BRIEF RESEARCH COMMUNICATION

# Role of Statin and Clinical Outcomes in COVID-19 Patients: A Protocol for Systematic Review and Meta-analysis of Randomized Controlled Trials

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## Abstract

**Objectives:** Statins have significant therapeutic implications in patients having high cardiovascular risk or preexisting cardiovascular disorders. Exploring the correlation between statin therapy and outcomes in coronavirus disease 2019 (COVID-19) patients is the objective of the current meta-analysis.

**Data sources:** PubMed, Web of Science, Google Scholar, and Cochrane Library database, as well as preprint services like medRxiv, Research Square, and Social Science Research Network (SSRN).

**Study selection:** All citations will be double-checked, and any differences will be examined and, if required, addressed with the help of a third author. Two authors will separately evaluate abstracts and titles of all potentially essential citations in two phases.

**Data extraction:** A data extraction table will be used to extract published outcomes from each study.

**Data synthesis:** The pooled risk ratio with a 95% confidence interval (CI) will be used to compute pooled effect size. DerSimonian and Laird random-effects models will be employed for heterogeneity greater than 50%; otherwise, the fixed-effects model will be implemented. To construct study weights, an inverse variance approach will be employed, and a funnel plot will also be examined to see whether there is any publishing bias.

**Trial registry:** International prospective register of systematic reviews (Prospero) acquired a prospective registration for this meta-analysis in the trial registry (CRD42022304331).

**Study highlights:** The evidence supporting the use of statins in COVID-19 patients will be reviewed in this study. Early statin has been correlated to a decreased risk of unfavorable effects in patients with COVID-19. At the time, these trials were predominantly observational, and all published meta-analyses were based on observational studies. Randomized controlled trials have recently been performed for reliable evidence, but no meta-analyses.

**Keywords:** Coronavirus disease 2019, Outcome, Statin.

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## Introduction

Nearly 3 years after the first COVID-19 infection, healthcare systems throughout the world faced major hurdles; as a result, understanding the qualities that portend unfavorable COVID-19 outcomes is critical. A lack of resources and treatment has resulted in the deaths of many people.[1] It's still a concern that a few organs may suffer long-term damage as a result of infection, and there's no functional data or imaging for COVID-19 patients.[2] In these uncertain times, using risk stratification methods for protocolized admission and determining the ceiling of care should aid decision-making and generate transparency. There has been a rise in interest in finding treatments that can minimize the disease's morbidity and death since the beginning of the pandemic. In the current situation, however, repurposing existing medications is a far more expedient and cost-effective option than developing a whole new drug. While we wait for more vaccines to be distributed around the world, one option is to repurpose existing therapeutics.

Proving statin efficacy in patients who were hospitalized or admitted with COVID-19, as well as those at high cardiovascular risk or with preexisting cardiovascular disease who have not yet been diagnosed with the disease, would have major therapeutic consequences.

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The pleiotropic effects of statins, which include immunomodulatory, antiinflammatory, antithrombotic, and antioxidant properties, as well as an increase in the expression of the angiotensin-converting enzyme 2 (ACE2) receptor, may assist COVID-19 patients to reduce cytokine storm.[3–6]

The relationship between statins and COVID-19 is attracting the attention of an increasing number of researchers. Numerous observational studies have established that starting statin therapy early in COVID-19 patients lowers the risk of unfavorable outcomes.[7,8] All of these studies are currently observational, and all systematic reviews and meta-analyses published so far have been based on observational studies. At present, randomized controlled trials (RCTs) have been published[9,10] for obtaining reliable evidence; however, no meta-analysis has been published so far.

### Review Questions

A systematic review and meta-analysis of RCTs are needed to answer the following research questions:

- To determine the causal relationship between statin usage at different doses and severe COVID-19 consequences.
- There's a correlation between statin use and negative outcomes, including mortality, disease severity, intensive care unit (ICU) admissions, and mechanical ventilation.

The results will help researchers and clinicians better understand how to optimally prescribe a statin to reduce adverse clinical outcomes.

### Inclusion Criteria

#### *Participants/Population*

Patients with COVID-19 were diagnosed using the reverse transcription polymerase chain reaction test. The criteria for exclusion were as follows—a 2×2 table of results cannot be extracted from retrospective or prospective cohort studies, case reports, case series (specifying only phenomenology without outcome assessment and with a sample size below 10), letter to the editor, review articles, abstracts, comments, or conference presentations.

#### *Intervention*

The statin intervention group consisted of people who took statins before or during their COVID-19 hospitalization.

#### *Comparators*

A nonintervention control group will provide as that of the comparator; that is, patients who did not get statins made-up the control group.

#### *Outcomes*

The outcomes will include all-cause mortality and a cumulative COVID-19 endpoint of severe disease, which is defined as a severe/critical course of disease that requires intubation, mechanical ventilation, and/or admission to an ICU.

### Types of Studies

For inclusion, only RCTs that have been published in English or another language will be considered, and other study designs will be excluded.

## Materials and Methods

International prospective register of systematic reviews (PROSPERO) CRD42022304331 has been assigned to this systematic review and meta-analysis. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[11] and the Cochrane Handbook for Systematic Reviews of Interventions[12] were used to construct the design and methodology.

### Data Sources

The search strategy sought to gather as much pertinent information as was feasible. Along with PubMed, Google Scholar, Web of Science, and the Cochrane Library, we will also search preprint sites like medRxiv, Research Square, and SSRN for articles. We'll also go over the Clinical Trials Database of the National Institutes of Health (http://www.ClinicalTrials.gov/), the International Clinical Trials Registry Platform of the World Health Organization (https://www.who.int/ictrp/en/), and the Clinical Trials Registry-India (http://www.ctri.nic.in). There won't be a language barrier, but only COVID-19 patients will have access to the filter. In order to make sure we don't overlook any study, we will additionally search for pertinent journal references.

Each reference will go through two rounds of evaluation, and any disagreements will be discussed and, if necessary, arbitrated by a third author. Two authors (JP and PKB) will independently and often examine all potentially significant references in two phases, first assessing titles and abstracts and then concluding publications for those who meet the requirements. A third author will resolve any disagreements (KS). The exclusion criteria will be kept under observation during the article assessment period.

### Search Strategy

To find the pertinent articles for our meta-analysis, we will search the electronic databases Google Scholar, PubMed, Web of Science, Cochrane Library, and Clinical Trial Registry. The literature will be searched separately by two authors for studies that discuss the role of statin medication in COVID-19 patients. Along with the Boolean operators "COVID-19" or "severe acute respiratory syndrome coronavirus 2" or "COV" or "statin" or "β-hydroxy β-methylglutaryl-CoA reductase" or "statins", the following search terms will be utilized. Only human subjects will be used in the search. The final hunt will end on the 15$^{th}$ March, 2023.

### Data Management

The articles that were acquired from various databases using the above mentioned comprehensive search technique will be organized using EndNote software. The studies that will be derived from various databases will be stored in a single EndNote library. Duplication of papers will be reviewed and removed after all studies have been uploaded to the library.

### Study Selection

Titles and abstracts will be reviewed by two independent authors, who will then go through the whole paper to see if it satisfies the inclusion and exclusion criteria. Studies that are qualified for full-text evaluation will thus be chosen. A third author will resolve any differences if there are any. In order to explain concerns and make the necessary adjustments to the standard method, the κ and percent agreement will be established and utilized as a reference. The PRISMA flow diagram will demonstrate how certain inclusion and exclusion criteria were applied in order to locate and include studies.

### Assessment of Methodological Quality

To evaluate the research's methodological quality, the "Cochrane risk of bias assessment tool" for randomized controlled trials will be

employed.[13] The following biases will be evaluated and graded—low-risk, high-risk, and uncertain risk. Selection bias, performance bias, detection bias, and attrition bias are among these biases.

### Data Extraction and Quality Assessment

Two authors will use a different data abstraction form to collect data. Conflicts between two authors who are doing data extraction will be handled in a two-step process—first, they will be discussed; if they are not addressed, a third author will be asked to perform independent data extraction before the disagreement is resolved. Studies' features, demographic information, findings, and risk of bias will all be abstracted.

### Data Synthesis

To get data, either direct extraction or indirect computation will be employed. Basic study parameters such as author, year, study country, sample size, duration of data collection, population, age, gender, statin regimen, control, comorbidity, and outcomes will be shown in summary tables. The meta-analysis will only include studies that have enough quantitative data to compute an effect size.

The pooled risk ratio with a 95% CI will be considered in our meta-analysis to calculate the pooled effect size. If the heterogeneity is greater than 50%, the DerSimonian and Laird random-effects models will be applied; otherwise, the fixed-effects model will be. Research weights will be produced using the inverse variance method. We will assess research heterogeneity using Cochran's Q test.[14] We'll also look at the funnel plot to check for any bias in the publication. Meta-regression analysis will also be used to investigate potential sources of study heterogeneity.

### Assessing Certainty in the Findings

The grading of recommendations, assessment, development, and evaluations method will be used to rate the certainty of evidence. The summary of Findings will prepare to represent the directness, precision, indirectness and publication bias. GRADEpro software will be used to conduct these analyses.

## Discussion

It is already evident that statins are related to reducing COVID-19 mortality, as evidenced by previous studies.[15–17] Statin users are more likely to be older and have more comorbid conditions than nonusers, which raises the mortality risk.[17,18] When the adjusted and unadjusted data were combined, the association between statin therapy and mortality could not be established since the positive benefits of statins could be counterbalanced by higher risks from host variables. Some speculated that statins might affect COVID-19 patients, noting a greater chance of developing acute respiratory distress syndrome (ARDS), among other factors. Because of a number of factors, including an increased chance of developing ARDS, statins were assumed to have an impact on COVID-19 patients.

The proposed study would contribute to the body of evidence regarding the use of statins to avoid multiorgan failure and ARDS, both of which can happen during the acute stages of COVID-19 infection. By controlling cytokine upregulation, ACE2 expressions, and the immunological response, statins may help COVID-19 patients delay the onset of severe lung damage and ARDS.[6,19] Nuclear factor B, a protein that encourages inflammatory responses during infections, has been found to be suppressed by statins in studies.[20] Additionally, cytokine storms, which can happen in severe viral infections like COVID-19, can be treated with statins.[21] Directionality problems will be examined using the advantages of RCTs and pooled analysis.

It has never been possible to undertake a systematic review and meta-analysis of RCTs to determine the impact of statins on the clinical outcomes of COVID-19 patients. The results of the current meta-analyses will be used to summarize the information previously available on the impact of statins on the outcomes of COVID-19 patients.

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