

# Statin and mortality in COVID-19: a systematic review and meta-analysis of pooled adjusted effect estimates from propensity-matched cohorts

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## ABSTRACT

**Purpose** Statin potentially improved outcome in patients with COVID-19. Patients who receive statin generally have a higher proportion of comorbidities than those who did not, which may introduce bias. In this meta-analysis, we aimed to investigate the association between statin use and mortality in patients with COVID-19 by pooling the adjusted effect estimates from propensity-score matching (PSM) matched studies or randomised controlled trials to reduce bias.

**Methods** A systematic literature search using the PubMed, Scopus and Embase databases were performed up until 1 March 2021. Studies that were designed the study to assess statin and mortality using PSM with the addition of Inverse Probability Treatment Weighting or multivariable regression analysis on top of PSM-matched cohorts were included. The effect estimate was reported in term of relative risk (RR).

**Results** 14 446 patients were included in the eight PSM-matched studies. Statin was associated with decreased mortality in patients with COVID-19 (RR 0.72 (0.55, 0.95),  $p=0.018$ ;  $I^2$ : 84.3%,  $p<0.001$ ). Subgroup analysis in patients receiving statin in-hospital showed that it was associated with lower mortality (RR 0.71 (0.54, 0.94),  $p=0.030$ ;  $I^2$ : 64.1%,  $p<0.025$ ). The association of statin and mortality was not significantly affected by age (coefficient:  $-0.04$ ,  $p=0.382$ ), male gender (RR 0.96 (0.95, 1.02),  $p=0.456$ ), diabetes (RR 1.02 (0.99, 1.04),  $p=0.271$ ) and hypertension (RR 1.01 (0.97, 1.04),  $p=0.732$ ) in this pooled analysis.

**Conclusion** In this meta-analysis of PSM-matched cohorts with adjusted analysis, statin was shown to decrease the risk of mortality in patients with COVID-19.

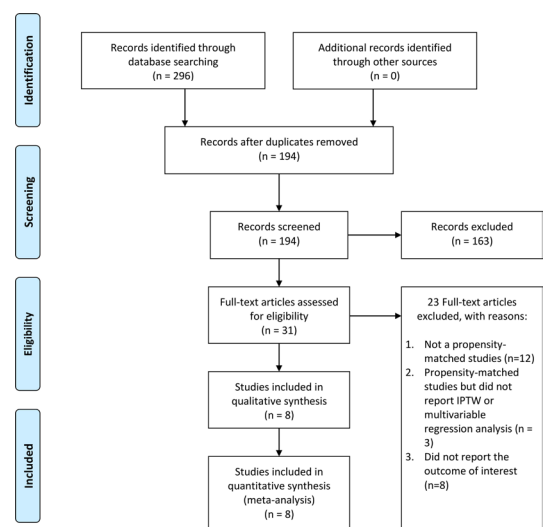
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## INTRODUCTION

Patients with COVID-19 with comorbidities such as diabetes, hypertension, cerebrovascular and cardiovascular diseases usually have a more severe infection compared with those without.<sup>1–7</sup> Patients with comorbidities usually receive drugs for treatment of chronic diseases.<sup>8,9</sup> During the pandemic, questions on whether we should discontinue these drugs in COVID-19 patients arise. On top of that, many drugs that have

been touted for treating COVID-19 fails. Thus, more importantly, can we repurpose these drugs to reduce in-hospital mortality in patients with COVID-19?

Statin is lipid-lowering drug with pleiotropic property.<sup>10</sup> It has an important immunomodulatory property that may be useful in attenuating inflammation.<sup>11</sup> Several studies have shown its potential benefit in patients with COVID-19.<sup>12,13</sup> However, patients who receive statin generally have a higher proportion of comorbidities than those who did not.<sup>13</sup> These may cause selection bias in observational studies and falsely increase the risk of mortality in these population. Ideally, randomised controlled trials are required. However, due to lack of randomised controlled trials, propensity-score matching (PSM) may be done to match the baseline characteristics between those receiving statin and those who did not in the observational studies, thus reducing bias. Adjusted analysis on top of a PSM-matched cohort provides more accurate results. The result of meta-analysis depends greatly on the included studies. Thus, by pooling results from these studies, we will be able to provide a better analysis. In this meta-analysis, we aimed to investigate the association between statin use and mortality in patients with COVID-19 by pooling

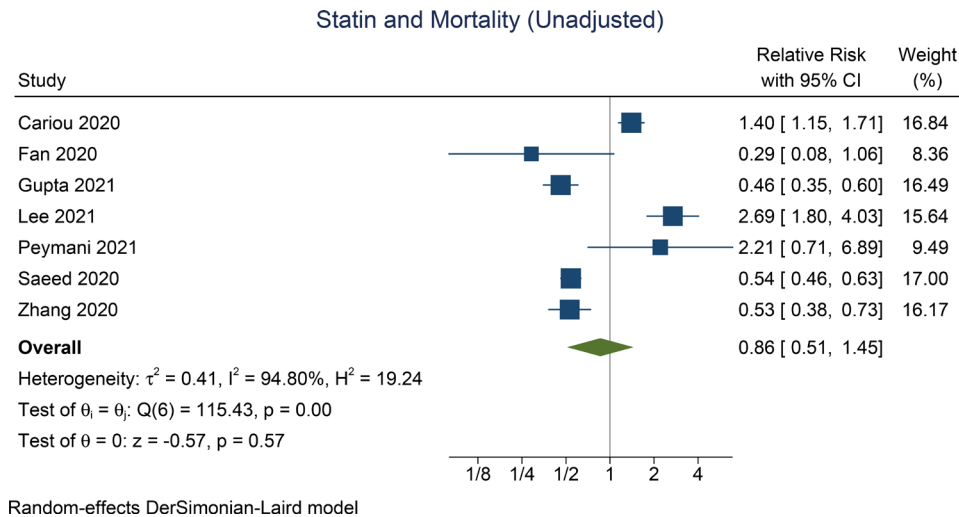


**Figure 1** PRISMA flowchart. IPTW, Inverse Probability Treatment Weighting; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

**Table 1** Characteristics of the included studies

Authors	Original samples	Patients setting	Types of statin	Samples (matched)	PSM ratio	Age (years)	Male (%)	CVD (%)	T2DM (%)	HT (%)	Statin use	Outcome	Adjustment	NOS
Caroui <i>et al</i> <sup>20</sup>	NR	Hospitalised	Unknown	2449	1:1	N/A	N/A	N/A	N/A	N/A	Routine. Continuation unclear	28 days	IPTW	8
Fan <i>et al</i> <sup>15</sup>	2147	Hospitalised	Atorvastatin (69.9) Rosuvastatin (29.6) Pravastatin (0.5%)	512	1:1	65	41	21	20	51	Routine and continued in-hospital	In-hospital	Multivariable Cox-regression age, gender, TC, triglyceride, LDL, procalcitonin, BNP	8
Gupta <i>et al</i> <sup>12</sup>	2626	Hospitalised	Unknown	1296	1:1	70	45	14	47	68	Routine	In-hospital (30 days)	Multivariable logistic regression age, gender, comorbidities, medications	8
Lee <i>et al</i> <sup>16</sup>	10448	Hospitalised	All	1599	1:2	65	34	19	57	71	Routine. Continuation unclear	60 days	Multivariable Cox-regression age, sex, history of comorbidities	8
Oh <i>et al</i> <sup>17</sup>	7780	Hospitalised	Unknown	2333	1:1	N/A	N/A	N/A	N/A	N/A	Routine and continued in-hospital	In-hospital	Multivariable logistic regression factors unclear	8
Peymani <i>et al</i> <sup>18</sup>	150	Outpatients+hospitalised	Atorvastatin (94.7) Rosuvastatin (2.7) Simvastatin (2.7)	150	1:1	63	59	2	21	29	Routine and continued	27 days	Multivariable Cox-regression factors unclear	8
Saeed <i>et al</i> <sup>19</sup>	4252	Hospitalised	Atorvastatin (76) Pravastatin (5) Rosuvastatin (1) Simvastatin (18)	1802	1:1	N/A	N/A	N/A	N/A	N/A	In-hospital	In-hospital	IPTW	9
Zhang <i>et al</i> <sup>13</sup>	13981	Hospitalised	Atorvastatin (83.2) Rosuvastatin (15.6)	4305	1:4	N/A	N/A	N/A	N/A	N/A	In-hospital	28 days	Multivariable logistic regression age, gender, and SpO <sub>2</sub> at admission	8

Age, male, CVD, T2DM and HT refer to the PSM cohort. BNP, brain natriuretic peptide; CVD, cardiovascular diseases; HT, hypertension; IPTW, inverse probability of treatment weighting; LDL, low-density lipoprotein; N/A, not applicable/available; NOS, Newcastle-Ottawa Scale; PSM, propensity-score matching; SpO<sub>2</sub>, O<sub>2</sub> saturation; TC, total cholesterol; T2DM, type 2 diabetes mellitus.



**Figure 2** Forest plot showing the association between statin and mortality (unadjusted).

the adjusted effect estimates from propensity-matched studies or randomised controlled trials.

## MATERIALS AND METHODS

This is a Preferred Reporting Items for Systematic Reviews and Meta-analyses compliant systematic review and meta-analysis. This study is registered in PROSPERO.

### Search strategy and study selection

A systematic literature search using PubMed, Scopus and Embase databases was performed using the terms '(SARS-CoV-2 OR COVID-19) AND (statin)' up until 1 March 2021. Two authors performed screening of title/abstracts independently. The eligibility of the potential articles was then assessed by evaluating the full-text against the inclusion and exclusion criteria. Discrepancies were resolved by discussion.

### Inclusion and exclusion criteria

The studies were included if they met all of the following criteria: (1) randomised trials or observational studies reporting patients with COVID-19, (2) reporting statin use, (3) mortality

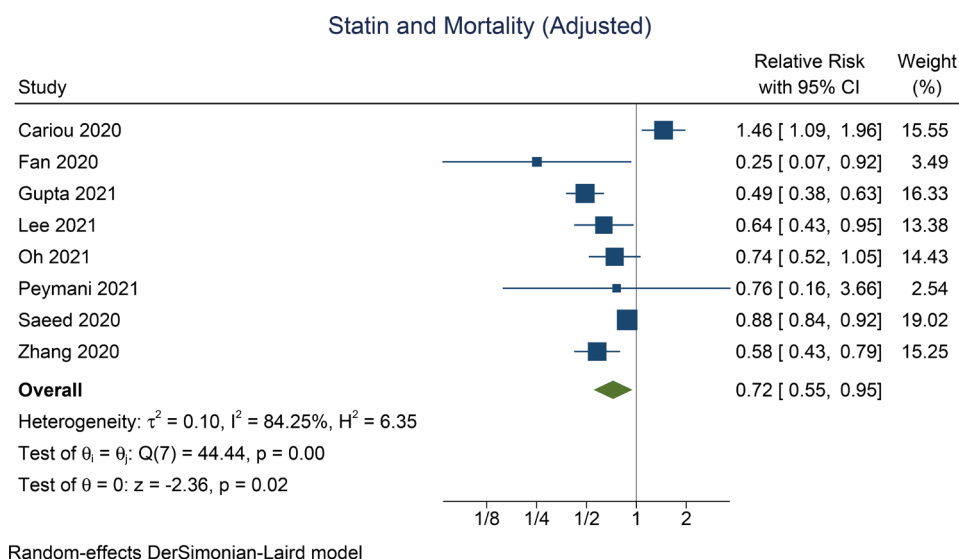
and (4) designed the study to assess statin and mortality using PSM with addition of Inverse Probability Treatment Weighting (IPTW) or multivariable regression analysis on top of PSM-matched cohorts.

The studies were excluded if they meet one of the following criteria: (1) preprints, (2) abstracts, (3) conference papers, (4) review articles, (5) nonresearch letters and (6) commentaries. There was no language restriction applied

### Data extraction

Extraction of data were performed by two independent authors for the first author, study design, sample size, baseline characteristics of patients, characteristics of analysis, the intervention and the outcome. Discrepancies were resolved by discussion.

Risk of bias assessment of the included studies was performed by two independent authors using the Newcastle-Ottawa Scale (NOS).<sup>14</sup> NOS consists of three domains: (1) selection, (2) comparability and (3) outcome. Discrepancies were resolved by discussion. The certainty of evidence was assessed based on Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework.



**Figure 3** Forest plot showing the association between statin and mortality (adjusted).

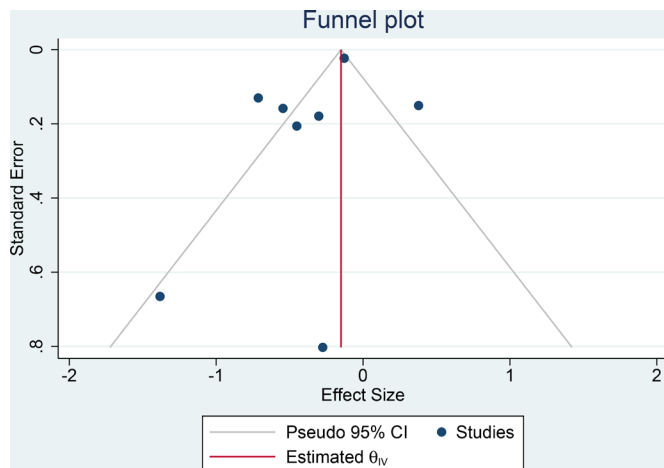


Figure 4 Funnel plot for publication bias.

### Intervention and outcome

The intervention group was statin, defined as statin used prior or/and during hospitalisation for COVID-19. The control group was patients who did not receive statin. The outcome was mortality, defined as clinically validated death or nonsurvivor. The effect estimate was reported in term of relative risk (RR), which is defined as either OR, risk ratio or HR.

### Statistical analysis

For pooling of unadjusted effect estimates, dichotomous data were extracted and calculated unless the study only reported univariable/unadjusted effect estimate. For the adjusted effect estimates, Der-Simonian Laird random-effects meta-analysis by extracting the point estimate and/or CI for reported associations and converting it into log form and using inverse variance-weighted meta-analysis was performed. Random effect analysis was performed regardless of the statistical heterogeneity, based on the assumption that there is a qualitative heterogeneity among most of the studies. P value of  $\leq 0.05$  was considered as statistically significant. Heterogeneity was assessed by using Cochran's Q test and  $I^2$  statistics; in which  $I^2$  values above 50% and p value below 0.10 indicate significant heterogeneity. Subgroup analyses were performed for patients receiving in-hospital statin. To assess publication bias and small-study effects, we perform funnel-plot analysis and Egger's test. Restricted maximum likelihood random-effects meta-regression analysis was performed to explore heterogeneity and address factors (age, sex, diabetes and hypertension) that may potentially affect the association between statin and mortality. STATA V.16.0 was used to perform meta-analysis.

## RESULTS

### Baseline characteristics

Of 14 446 patients were included in eight studies (figure 1).<sup>12 13 15–20</sup> For the analysis, two studies used IPTW and six studies used multivariable regression analysis. Risk of bias assessment using NOS showed that the studies have low risk of bias. However, missing data are significant or inadequately reported. The characteristics of the included studies are presented in table 1.

### Statin and mortality

The pooled estimate for unadjusted analysis demonstrates that statin was not associated with change in mortality (RR 0.86 (0.51, 1.45),  $p=0.568$ ;  $I^2: 94.8\%$ ,  $p<0.001$ ) (figure 2). Statin was associated with decreased mortality in patients with COVID-19 (RR 0.72 (0.55, 0.95),  $p=0.018$ ;  $I^2: 84.3\%$ ,  $p<0.001$ ) (figure 3). Subgroup analysis in patients receiving statin in-hospital showed that it was associated with lower mortality (RR 0.71 (0.54, 0.94),  $p=0.030$ ;  $I^2: 64.1\%$ ,  $p<0.025$ ).

#### Publication bias

The funnel plot was asymmetrical (figure 4), and Egger's test did not show evidence of small-study effects ( $p=0.306$ ). Based on GRADE framework, this pooled effect estimate has a low certainty of evidence (table 2).

The association of statin and mortality was not significantly affected by age (coefficient:  $-0.04$ ,  $p=0.382$ ), male gender (RR 0.96 (0.95, 1.02),  $p=0.456$ ), diabetes (RR 1.02 (0.99, 1.04),  $p=0.271$ ) and hypertension (RR 1.01 (0.97, 1.04),  $p=0.732$ ) in this pooled analysis.

## DISCUSSION

In this meta-analysis of PSM-matched cohorts with adjusted analysis, statin was shown to decrease the risk of mortality in patients with COVID-19. Subgroup analysis in patients receiving in-hospital statin also showed lower rate of mortality.

We observe significant heterogeneity in both main analysis and subgroup analysis, this is also accompanied by asymmetrical funnel plot, which indicates publication bias. Thus, despite the well-designed studies using PSM and IPTW/multivariable regression analysis for statin and the outcome, the certainty of evidence remains low. Possibly there were confounding factors that were not adequately reported or analysed by the included studies that may contribute to the unexplained heterogeneity. Differences in statin types and dosage, as well as compliance, may affect the outcome. Randomised controlled trials are required for definite conclusion and there are several studies registered in clinicaltrials.gov. Nevertheless, this study is able to show that statin was associated with decreased mortality in adjusted, but not unadjusted analysis, which provides answer to

Table 2 GRADE assessment

#### Certainty assessment

Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect estimate (95% CI)	Certainty
8	Observational studies	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected* all plausible residual confounding would reduce the demonstrated effect	RR 0.72 (0.55 to 0.95)	LOW

Meta-regression analysis.  
\*Asymmetrical funnel plot.  
RR, relative risk.

the aim of our study. This also provides distinction to previous meta-analysis that showed limited effect of statin in patients with COVID-19.<sup>21</sup>

The use of statin as an adjunct treatment for patients with COVID-19 has been considered because of their known immunomodulatory properties.<sup>11</sup> Statins have been traditionally used as lipid-lowering drugs in patients with cardiovascular and cerebrovascular diseases, diabetes mellitus as well as other systemic conditions. The presence of such comorbidities is associated with increased severity and mortality of COVID-19, and patients with these chronic conditions are frequently prescribed statins before contracting and during COVID-19 infection.<sup>4 5 22</sup> Cholesterol plays a crucial part in dysfunction of immunity, dysregulation of pro-inflammatory and anti-inflammatory cytokine secretion and in the onset and pathogenesis of acute respiratory distress syndrome (ARDS).<sup>23</sup> High levels of cholesterol contribute to the growth of atherosclerosis and also accumulate in immune cells, including macrophages, which provokes systemic inflammatory reactions, such as toll-like receptor and nuclear factor kappa-light-chain-enhancer of activated B cell (NF- $\kappa$ B) signalling.<sup>24–26</sup>

Statin exerts its pharmacologic effect by inhibiting the formation of isoprenoids, which are essential components of small GTPases (such as Rac, Rho and Ras) and in the consequential downregulation of redox-sensitive proinflammatory transcriptional factors (such as NF- $\kappa$ B). Through these actions, statin modulates immune response at various stages, including antigen presentation, immune cell adhesion and migration and cytokine generation.<sup>11</sup> The anti-inflammatory effects are clinically evident through a decrease in inflammatory biomarkers, including IL and C reactive protein.<sup>19</sup> The exaggerated immune response that results in cytokine storm is thought to be the mechanism underlying the development of COVID-19-induced complications, including ARDS, sepsis, disseminated intravascular coagulation and multiorgan failure.<sup>27 28</sup>

In addition, statin counteracts inflammation, neutralises oxidative stress by enhancing antioxidants and reducing reactive oxygen species and rectifies nitric oxide availability, endothelial function and integrity. These positive impacts contribute to the cardiovascular and lung protection from statin.<sup>11</sup> Given the beneficial effects of statin, any use can lead to less severe infection, better outcome and reduced risk of mortality during clinical course of COVID-19 infection.<sup>29</sup>

This drug is widely available at low cost, generally safe and well tolerated.<sup>11</sup> However, statin may induce several side effects such as myotoxicity and hepatotoxicity. Myalgia (more common), elevated creatine phosphokinase, rhabdomyolysis (rare) and consequently acute kidney injury, is a possible adverse event.<sup>26</sup> In some patients, statin may cause elevated liver enzyme and, rarely, liver injury in severe cases of COVID-19.<sup>29</sup> It remains controversial whether statin upregulates expression and signalling of ACE 2, an enzyme that serves as a port of entry for the novel coronavirus, and consequently predisposes to severe form and poor outcomes during COVID-19 infection.<sup>11 30</sup>

### Clinical implications

Statin should not be discontinued in patients with COVID-19. Moreover, discontinuing statin may cause increase adverse cardiovascular outcomes postpandemic.<sup>31</sup> In-hospital statin use has been shown to be associated with reduced mortality, however, the percentage of statin naïve patients was unknown. Thus, further randomised controlled trials are required for strong conclusion.

### CONCLUSION

In this meta-analysis of PSM-matched cohorts with adjusted analysis, statin was shown to decrease the risk of mortality in patients with COVID-19. Statin was associated with lower mortality in in-hospital statin subgroup.

#### Main message

- ▶ Statin was independently associated with decreased mortality in patients with COVID-19.
- ▶ Subgroup analysis in patients receiving statin in-hospital showed similar benefit.
- ▶ The association was not significantly affected by age, male gender, diabetes and hypertension.

#### Current research question

- ▶ Further randomised controlled trials are required for strong conclusion.
- ▶ The intensity of statin for this purpose remains to be determined.

#### What is already known on the subject

- ▶ Statin is lipid-lowering drug with pleiotropic property. It has an important immunomodulatory property that may be useful in attenuating inflammation.
- ▶ Several studies have shown statin's potential benefit in patients with COVID-19.
- ▶ However, patients who receive statin generally have a higher proportion of comorbidities than those who did not. These may cause selection bias in observational studies and falsely increase the risk of mortality in these populations.

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