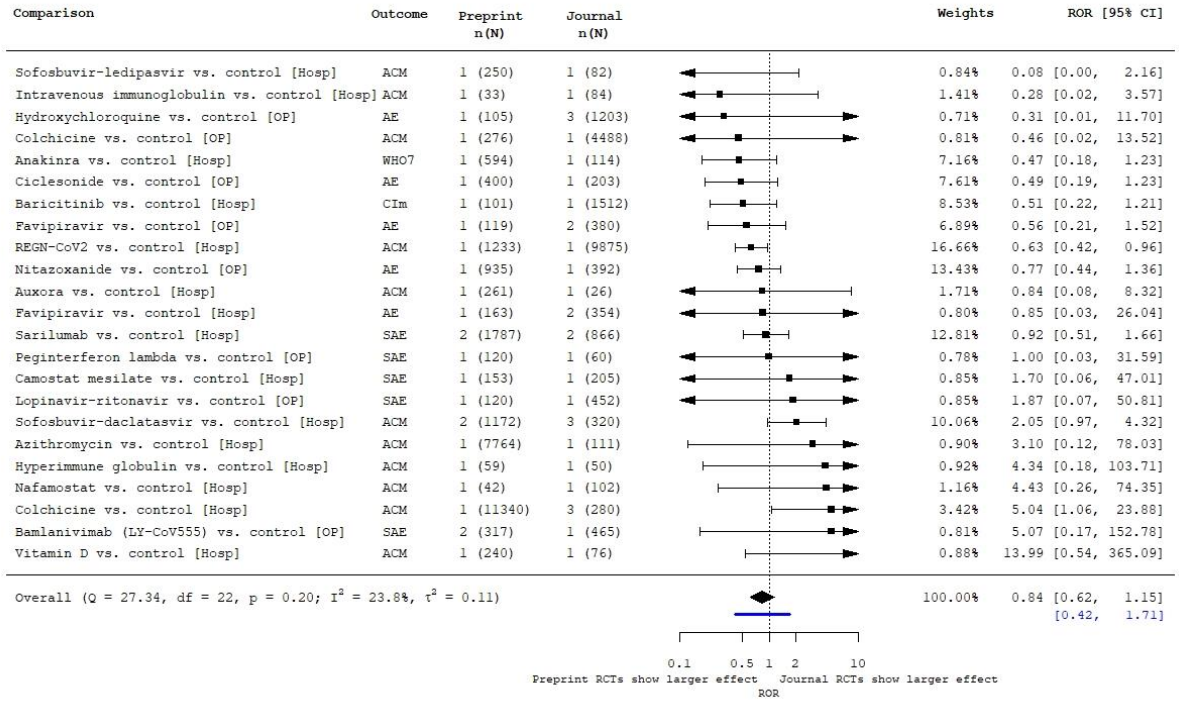
RCT, randomized controlled trial; n, number of RCTs; N, number of participants analyzed; journal, peer-reviewed journal; ROR, ratio of odds ratio; CI, confidence interval; control, standard of care or placebo; REGN-CoV2, casirivimab-imdevimab; Hosp, hospitalized patients; OP, outpatients; ACM, all-cause mortality; AE, adverse event; SAE, Serious Adverse Event; WHO7, World Health Organization Clinical Progression Score of level 7 or above; CIm, clinical improvement

eFigure 3: Post-hoc sensitivity analysis – Homogenous Registration Timing. Difference in treatment effect estimates between preprint and peer-reviewed journal RCTs



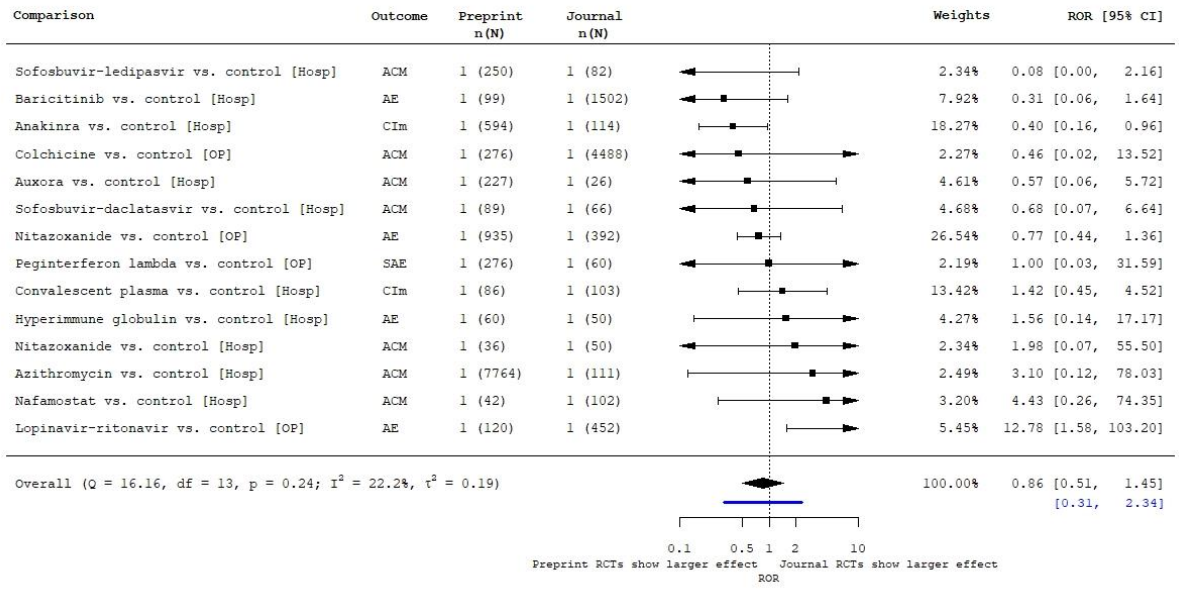
RCT, randomized controlled trial; n, number of RCTs; N, number of participants analyzed; journal, peer-reviewed journal; ROR, ratio of odds ratio; CI, confidence interval; control, standard of care or placebo; REGN-CoV2, casirivimab-imdevimab; UC-MSC, umbilical cord mesenchymal stem cell infusion; Hosp, hospitalized patients; OP, outpatients; ACM, all-cause mortality; AE, adverse event; SAE, Serious Adverse Event; WHO7, World Health Organization Clinical Progression Score of level 7 or above; CIm, clinical improvement

eFigure 4: Post-hoc sensitivity analysis – Homogenous Overall Risk of Bias Assessment. Difference in treatment effect estimates between preprint and peer-reviewed journal RCTs



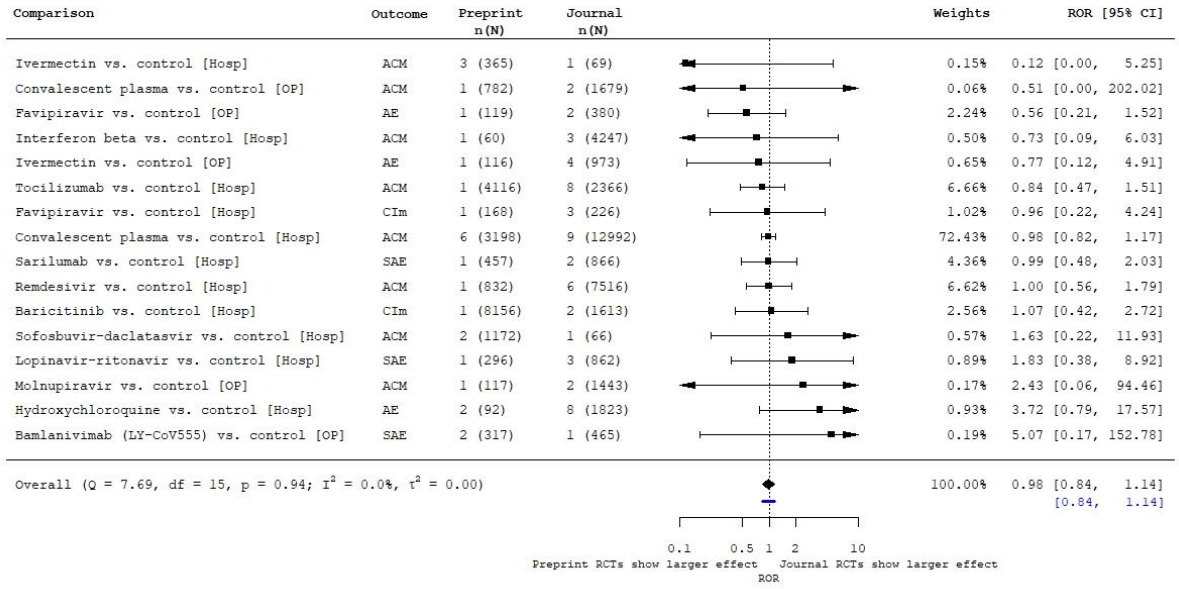
RCT, randomized controlled trial; n, number of RCTs; N, number of participants analyzed; journal, peer-reviewed journal; ROR, ratio of odds ratio; CI, confidence interval; control, standard of care or placebo; REGN-CoV2, casirivimab-imdevimab; Vitamin D, calcifediol/cholecalciferol; Hosp, hospitalized patients; OP, outpatients; ACM, all-cause mortality; AE, adverse event; SAE, Serious Adverse Event; WHO7, World Health Organization Clinical Progression Score of level 7 or above; CIm, clinical improvement

eFigure 5: Post-hoc sensitivity analysis – Early evidence synthesis. Difference in treatment effect estimates between preprint and peer-reviewed journal RCTs of meta-analyses with only 2 RCTs



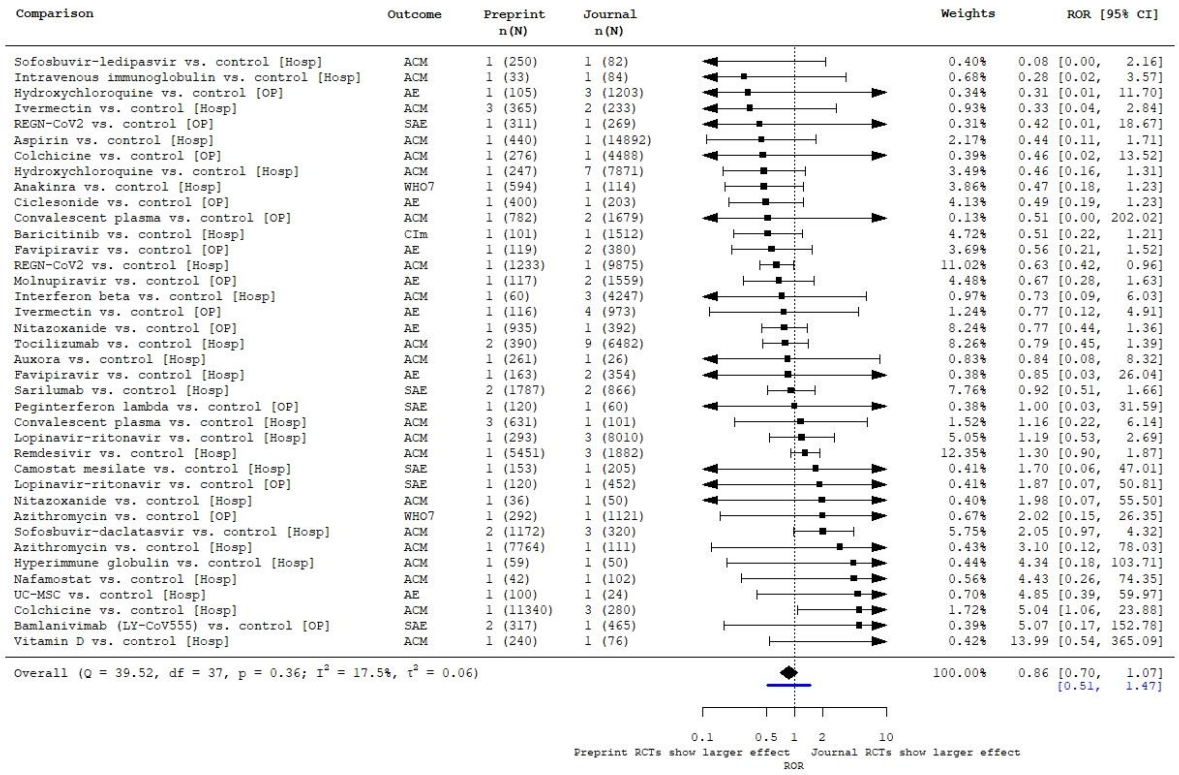
RCT, randomized controlled trial; n, number of RCTs; N, number of participants analyzed; journal, peer-reviewed journal; ROR, ratio of odds ratio; CI, confidence interval; control, standard of care or placebo; Hosp, hospitalized patients; OP, outpatients; ACM, all-cause mortality; AE, adverse event; CIm, clinical improvement; SAE, Serious Adverse Event

eFigure 6: Post-hoc sensitivity analysis – Late evidence synthesis. Difference in treatment effect estimates between preprint and peer-reviewed journal RCTs of meta-analyses with at least 3 RCTs



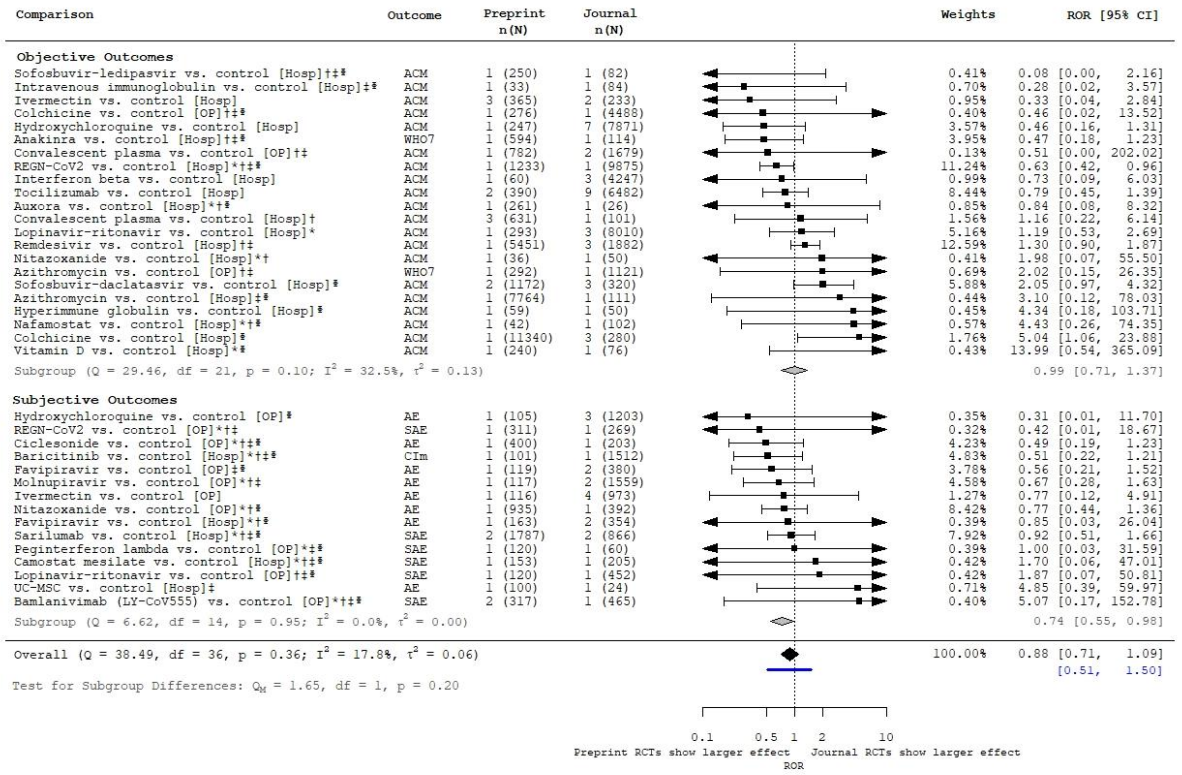
RCT, randomized controlled trial; n, number of RCTs; N, number of participants analyzed; journal, peer-reviewed journal; ROR, ratio of odds ratio; CI, confidence interval; control, standard of care or placebo; Hosp, hospitalized patients; OP, outpatients; ACM, all-cause mortality; AE, adverse event; CIm, clinical improvement; SAE, Serious Adverse Event

eFigure 7: Post-hoc sensitivity analysis – Retracted RCTs. Difference in treatment effect estimates between preprint and peer-reviewed journal RCTs



RCT, randomized controlled trial; n, number of RCTs; N, number of participants analyzed; journal, peer-reviewed journal; ROR, ratio of odds ratio; CI, confidence interval; control, standard of care or placebo; Hosp, hospitalized patients; OP, outpatients; ACM, all-cause mortality; AE, adverse event; CIm, clinical improvement; SAE, Serious Adverse Event

eFigure 8: Post-hoc subgroup analysis – Objective vs. Subjective outcomes. Difference in treatment effect estimates between preprint and peer-reviewed journal RCTs



RCT, randomized controlled trial; n, number of RCTs; N, number of participants analyzed; journal, peer-reviewed journal; ROR, ratio of odds ratio; CI, confidence interval; control, standard of care or placebo; Hosp, hospitalized patients; OP, outpatients; ACM, all-cause mortality; AE, adverse event; CIm, clinical improvement; SAE, Serious Adverse Event

eReferences

1. Pierre O, Riveros C, Charpy S, Boutron I. Secondary electronic sources demonstrated very good sensitivity for identifying studies evaluating interventions for COVID-19. *J Clin Epidemiol*. 2022;141:46-53. doi:10.1016/j.jclinepi.2021.09.022
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RCTs included in meta-analyses of at least one preprint and one peer-reviewed journal article (Figure 2)

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Annex 2. Supplementary article files for Davidson et al, BMC Medical Research Methodology, 2024

Text S1. Definitions of trial characteristics

Methods S1. Search Strategy

Table S1: Description of RCTs that were retracted or removed before the search date

Table S2. Characteristics of preprint RCTs

Figure S1. Relationship between delay to publication and discrepancies in preprint-article RCTs

References S1

Text S1. Definitions of trial characteristics

Registration timing

- Prospective – registered before the start date of the trial
- Retrospective – registered after the start date of the trial

Funding type

- Mixed – received industry and public funding
- Others – received no funding or funding was not reporting or unclearly reported

Geographical location (classified using the World Bank Country Income Classifications[2])

- Low-/middle-income country – countries classified as:
    - low-income – GNI per capita, calculated using the World Bank Atlas method, of $1,135 or less in 2022
    - lower middle-income – GNI per capita between $1,136 and $4,465 and/or
    - upper middle-income – GNI per capita between $4,466 and $13,845
- High-income country – GNI per capita of $13,846 or more

Risk of bias (classified according to the Cochrane Risk of Bias 2.0 tool[1])

Using signaling questions, risk of bias is assessed for all outcomes across five domains – 1) Randomization, 2) Deviations from the intervention, 3) Missing outcome data, 4) Measurement of the outcome and 5) Selection of the reported result. An algorithm analyzed the responses to these signaling questions to generate an assessment for each domain, which were categorized as "low," "some concerns," or "high."

- Overall risk of bias – highest risk of bias found in any domain for an outcome in the trial

Methods S1

Search strategy

The initial search strategy was developed with Robin Featherstone, Information Specialist, at the Cochrane Editorial & Methods Department and evolved following assessment of bibliographic databases. The search was updated on September 4, 2020 following an evaluation of the sensitivity of the L-OVE platform and Cochrane COVID-19 Study Register by Pierre et al[3], which identified all RCTs identified through the initial extensive search strategy.

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05156b5f5e032a&intervention_variable=603b9fe03d05151f35cf13dc&section=methods&classification=all.

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- Wanfang Database (updated every 2 weeks)
- CBM - Chinese Biomedical Literature Database (updated every 2 weeks)
- CNKI - Chinese National Knowledge Infrastructure (updated every 2 weeks)
- VIP - Chinese Scientific Journal Database (updated every 2 weeks)
- IRIS (WHO Institutional Repository for Information Sharing) (updated weekly)
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- Microsoft Academic (last searched: 23 August 2021)
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- ISRCTN registry (updated daily)
- Chinese Clinical Trial Registry (updated daily)
- IRCT - Iranian Registry of Clinical Trials (updated daily)
- EU Clinical Trials Register: Clinical trials for covid-19 (updated daily)
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- UMIN-CTR - UMIN Clinical Trials Registry (updated daily, via ICTRP search portal)
- JRCT - Japan Registry of Clinical Trials (updated daily, via ICTRP search portal)
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- Clinical Research Information Service (CRiS), Republic of Korea (updated daily, via ICTRP search portal)
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2) The Cochrane Covid-19 Study Register

Details related to the search performed by this register and the process are described here: https://community.cochrane.org/about-covid-19-study-register. It is a specialised register built within the Cochrane Register of Studies (CRS) and is maintained by Cochrane Information Specialists. The register contains study reports from several sources, including:

- daily searches of PubMed
- daily searches of ClinicalTrials.gov
- weekly searches of Embase.com
- weekly searches of the WHO International Clinical Trials Registry Platform (ICTRP)
- weekly searches of medRxiv
- monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)

3) Retraction Watch

We also searched the Retraction Watch Database for retracted studies (retractionwatch.com/retracted-coronavirus-covid-19-papers/).

Screening

We used an Excel spreadsheet to document search dates and citations identified. The Rayyan QCRI software (https://www.rayyan.ai/) was used to manage the records and data obtained for screening. Duplicates were removed, then title/abstract screening and full-text consideration were done by pairs of researchers, in duplicate and independently, with a third researcher resolving any disagreements.

Table S1: Description of RCTs that were retracted or removed before the search date

Reference	Treatment	Publication type	Registration number	Retracted date	Reason for retraction	Link to retraction note
Bosaeed M, SSRN, 2021	Favipiravir	Preprint	NCT04392973	Not reported	Not reported	https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3829663
Dabbous HM, Arch Virol, 2021	Favipiravir	Journal article	NCT04351295	2021-11-22	Methodological concerns	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8608235/
Dabbous HM, Sci Rep, 2021	Favipiravir	Preprint to Journal article	NCT04349241	2021-09-18	Methodological concerns	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8462367/
Elgazzar A, Research Square, 2021	Ivermectin	Preprint	NCT04668469	2021-07-14	Potential fabrication and plagiarism	https://grftr.news/why-was-a-major-study-on-ivermectin-for-covid-19-just-retracted/
Ghati N, SSRN, 2021	Atorvastatin and Aspirin	Preprint	CTRI/2020/07/026791	Not reported	Not reported	https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3820512
McCoy J, Frontiers, 2021	Proxalutamide	Preprint to Journal article	NCT04446429	2022-06-08	Methodological concerns	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9226906/
Pott-Junior H, Toxicology Reports, 2021	Ivermectin	Journal article	NCT04431466	2022-05-02	Methodological concerns and insufficient reporting	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9060540/
Samaha AA, Viruses, 2021	Ivermectin	Journal article	Not reported	2021-09-18	Error and potential falsification	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8577689/
Youssef J, SSRN, 2021	Aviptadil	Preprint	NCT04311697	Not reported	Not reported	https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3794262

Table S2: Characteristics of unpublished and published RCTs

Characteristics		**Total preprint RCTs** n = 177 (%)	**Preprint–Article RCTs** n = 109 (%)	**Preprint only RCTs** n = 68 (%)
Sample size, median (IQR)		120 (60–388)	150 (71–464)	85 (49–287)
Registration timing, n (%)	Prospective	133 (75)	83 (76)	50 (74)
	Retrospective	42 (24)	25 (23)	17 (25)
	Not reported/unclear	2 (1)	1 (1)	1 (1)
Funding type, n (%)	Industry/mixed	101 (57)	65 (60)	36 (53)
	Public	57 (32)	34 (31)	23 (34)
	Others	19 (11)	10 (9)	9 (13)
Study centers, n (%)	Single	56 (32)	30 (28)	26 (38)
	Multicenter	121 (68)	79 (72)	42 (62)
Overall risk of bias[⁑], n (%)	Low	18 (10)	13 (12)	5 (7)
	Some concerns	141 (80)	87 (80)	54 (79)
	High	18 (10)	9 (8)	9 (13)
Setting, n (%)	Hospital	142 (80)	93 (85)	49 (72)
	Outpatient clinic	35 (20)	16 (15)	19 (28)
Geographical location[‡], n (%)	High-income countries	73 (41)	42 (39)	31 (46)
	Low-/middle-income countries	79 (45)	49 (45)	30 (44)
	Countries of different income levels	25 (14)	18 (17)	7 (10)
Preprint post[§], n (%)	< 6 months	29 (16)	21 (19)	8 (12)
	6–12 months	57 (32)	45 (41)	12 (18)
	> 12 months	91 (51)	43 (39)	48 (71)

RCT, randomized controlled trial; Preprint only, preprint RCTs that were never published; Mixed, industry and public funding; Others, no funding/not reported/unclear

[†]Number of days between preprint post and journal article publication online

[⁑]Highest risk of bias assessed for any outcome in any domain

[‡]World Bank Country Income Classifications [2]

[§]Relative to March 2020 i.e., start of the pandemic

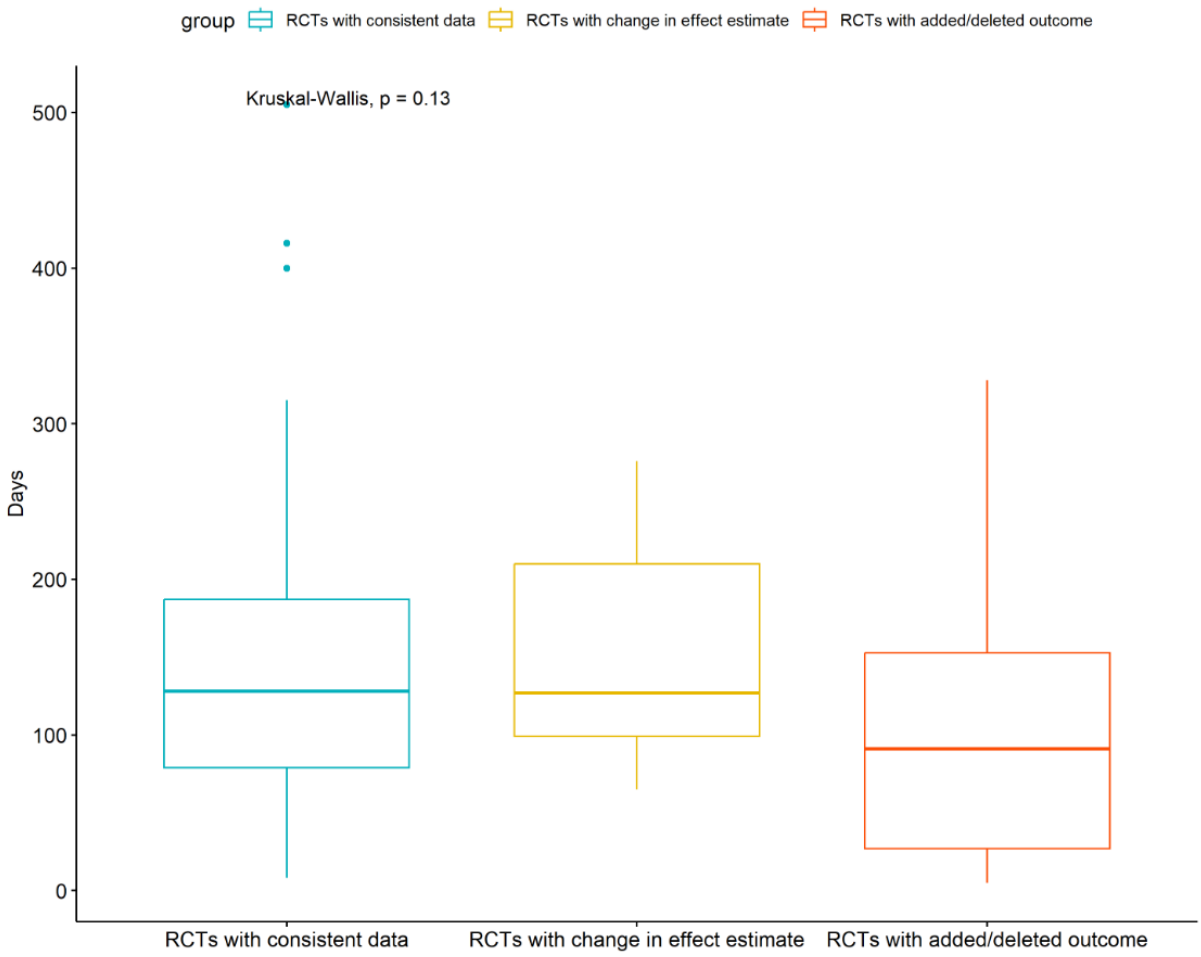

Figure S1: Relationship between delay to publication and discrepancies in preprint-article RCTs

References S1

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2. World Bank Country and Lending Groups – World Bank Data Help Desk. Accessed November 17, 2022. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups

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Annex 3. Supplementary article files for Davidson et al, BMJ Evidence-Based Medicine *[under review]*

Methods S1. Search Strategy; Screening

Methods S2. Dates for individual treatment comparisons; COVID-NMA review pre-specified outcomes; Risk of Bias assessment; Outcome Reporting Bias assessment

Table S1. Standards for Reporting Qualitative Research (SRQR) Checklist

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- daily searches of ClinicalTrials.gov
- weekly searches of Embase.com
- weekly searches of the WHO International Clinical Trials Registry Platform (ICTRP)
- weekly searches of medRxiv
- monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)

3) Retraction Watch

We also searched the Retraction Watch Database for retracted studies (retractionwatch.com/retracted-coronavirus-covid-19-papers/).

Screening

We used an Excel spreadsheet to document search dates and citations identified. The Rayyan QCRI software (https://www.rayyan.ai/) was used to manage the records and data obtained for screening. Duplicates were removed, then title/abstract screening and full-text consideration were done by pairs of researchers, in duplicate and independently, with a third researcher resolving any disagreements.

Methods S2

Dates for individual treatment comparisons

Treatment comparison	Date of last search
Antivirals	**14/12/2022**
except, Atazanavir + Ritonavir + Dolutegravir + HCQ vs HCQ + Lopinavir-Ritonavir	
Favipiravir + Interferon beta-1b vs HCQ	
HCQ vs Remdesivir	
HCQ + Ribavirin vs Standard care	28/02/2022
HCQ + Sofosbuvir vs HCQ + Lopinavir-Ritonavir	
Ivermectin vs Lopinavir-Ritonavir	
Lopinavir-Ritonavir vs HCQ	
Lopinavir-Ritonavir + Interferon beta-1a vs HCQ	
Interferons	**14/12/2022**
except, Interferon kappa + TFF2 vs Standard care	28/02/2022
Kinase inhibitors	**14/12/2022**
Corticosteroids	**14/12/2022**
Monoclonal antibodies	**14/12/2022**
Other immunomodulators	**14/12/2022**
Convalescent plasma	**14/12/2022**
Other antimicrobials (antibiotics, antimalarials, antiparasitics)	**14/12/2022**
NSAIDs and Anti-inflammatories	**14/12/2022**
Antithrombotic (antiplatelet, anticoagulant, thrombolytic drug)	**14/12/2022**
Other Advanced therapy medicinal products (ATMP)	**14/12/2022**
Others	**28/02/2022**
except, Bromhexine vs Standard care	
Dutasteride vs Placebo	21/01/2022
Finasteride vs Standard care	
Progesterone vs Standard care	
a-Lipoic acid vs Placebo	
Ammonium chloride vs Placebo	
Combined metabolic cofactor supplementation vs Placebo	
Compound 21 vs Placebo	
Famotidine vs Standard care/Placebo	22/10/2021
KB109 vs Standard care	
Mycobacterium vaccae vs Standard care	
N-acetylcysteine vs Placebo	
Sitagliptin vs Standard care	
Vitamin C vs Zinc	

Vitamin C vs Vitamin C + Zinc	
Vitamin C vs Standard of care/Placebo	
Vitamin C + Zinc vs Standard care	
Vitamin D vs Standard care/Placebo	
Vitamin D 5000 IU vs Vitamin D 1000 IU	
Zinc vs Standard care/Placebo	
Zinc vs Vitamin C + Zinc	

HCQ, hydroxychloroquine

COVID-NMA review pre-specified outcomes

- Clinical improvement (D28/D60) defined as a hospital discharge or improvement on the scale used by trialists to evaluate clinical progression and recovery.
- WHO Clinical Progression Score of level 7 or above (i.e., mechanical ventilation +/- additional organ support (extra corporeal membrane oxygenation (ECMO), vasopressors or dialysis) or death (D28/D60)
- All-cause mortality (D28/D60)
- Hospitalization or death (outpatient setting)
- Incidence of any adverse events (AEs)
- Incidence of serious AEs (SAEs)
- Incidence of viral negative conversion
- Time to clinical improvement
- Time to WHO Clinical Progression Score level 7 or above
- Time to death
- Time to viral negative conversion

Risk of Bias assessment

Risk of bias assessments were conducted in duplicate for the COVID-NMA living systematic using the Cochrane Risk of Bias (RoB) 2 tool for RCTs.(2) RoB was assessed for all outcomes, at all timepoints using an online tool. Assessments were performed by researchers who participated in a comprehensive training program that included performing data extraction and RoB assessments with a team of experts. Quality control of the data was done regularly by the Cochrane Bias Methods group. The RoB 2 tool is structured into five domains: 1) risk of bias arising from the randomization process; 2) risk of bias due to deviations from intended interventions; 3) risk of bias due to missing outcome data; 4) risk of bias in measurement of the outcome; and 5) risk of bias in selection of the reported result. Each domain in the assessment of RoB was addressed using signaling questions to which the responses are either “yes”, “probably yes”, “probably no”, “no”, and “no information”. An algorithm analyzed the responses to generate an assessment for each domain, which were categorized as “low”, “some concerns”, or “high”.

Outcome Reporting Bias assessment

Outcome reporting bias (ORB) assessment was also available for all outcomes.(3) A judgement was determined after verifying that outcomes in the prospective register, protocol or SAP were reported in the main article. This was categorized as:

A. A study result is available for inclusion in the synthesis, as reported in the clinical trial registry or trial protocol.
B. A study result is available for inclusion in the synthesis, but not reported in the clinical trial registry or trial protocol.
C. No study result is available for inclusion, (probably) because the P value, magnitude or direction of the results were considered unfavorable by the study investigators. The outcome was planned in the clinical trial registry or protocol.
D. No study result is available for inclusion, (probably) because the outcome was not assessed, or for a reason unrelated to the P value, magnitude or direction of the results. The outcome is not reported in the clinical trial registry or trial protocol.
E. No study result is available for inclusion, and it is unclear if the outcome was assessed in the study. There is no clinical trial registry or trial protocol available for assessment
F. A study result is available for inclusion in the synthesis. There is no clinical trial registry or trial protocol available for assessment.
G. A study result is available, but data is not extractable. Outcome is reported/not reported in the clinical trial registry or protocol.

References S1

1. Pierre O, Riveros C, Charpy S, Boutron I. Secondary electronic sources demonstrated very good sensitivity for identifying studies evaluating interventions for COVID-19. J Clin Epidemiol. 2022 Jan;141:46–53.
2. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019 Aug 28;366:l4898.
3. Kirkham JJ, Altman DG, Chan AW, Gamble C, Dwan KM, Williamson PR. Outcome reporting bias in trials: a methodological approach for assessment and adjustment in systematic reviews. BMJ. 2018 Sep 28;362:k3802.