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Original Article

# Association of Statin Therapy on Clinical Outcomes in Covid-19 Patients: An Updated Systematic Review and Meta-Analysis on All Related Evidences

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ABSTRACT

**Introduction:** Statins is a class of lipid-lowering drugs and our previous investigations showed that statins have antiviral effects and have a wound healing effect in the lung. This systematic review and meta-analysis aimed to evaluate the effects of statin therapy on mortality and clinical outcomes in COVID-19 patients.
**Methods:** A comprehensive search was conducted in international databases, including MEDLINE, Scopus, Web of Science, and Embase from December 1, 2019 until January 26, 2022 without any restriction in language. The random-effects model was used to estimate the pooled odds ratio (OR).
**Results:** The statin therapy overally was associated with decrease in odds of ventilation [pooled OR (95% CI): 0.85 (0.70 to 0.99)] and mortality [pooled OR (95% CI): 0.73 (0.66 to 0.81)] but had no effects on the ICU admission [pooled OR (95% CI): 0.93 (0.77 to 1.12)], oxygen therapy [pooled OR (95% CI): 0.85 (0.70 to 0.99)], recovery [pooled OR (95% CI): 1.85 (0.35 to 9.92)], kidney failure [pooled OR (95% CI): 1.01 (0.73 to 1.40)], hospitalization [pooled OR (95% CI): 1.45 (0.88 to 2.36)], asymptomatic disease [pooled OR (95% CI): 1.33 (0.24 to 7.44)], and ARDS [pooled OR (95% CI): 1.15 (0.88 to 1.49)].
**Conclusion:** The present meta-analysis showed that statin therapy was associated with a reduced risk of mortality and ventilation in patients with COVID-19 but had no effects on other clinical outcomes.

## Introduction

Acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of coronavirus disease 2019 (COVID-19) clinical syndrome, which began to spread into a global epidemic in early December 2019. This disease has caused significant socioeconomic burdens, complications, coinfections[1-4] and mortality worldwide.[5, 6]

People with cardiovascular diseases (CVD) and high blood pressure are identified as the

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high-risk group for SARS-CoV-2 infection, acute respiratory distress syndrome (ARDS), and death.[7-9] Angiotensin converting enzyme (ACE2) is a membrane-bound aminopeptidase that is specifically expressed in human cells, including in the heart and alveolar epithelial cells.[10] ACE2 may be a link between the use of statins, the angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), and COVID-19. It also plays an important role in the activation of the renin-angiotensin-angiotensinogen system.[11] ACE acts on angiotensin II to form angiotensin (1 to 7), which has antifibrinolytic, vasodilating, and diuretic functions. Statins regulate ACE2 expression and have pleiotropic function against oxidative stress and inflammation.[12] Statins perform as one of the β-Hydroxy β-methylglutaryl-CoA (HMG-CoA) inhibitors and a class of low-density lipoprotein (LDL) decreasing drugs in cardiovascular patients. Statins also act as the C-reactive protein (CRP) and pre-inflammatory cytokines levels reducer, anti-inflammatory, and immunological effects.[13-19] Statins are also known for their immunological and antiviral potential efficacy in pneumonia. In addition, statins may induce SARS-Co-V2 by binding to their primary protease.[20] In proven studies, in patients with pneumonia, hospital mortality was significantly reduced following statin therapy. It has been suggested that statins might be more effective in the treatment of patients infected by Ebola virus.[19] Although most of these studies confirmed that statins are beneficial for the clinical outcomes and prognosis in patients with pneumonia, some studies have shown that in-hospital mortality was significantly higher after statins treatment.[21] Therefore, whether statin usage is associated with reduced mortality in patients with pneumonia remains disputed. To our knowledge, there is no experimental or clinical evidence that statins are health effective for hospital outcomes in patients with COVID-19 and there are not many available data about statin therapy in patients with COVID-19. In this study, the relationship between statins usage and hospital outcomes in COVID-19 patients has been investigated.

## Methods

All steps in this systematic review and meta-analysis study were reported based on preferred reporting items for systematic review and meta-analysis guidelines according to PRISMA 2021.[22] Our study design was registered in the International Prospective Register of Systematic Reviews with CRD42022340309 registration number.

## Method of literature search

A systematic search of Medline, Scopus, Web of Science and Embase was conducted for studies on the statin use and clinical outcomes in COVID-19 patients. Without any language restrictions, publications from December 1, 2019 to January 26, 2022 were considered. To identify preprint papers, servers such as medRxiv and Social Science Research Network (SSRN) were also searched. Detailed search strategy was showed in supplement box 1. The search strategy included a combination of medical subject headings (MeSH) terms and text words such as COVID-19, coronavirus, SARS-CoV-2, clinical outcomes, mortality, morbidity, symptoms and sign. The PICOTS (population, intervention, comparison, outcome, time, study design) components were COVID-19 patient,

Statin use, no-statin, clinical outcomes including mortality and morbidity, December 1st, 2019 to January 26th, 2022, and observational studies, respectively. Additionally, Google Scholar was searched to identify gray literature, and a virologist was consulted in the selection of important articles. The reference list of all articles was scanned manually to identify additional relevant studies. Identified citations were uploaded into Endnote X6 (Clarivate Analytics, United State) and duplicate citations were excluded. The remaining articles were initially screened independent reviewers (R. P and F. H) in three steps: 1-title, 2-abstract and 3-full text. Inter-rater disagreements were resolved after consultations with the third author (I. P). Blinding and a clear division of tasks were implemented in the article selection process. The kappa index for inter-rater agreement was 89%.

**Inclusion and exclusion criteria**

Inclusion criteria were all observational epidemiological studies (prospective cohort, retrospective cohort and cross-sectional) on the effects of stains on clinical outcomes in COVID-19 patients. The exclusion criteria were case reports, case series, all studies with a sample size <5, longitudinal studies without control groups and studies in the form of editorials, commentaries, letters to editors, and narrative reviews.

**Quality assessment**

The quality of eligible studies was appraised independently by two of the authors (R. P and F. H) using the Newcastle-Ottawa Quality Assessment Form for Cohort[23] and cross-sectional Studies.[24] The scale consists of three parts, namely selection (four items), comparability (one item), and outcome (two items for cross sectional and three item for cohort studies). Detail of scoring was available at their guidelines.

**Data extraction**

The extracted data from the selected studies were the name of authors, publication year, country, study design, sample size, the age and sex of COVID-19 patients, statin regimen, co-morbidity, type of clinical outcomes (including mortality, ICU admission, ventilation, severe COVID-19, recovery, oxygen therapy, kidney failure, hospitalization, asymptomatic COVID-19 and ARDS) and effect size (including odds ratio, risk ratio and hazard ratio).

**Statistical Analysis**

Data were analyzed using Stata software, version 14.0 (StataCorp LLC, College Station, Texas, USA). Since the effect size were different in including studies, the risk ratio or hazard ratio converted to odds ratio using below Equation 1 and 2. It is possible to pooling studies:

Equation 1: $RR= (1-e^{HR*\ln (1-r)})/r$

where HR is the hazard ratio and r is the rate for the reference group.

Equation 1: $OR=((1-p)*RR)/((1-RR)*p)$

where RR is risk ratio, and p is the risk in the control group.[25] Then heterogeneity between the studies was examined using Cochran's Q test and the $I^2$ index. Based on the Higgins classification approach, I2>0.7 was considered with high heterogeneity. The pooled odds ratio with a 95% confidence interval (CI) was

calculated using the Stata command "metan" using the random-effects model. The meta-regression analysis was used to examine the effect of age, sample size, study design and other variables on heterogeneity between the studies. Adj-$R^2$ was used to evaluate the effect of each variable on outcome variance. The Stata command "metabias" was used to check publication bias. In case of any publication bias, the bias was adjusted with the Stata command "metatrim" using the trim-and-fill method. P values less than 5% were considered statistically significant.

## Results

### Study characteristics

A total of 1346 articles were retrieved from various databases, of which 459 duplicate studies were removed. The remaining 887 articles were screened for eligibility and 836 articles failed to meet one or more inclusion criteria. Eventually, 59 studies selected in the systematic review[26-83] and 51 articles were included in the meta-analysis[26-34, 36-41, 43-45, 50-55, 57-70, 72-74, 76-78, 80-83] as shown in Figure 1. Of the 51 included articles, 5 (9.80%) were cross-sectional, 40 (80.39%) retrospective cohort, and 5 (9.80%) prospective cohort studies. The studies included a total of 308,569 COVID-19 patients (Table 1). The studies were primarily conducted in USA (21 studies, 41.18%), Spain (6 studies, 11.76%),

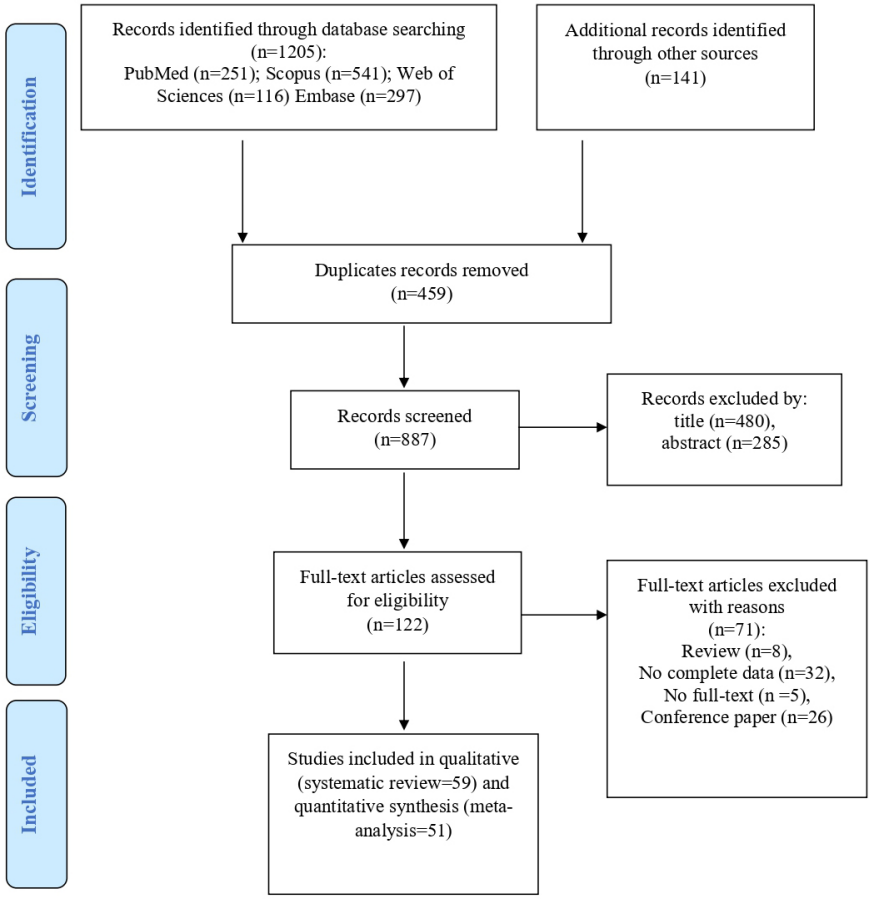


Figure 1. Flowchart of systematic review and meta-analysis

Table 1. Characteristics of studies included in the systematic review and meta-analysis

| Author | Publication year | Place | de-sign | Sample size | Mean (range) of Age | Gender | co-morbidity | Statin regimen | situation |
|---|---|---|---|---|---|---|---|---|---|
| Aghajani et al. (41) | 2021 | Iran | Retrospective Cohort | Satin: 421<br>Non-statin: 570<br>Total: 991 | Statin: 65.46±14.94<br>Non-statin: 58.82±17.88<br>Total: NA | Statin: Male: 225 (53.44%);<br>Female: 196 (46.56%)<br>Non-statin: Male: 319 (55.97%);<br>Female: 251 (44.03%) | HTN, Diabetes, CHD, CKD, Malignancy, COPD/Asthma | Atorvastatin | * |
| Aparisi et al. (26) | 2021 | Spain | Retrospective Cohort | Satin: 295<br>Non-statin: 545<br>Total: 840 | Statin: 73.47±10.08<br>Non-statin: 65.66±15.93<br>Total: NA | Statin: Male: 156 (52.9%);<br>Female: 139 (47.1%)<br>Non-statin: Male: 271 (49.7%);<br>Female: 274 (50.3%) | CKD, COPD, DM, Dyslip-idemia, CHD, HTN | NA | * |
| Bui et al. (27) | 2021 | USA | Retrospective Cohort | Statin: 8<br>Non-statin: 17<br>Total: 25 | Statin: 68<br>Non-statin: NA<br>Total: 36-87 (range) | Statin: NA<br>Non-statin: NA<br>Total: Female:11 (44%);<br>Male: 14 (56%) | HTN, Hyperlip-idemia, COPD, Obesity, Autoim-mune Disease | NA | * |
| Butt et al. (28) | 2020 | Denmark | Retrospective Cohort | Statin: 843<br>Non-statin: 3999<br>Total:4842 | Statin: 73 (63-79)<br>Non-statin: 50 (37-65)<br>Total: 45 (Median) | Statin: Male: 515 (61.1%);<br>Female: 268 (58.9%)<br>Non-statin: 1766 (44.2%);<br>Female: 2233 (44.2%), | IHD, CVD, DM, HF, AF, HTN, Malignancy, CKD, COPD, LD | Atorvastatin, Simvastatin, Rosuvastatin, Pravastatin | * |
| Byttebier et al. (29) | 2021 | Belgium | Prospective Cohort | Statin: 178<br>Non-statin: 571<br>Total: 749 | Statin: 76.2 (40-96)<br>Non-statin: 64.9 (0-98)<br>Total: 69.2 (0-98) | Statin: Male: 104 (58.4%);<br>Female: 74 (41.6%)<br>Non-statin: Male: 303 (53.1%);<br>Female: 268 (55.8%) | HTN, Asthma, COPD, CKD, DM, IHD, CVD, HF | NA | * |
| Cariou et al. (32) | 2020 | France | Cross-Sec-tional | Statin: NA<br>Non-statin: NA<br>Total:627 | Statin: NA<br>Non-statin: NA<br>Total: 69.8±13.0 | Total: Male: 165 (26.32%); Female: 462 (73.68%); | CHD, NAFLD, LD, Malignancy, COPD, OSA, ESRD | NA | * |

| Fan et al. (37) | Spiegeleer et al. (36) | Daniels et al. (34) | Daniels et al. (35) | Chacko et al. (33) | Cariou et al. (31) |
|---|---|---|---|---|---|
| 2020 | 2020 | 2021 | 2021 | 2021 | 2021 |
| China | Belgium | USA | USA | USA | France |
| Retrospective Cohort | Retrospective Cohort | Retrospective Cohort | Retrospective Cohort | Retrospective Cohort | Cross-Sectional |
| Statin: 250<br>Non-statin: 1897<br>Total: 2147 | Statin: 31<br>Non-statin: 123<br>Total: 154 | Statin: 6943<br>Non-statin: 3598<br>Total: 10541 | Satain:46<br>Non-statin: 124<br>Total:170 | Statin:116<br>Non-statin: 139<br>Total:255 | Statin: NA<br>Non-statin: NA |
| Statin: 66 (57-72)<br>Non-statin: 58 (48-68)<br>Total: 56-69 (range) | Statin: 85.6±5.7<br>Non-statin: 85.9±7.6<br>Total: 66±14 | Statin: 69.3±13.2<br>Non-statin: 60.3±14.0<br>Total: 66±14 | Statin: NA<br>Non-statin: NA<br>Total: 59±19 | Statin: 69±10.6<br>Non-statin: 62.4±17.7<br>Total: 65.4±15.2 | Statin: NA<br>Non-statin: NA<br>Total: 70.9±12.5 |
| Statin: Male: 115 (46.0%);<br>Female: 135 (54%)<br>Non-statin: Male: 926 (48.8%);<br>Female: 971 (51.2%) | Statin: Male: 10 (32.3%);<br>Female: 21 (67.7%)<br>Non-statin: Male: 41 (33.3%);<br>Female: 82 (66.7%) | Statin: Male: 3690 (53%);<br>Female: 3253 (47%)<br>Non-statin: Male 2125 (59%);<br>Female: 1473 (41%) | Statin: NA<br>Non-statin: NA | Statin: Male:59 (50.86%);<br>Female: 57 (49.14%)<br>Non-statin: Male: 71 (51.08%);<br>Female: 68 (48.92%) | Statin: Male: (67.8%);<br>Female: (32.2)<br>Non-statin: Male: (60.5%);<br>Female: (39.5%) |
| HTN, CHD, DM, CVD, COPD, LD, CKD, Malignancy | DM, HTN | CVD, HTN, DM, Malignancy, CKD, Dyslipidemia, Obesity, Autoimmune Disease, RD | Obesity, HTN, CVD, HF, CKD, Asthma, COPD, Malignancy, HIV | ESRD, DM, HTN, CHD | NA |
| Atorvastatin, Rosuvastatin, Pravastatin | Fluvastatin, Pravastatin, Rosuvastatin, Simvastatin | NA | NA | NA | NA |
| * | * | * | * | * | * |

| | | | | | | |
|---|---|---|---|---|---|---|
| Ikari et al. (45) | Huh et al. (44) | Holt et al. (43) | Higuchi et al. (42) | Gupta et al. (40) | Greco et al. (39) | Grasselli et al. (38) |
| 2021 | 2020 | 2020 | 2021 | 2020 | 2021 | 2020 |
| Japan | Korea | Denmark | Japan | USA | Italy | Italy |
| Retrospective Cohort | Case-control | Cross-sectional | Retrospective Cohort | Retrospective Cohort | Retrospective Cohort | Retrospective Cohort |
| Statin: 214<br>Non-statin: 479<br>Total: 693 | Statin: 690<br>Non-statin: 10413<br>Total: 11103 | Statin: NA<br>Non-statin: NA | Statin: 12<br>Non-statin: 45<br>Total: 57 | Statin:648<br>Non-statin: 648<br>Total: 1296 | Statin:51<br>Non-statin: 450<br>Total: 501 | Statin: NA<br>Non-statin: NA<br>Total: 3988 |
| Statin: 67.8±12.9<br>Non-statin: 68.5±15.6<br>Total: 68.3±14.9 | Statin: NA<br>Non-statin: NA<br>Total: 44.6±18.0 | Statin: NA<br>Non-statin: NA<br>Total: NA | Statin: NA<br>Non-statin: NA<br>Total: 52 (Median) | Statin:69 (61-77)<br>Non-statin: 71 (60-81)<br>Total: NA | Statin: 76±10<br>Non-statin: 71±17<br>Total: 72±17 | Statin: NA<br>Non-statin: NA<br>Total: 56-69 (range) |
| Statin: Male: 139 (65%);<br>Female: 75 (35%)<br>Non-statin: Male 168 (65%);<br>Female: 311 (35%) | Statin: NA<br>Non-Statin: NA | Statin: NA<br>Non-statin: NA | Satin: NA<br>Non-statin: NA<br>Total: male: 56.1% | Statin: Male 366 (56.5%);<br>Female 282 (43.5%)<br>Non-statin: Male 366 (56.5%);<br>Female 282 (43.5%) | Statin: Male: 27 (52.9%);<br>Female: 24 (47.1%)<br>Non-statin: Male: 227 (50.3%);<br>Female: 224 (49.7%) | Statin: NA<br>Non-statin: NA<br>Total: Male: 79.9% |
| HTN, DM, Edema, RD, CHD, Asthma, COPD, obesity, CKD, LD, Autoimmune Disease, Malignancy | RD, LD, HTN, DM | NA | HTN, CAD, COPD, Asthma, DM, Hyperlipidemia, CKD, Malignancy | HTN, DM, CHD, HF, LD, CKD, CVD, LD | HTN, DM, HF, CKD, COPD, Malignancy, Dementia | COPD, Hyperlipidemia, DM |
| NA | NA | NA | NA | NA | Atorvastatin, Simvastatin Pravastatin | NA |
| * | # | * | # | * | * | * |

| Yetmar et al. (82) | Zhang et al. (83) | Khalili et al. (49) | Jia et al. (48) | Jakob et al. (47) | Israel et al. (46) |
|---|---|---|---|---|---|
| 2020 | 2020 | 2021 | 2021 | 2021 | 2021 |
| USA | China | Iran | USA | Germany | Israel |
| Retrospective Cohort | Retrospective Cohort | Retrospective Cohort | | Cohort | Cross-Sectional |
| Statin: 500<br>Non-statin: 795<br>Total: 1295 | Statin: 12762<br>Non-statin: 12762<br>Total: 25524 | Statin: 66<br>Non-statin: 188<br>Total: 254 | Statin: NA<br>Non-statin: NA | Statin: NA<br>Non-statin: NA<br>Total: 2155 | Statin: 235<br>Non-statin: 1556<br>Total: 1791 |
| Statin: 65 (57-73)<br>Non-statin: 55 (43-65)<br>Total: NA | Statin: 66.0 (59.0-72.0)<br>Non-statin: 57.0 (45.0-67.0)<br>Total: 18-85 (range) | Statin: NA<br>Non-statin: NA<br>Total: NA | Statin: NA<br>Non-statin: NA | Statin: NA<br>Non-statin: NA<br>Total: 66-85 (range) | STATIN: 56.8±18.9<br>Non-statin: NA<br>Total: NA |
| Statin: Male: 307 (61%);<br>Female: 193 (39%)<br>Non-statin: Male: 410 (52%);<br>Female: 385(48%) | Statin: Male: 602 (49.4%);<br>Female: 12160 (50.6%)<br>Non-statin: Male: 6228 (48.8%);<br>Female: 6534 (51.2%) | Statin: NA<br>Non-statin: NA<br>Total: Male: 142 (55.9%);<br>Female: 112 (44.1%) | Statin: NA<br>Non-statin: NA | Statin: NA<br>Non-statin: NA<br>Total: Male: 1287 (59.7%);<br>Female: 868 (40.3%) | Statin: NA<br>NON-STATIN: NA |
| DM, CHF, CHD | COPD, HTN, DM, CHD, CVD, LD, CKD | CHD, HTN, COPD, DM | ---- | CHD, DM, RD, Malignancy, Neurological disease, CKD | HTN, DM, CKD, CHF, COPD, Malignancy, IHD |
| Atorvastatin, Rosuvastatin, Fluvastatin, Pitavastatin Y, Pravastatin | Atorvastatin, Rosuvastatin, Simvastatin, Pravastatin, ACEi/ARB | NA | NA | NA | Rouvastatin |
| * | * | # | # | # | * |

| Terlecki et al. (76) | Tignanelli et al. (77) | Torres Peña et al. (78) | Villalba et al. (30) | Wander et al. (80) | Wang et al. (84) | Yan et al. (81) |
|---|---|---|---|---|---|---|
| 2021 | 2021 | 2021 | 2021 | 2021 | 2020 | 2019 |
| Poland | USA | Spain | Spain | US | USA | China |
| Retrospective Cohort | Retrospective Cohort | Retrospective Cohort | Retrospective Cohort | Cohort | Retrospective Cohort | Cohort |
| Statin: 269<br>Non-statin: 1460<br>Total: 1729 | Statin: 25962<br>Non-statin: 934<br>Total: 26896 | Statin: 1130<br>Non-Statin: 1791<br>Total: 2921 | Statin: 295<br>Non-statin: 564<br>Total: 859 | Statin: 12781<br>Non-statin: NA<br>Total: 35879 | Statin: 27<br>Non-statin: 31<br>Total: 58 | Statin: 15<br>Non-statin: 563<br>Total: 578 |
| Statin: NA<br>Non-statin: NA<br>Total: 63 (50-75) | Statin: NA<br>Non-statin: NA<br>Total: NA | Statin: 72±10<br>Non-statin: 73±11<br>Total: NA | Statin: NA<br>Non statin: NA<br>Total: 68.1 | Statin: NA<br>Non-statin: NA<br>Total: NA | Statin: NA<br>Non-statin: NA<br>Total: 67 | Statin: NA<br>Non statin: NA<br>Total: 49.18 |
| Statin: NA<br>Non-statin: NA<br>Total: Male: 886 (51.02%);<br>Female: 843 (48.8%) | Statin: NA<br>Non-statin: NA | Statin: Male: (60.3%);<br>Female: (39.7%)<br>Non-statin: Male: (60.3%);<br>Female: (39.7%) | Statin: NA<br>Non-statin: NA<br>Total: Male: 434 (51.5%);<br>Female: 425 (49.5%) | Statin: NA<br>Non-statin: NA | Statin: NA<br>Non-statin: NA | Statin: NA<br>Non-statin: NA<br>Total: Male: 293 (50.7%);<br>Female: 285 (49.3%) |
| HTN, Hyperlipidemia, DM, CHD, HF, CVD, Asthma, COPD | DM, Obesity, NAFLD, NASH | HTN, DM, CHD, CVD, PAD, Dyslipid-emia | HTN, DM, CKD, Dyslipidemia, COPD | CVD, HF, CKD | HTN, hyperlip-idemia, obesity, DM, CKD, RD | LD, DM, HTN, CVD, Malignancy |
| NA | NA | Atorvastatin, Rosuvas-tatin, Fluvastatin | NA | NA | NA | NA |
| # | * | # | * | * | * | * |

| Salvador et al. (70) | Saeed et al. (69) | M. Satué et al. (71) | Soldevila et al. (72) | Song et al. (74) | Soleimani et al. (73) | Strandberga et al. (75) |
|---|---|---|---|---|---|---|
| 2021 | 2020 | 2021 | 2021 | 2020 | 11 | 2021 |
| Portugal | USA | Spain | Spain | USA | Iran | Finland |
| Prospective Cohort | Retrospective Cohort | Cohort | Cross-sectional | Retrospective Cohort | Retrospective Cohort | Coronado study |
| Statin: 106<br>Non-statin: 139<br>Total: 254 | Statin: 1355<br>Non-statin: 2897<br>Total: 4252 | Statin: 16,134<br>Non-statin: 62949<br>Total: 79083 | Statin: 224<br>Non-statin: 1082<br>Total: 1306 | Statin: 123<br>Non-statin: 126<br>Total: 249 | Statin: 66<br>Non-statin: 188<br>Total: 254 | Statin: NA<br>Non-statin: NA<br>Total: NA |
| Statin: NA<br>Non-statin: NA<br>Total: 79 | Statin: 69±12<br>Non-statin: 63±17<br>Total: 65±16 | Statin: NA<br>Non-statin: NA<br>Total: ≥50 | Statin: NA<br>Non-statin: NA<br>Total: 86.7 | Statin: 71.0 (60.0-79.0)<br>Non-statin: 54.5 (42.0-67.0)<br>Total: 62.0 (51.0-75.0) | Statin: NA<br>Non statin: NA<br>Total: 66.4±12.9 | Statin: NA<br>Non-statin: NA<br>Total: NA |
| Statin: NA<br>Non-statin: NA | Statin: Female: 618 (45%); Male: 737(55%)<br>Non-statin: Male: 1518 (53%);<br>Female: 1379 (47%) | Statin: NA<br>Non-statin: NA<br>Total: Male: 37,626 (47.6%);<br>Female: 41457 (52.4%) | Statin: NA<br>Non-statin: NA<br>Total: Male: 353 (27%);<br>Female: 953 (73%) | Statin: NA<br>Non-statin: NA | Statin: NA<br>Non-statin: NA | Statin: NA<br>Non-statin: NA |
| HTN, COPD, Obesity, Malignancy, CKD, DM, CHD, Autoimmune Disease, Dyslipidemia, AF | DM, HTN, CHD, RD | Neurological disease, CKD, Malignancy, IBD, RD, CHD, AF, LD, DM, HTN, Obesity, Hyperlipidemia, | HTN, dementia, DM | HTN, CVD, COPD, DM, LD, Obesity | DM, CHD, CVD, LD, CKD, Malignancy | DM, HTN, HF, COPD |
| NA | Atorvastatin, Pravastatin, Rosuvastatin, Simvastatin | NA | Atorvastatin, Lovastatin, Rosuvastatin, Simvastatin | NA | NA | NA |
| * | * | # | # | # | * | * |

| Oh et al. (63) | Pareek et al. (64) | Peymani et al. (65) | Ramos-Rincón et al. (66) | Rodriguez-Nava et al. (67) | Russo et al. (68) |
|---|---|---|---|---|---|
| 2021 | 2021 | 2021 | 2021 | 2020 | 2021 |
| Korea | USA | Iran | Spain | USA | Italy |
| Retrospective Cohort | Prospective Cohort | Retrospective Cohort | Retrospective Cohort | Retrospective Cohort | Retrospective Cohort |
| Statin: 22633<br>Non-statin: 101697<br>Total:122040 | Statin: NA<br>Non-statin: NA | Statin: 75<br>Non-statin: 75<br>Total: 150 | Statin: NA<br>Non-statin: NA<br>Total: NA | Statin: NA<br>Non-statin: NA<br>Total: 87 | Statin: 167<br>Non-statin: 300<br>Total: 467 |
| Statin: NA<br>Non-statin: NA<br>Total: > 20 | Statin: NA<br>Non-statin: NA<br>Total: 67 (IQR: 55-80) | Statin: 63.59±13.18<br>Non-statin: 61.72±15.83<br>Total: NA | Statin: NA<br>Non-statin: NA<br>Total: >80 | Statin: NA<br>Non-statin: NA<br>Total: 68 (58-75) | Statin:70.58±12.03<br>Non-statin: 64.82±15.41<br>Total: 66.88±14.55 |
| Statin: Male: 8147 (36.0%);<br>Female: 14486 (64%)<br>Non-statin: Male: 40579 (39.9%);<br>Female: 61118 (59.9%) | Statin: NA<br>Non-statin: NA | Statin: Male:45 (60%);<br>Female: 30 (40%)<br>Non-statin: Male:43 (57.3%);<br>Female: 32 (42.7%) | Statin: NA<br>Non-statin: NA | Statin: NA<br>Non-statin: NA<br>Total: Male: 56 (64.4%);<br>Female: 31 (35.6%) | Statin: Male: 115 (68.9%);<br>Female: 52 (31.1%)<br>Non-statin: Male: 179 (59.7%);<br>Female: 121 (40.3%) |
| HTN, DM, PVD, CKD, Rheumatic disease, Dementia, Peptic ulcer disease, Hemiplegia or paraplegia, LD, COPD, CVD, CHF, MI, Malignancy, AIDS/HIV | NA | HTN, DM, CHD, RD, CKD | DM, HTN, Dyslipidemia, Dementia, AF, CHD, CVD, PVD, COPD, Obesity, Malignancy, CKD | HTN, CHD | HTN, DM, Dyslipidemia, AF, CHD, Stroke, CKD, COPD |
| NA | NA | Atorvastatin, Rosuvastatin, Simvastatin | NA | Atorvastatin | NA |
| * | * | * | * | * | * |

| Memel et al. (58) | Mitacchio et al. (59) | Valeri et al. (79) | Nguyen et al. (60) | Nicholson et al. (61) | Oddy et al. (62) |
|---|---|---|---|---|---|
| 2021 | 2020 | 2020 | 2020 | 2021 | 2020 |
| USA | Italy | USA | USA | USA | United Kingdom |
| Retrospective Cohort | Retrospective Cohort | Cohort | Retrospective Cohort | Retrospective Cohort | Retrospective Cohort |
| Statin: 311<br>Non-statin: 360<br>Total: 671 | Statin: 179<br>Non-statin: 663<br>Total: 842 | Statin: 43<br>Non-statin: 16<br>Total: 59 | Statin: 115<br>Non-statin: 574<br>Total: 689 | Statin:511<br>Non-statin:531<br>Total: 1042 | Statin: NA<br>Non-statin: NA |
| Statin: 55 (43-66)<br>Non-statin: NA<br>Total: NA | Statin: NA<br>Non-statin: NA<br>Total: NA | Statin: NA<br>non-statin: NA<br>Total: 63 | Statin: NA<br>Non-statin: NA<br>Total: 55 (40-68) | Statin: NA<br>Non-statin: NA<br>Total: 64 (Median) | Statin: NA<br>Non-statin: NA<br>Total: NA |
| Statin: NA<br>Non-statin: NA<br>Total: Male: 173 (55.6%);<br>Female: 138 (44.4%) | Statin: Male: 126 (70.4%);<br>Female: 53 (29.6%)<br>Non-statin: Male: 393 (59.3%);<br>Female: 270 (40.7%) | Statin: NA<br>Non-statin: NA | Statin: NA<br>Non-statin: NA | Statin: NA<br>Non-statin: NA | Statin: NA<br>Non-statin: NA |
| CHD, CHF, HTN, DM, Dyslipidemia, CKD, LD, NAFLD, Viral Hepatitis, HIV, Malignancy, COPD, Asthma, OSA | Obesity, CHF, MI, DM, CHD, HF, CKD, COPD, CVD, Malignancy | HTN, DM, CAD, RD | Obesity, DM, HTN, CVD, CKD, COPD, Asthma, HTN, CHD, HF, AF | DM, CHD, HTN, CKD, COPD, Malignancy | DM, CKD, HTN, CHD, hyperlipidemia, PVD, COPD, Asthma, CVD, Dementia, Osteoporosis, Vitamin D Deficiency, Malignancy |
| Atorvastatin, Rosuvastatin | Atorvastatin, Simvastatin, Rosuvastatin | NA | NA | NA | Atorvastatin, Simvastatin |
| * | * | # | * | * | * |

| Lohia et al. (53) | Lohia et al. (52) | Mallow et al. (54) | Maric et al. (55) | Masana et al. (56) | Meintrup et al. (57) |
|---|---|---|---|---|---|
| 2020 | 2021 | 2020 | 2021 | 2020 | 2021 |
| USA | USA | USA | USA | Spain | Germany |
| Retrospective Cohort | Retrospective Cohort | Retrospective Cohort | Retrospective Cohort | Retrospective Cohort | Retrospective Cohort |
| Statin: 454<br>Non-statin: 560<br>Total: 1014 | Statin: 250<br>Non-statin: 672<br>Total: 922 | Statin: 5313<br>Non-statin: 16303<br>Total: 21676 | Statin: 2297<br>Non-statin: 16169<br>Total: 18466 | Statin: 581<br>Non-statin: 1576<br>Total: 2157 | Statin: NA<br>Non-statin: NA |
| Statin: 18-65<br>Non-statin: NA<br>Total: 65 | Statin: 66 (59-75)<br>Non-statin: 65 (54-73)<br>Total: 66 (56-73.25) | Statin: NA<br>Non-statin: NA<br>Total: NA | Statin: NA<br>Non-statin: NA<br>Total: 18-65 | Statin: 73 (65-80)<br>Non-statin: NA<br>Total: 67 (54-78) | Statin: NA<br>Non-statin: NA |
| Statin: Male: 240 (52.9%);<br>Female: 214 (48.1%)<br>Non-statin: Male: 290 (51.8%);<br>Female: 270 (49.2%) | Stain: Male: 139 (55.6%);<br>Female: 111(44.4%)<br>Non-statin: Male: 351 (52.2%);<br>Female: 321 (48.8%) | Statin: NA<br>Non-statin: NA | Statin Male: 1222 (53.2%);<br>Female: 1075 (46.8%)<br>Non-statin: NA | Statin: Male: 356 (61%);<br>Female: 225 (39%)<br>Non-statin: Male: 878 (55.71%);<br>Female: 698 (44.29%) | Statin: NA<br>Non-statin: NA |
| RD, CHD, HTN, DM, Hyperlipidemia, CHF, CVD, Malignancy, LD, CKD, ESRD | RD, CHD, HTN, DM, Hyperlipidemia, CHF, CVD, Cancer, LD, CKD, ESRD | RD, Asthma, CHD, Obesity, DM, CKD, LD, HTN, Hypothyroidism | HTN, DM, COPD, Obesity, Hyperlipidemia, CVD | HTN, Hyperlipidemia, DM, Obesity, CHD, CVD, PAD, HF, COPD, Asthma, LD, CKD, Malignancy | NA |
| Atorvastatin, Pravastatin, Rosuvastatin, Simvastatin, Lovastatin | NA | NA | NA | NA | NA |
| * | * | * | * | * | * |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Lala et al. (50) | 2020 | USA | Retrospective Cohort | Statin: 984<br>Non-statin: 1752<br>Total: 2736 | Statin: NA<br>Non-statin: NA<br>Total: 66.4 | Statin: NA<br>Non-statin: NA | CHD, DM, HF, HTN, AF, CKD | NA | * |
| Lee et al. (51) | 2021 | Korea | Retrospective Cohort | Statin: 533<br>Non-statin: 9915<br>Total: 10448 | Statin: 65.53<br>Non-statin: NA<br>Total: 45 (Median) | Statin: Male: 181 (33.6%);<br>Female: 352 (66.04%)<br>Non-statin: NA | HTN, DM, CHD, HF, CVD, COPD, Malignancy, CKD | NA | * |

* Included to meta-analysis
# Not included to meta-analysis
PAD, Peripheral artery disease; HF, Heart failure; RD, Respiratory disease including Chronic/acute lung disease; CKD, Chronic kidney disease; RF, Renal failure; IBD, Inflammatory bowel disease; AF, Atrial fibrillation; CHF, Congestive heart failure; MI, Myocardial infarction; IHD, Ischemic heart disease; CHD, Coronary Heart disease including coronary artery disease and arteriosclerotic heart disease; HTN, Hypertension; CVD, Cerebrovascular disease including stroke, Transient ischemic attack and cerebrovascular accident; LD, Liver disease including chronic/acute liver disease, Chronic hepatic dysfunction, cirrhosis and non-viral hepatitis; OSA, Obstructive Sleep Apnea; DM, Diabetic mellites; NASH, Non-alcoholic steatohepatitis

and Italy (4 studies, 7.84%).

## Summary measure of clinical outcomes for statin use

Table 2 showed the calculated odds ratio with 95% confidence interval (CI) for different clinical outcomes in included studies to meta-analysis. Also Figure 2 shows the forest plot for mortality odds ratio with 95% CI for included studies. As showed in Figure 2, the pooled estimate of mortality odds ratio (95% CI) for statins therapy was 0.73 (0.66 to 0.81) [Number of included studies=49; $I^2$=76.8%, P<0.001]. It means, in overall, the use of statin decreases the COVID-19 risk of mortality about 27%. Table 3 shows the summary measure of mortality odds ratio for statins therapy in different subgroups. The pooled estimate of odds ratio (95% CI) for statins therapy were 0.79 (0.55 to 1.13) [Number of included studies=6; $I^2$=84.9%, P<0.001] for mortality <28 days and 0.72 (0.64 to 0.80) [Number of included studies=42; I^2=74.4%, P<0.001]; for mortality >28 days. It means, in overall, the use of statin decreases the COVID-19 risk of mortality >28 days about 28% but have no effects on the mortality <28 days. The pooled estimate of mortality odds ratio (95% CI) for statins therapy was 1.05 (0.70 to 1.56), 0.69 (0.62 to 0.77), 0.88 (0.45 to 1.71) in cross-sectional studies, retrospective studies and prospective studies; respectively. Additionally, the forest plot for the other clinical outcomes including ICU admission, ventilation, severe COVID-19, recovery, oxygen therapy, kidney failure, hospitalization, asymptomatic COVID-19 and ARDS is presented in supplementary Figures 1 to 8 and summary measures reported in Table 3. As shown in Table 3, the use of statins overally lead to decrease

Table 2. calculated odds ratio and 95% confidence interval for different clinical outcomes in included studies to meta-analysis

| Author | Outcomes | OR (95% CI) | Author | Outcomes | OR (95% CI) |
|---|---|---|---|---|---|
| Aghajani et al.[41] | > 28-Day Mortality | 0.68 (0.52-0.89) | Villalba et al.[30] | > 28-Day Mortality | 0.55 (0.33-0.92) |
| | Mechanical Ventilation | 0.60 (0.39-0.92) | Torres Peña et al.[78] | > 28-Day Mortality | 0.67 (0.54-0.83) |
| | Recovery | 0.91 (0.68-1.21) | | Kidney Failure | 0.76 (0.60-0.97) |
| Aparisi et al.[26] | > 28-Day Mortality | 0.48 (0.30-0.77) | Tignanelli et al.[77] | > 28-Day Mortality | 0.81 (0.66-0.98) |
| | Mechanical Ventilation | 0.84 (0.50-1.42) | Terlecki et al.[76] | > 28-Day Mortality | 0.50 (0.30-0.80) |
| | ARDS | 1.18 (0.88-1.58) | | Oxygen therapy | 0.84 (0.58-1.21) |
| Bui et al.[27] | > 28-Day Mortality | 0.08 (0.01-0.63) | Soleimani et al.[73] | Severe-COVID-19 | 1.80 (0.92-3.50) |
| Butt et al.[28] | < 28-Day Mortality | 0.98 (0.79-1.21) | | > 28-Day Mortality | 0.93 (0.49-1.76) |
| | Severe-COVID-19 | 1.22 (0.99-1.53) | Song et al.[74] | < 28-Day Mortality | 0.88 (0.37-2.08) |
| Byttebier et al.[29] | < 28-day Mortality | 0.56 (0.39-0.93) | | ICU Admission | 0.90 (0.49-1.67) |
| Cariou et al.[32] | < 28-day Mortality | 1.19 (0.84-1.68) | | Mechanical Ventilation | 0.45 (0.20-0.99) |
| Cariou et al.[31] | < 28-day Mortality | 1.64 (1.08-1.95) | Soldevila et al.[72] | > 28-Day Mortality | 0.69 (0.50-1.00) |
| Chacko et al.[33] | > 28-Day Mortality | 0.14 (0.03-0.61) | Saeed et al.[69] | > 28-Day Mortality | 0.49 (0.41-0.59) |
| | Mechanical Ventilation | 1.10 (0.60-2.00) | Salvador et al.[70] | > 28-Day Mortality | 0.73 (0.43-1.25) |
| Daniels et al.[35] | Asymptomatic COVID-19 | 0.60 (0.28-1.24) | | Mechanical Ventilation | 1.00 (0.51-1.92) |
| Daniels et al.[34] | > 28-Day Mortality | 0.59 (0.50-0.69) | Russo et al.[68] | ARDS | 1.10 (0.56-2.44) |
| | ICU Admission | 1.30 (1.18-1.42) | Rodriguez-Nava et al.[67] | > 28-Day Mortality | 0.36 (0.16-0.76) |
| | Mechanical Ventilation | 1.12 (1.01-1.24) | Ramos-Rincón et al.[66] | > 28-Day Mortality | 0.92 (0.72-1.98) |
| | Severe disease | 1.32 (1.22-1.44) | Peymani et al.[65] | > 28-Day Mortality | 0.85 (0.01-5.65) |
| Spiegeleer et al.[36] | Asymptomatic COVID-19 | 3.52 (1.11-16.2) | | Mechanical Ventilation | 0.96 (0.61-2.99) |
| | Severe-COVID-19 | 0.86 (0.25-2.50) | Pareek et al.[64] | > 28-Day Mortality | 1.67 (1.05-2.67) |
| | > 28-Day Mortality | 0.51 (0.14-1.35) | Oh et al.[63] | > 28-Day Mortality | 0.74 (0.52-1.05) |
| Fan et al.[37] | > 28-Day Mortality | 0.25 (0.07-0.94) | Oddy et al.[62] | > 28-Day Mortality | 0.72 (0.44 - 1.19) |
| | ARDS | 0.22 (0.05-0.90) | | ICU Admission | 0.33 (0.15 - 0.72) |
| Grasselli et al.[38] | > 28-Day Mortality | 1.00 (0.81-1.25) | | Kidney Failure | 1.09 (0.83 - 1.46) |
| Greco et al.[39] | > 28-Day Mortality | 0.63 (0.29-1.35) | Nicholson et al.[61] | Mechanical Ventilation | 0.84 (0.65 - 1.09) |
| Gupta et al.[40] | > 28-Day Mortality | 0.49 (0.38-0.63) | | > 28-Day Mortality | 1.63 (1.20 - 2.22) |
| | Mechanical Ventilation | 0.78 (0.60-1.01) | Nguyen et al.[60] | Hospitalization | 3.56 (2.20 - 5.78) |
| Holt et al.[43] | > 28-Day Mortality | 0.85 (0.54-1.33) | | > 28-Day Mortality | 0.83 (0.33 - 1.75) |
| Ikari et al.[45] | Oxygen saturation | 0.29 (0.09-0.99) | Mitacchione et al.[59] | ICU Admission | 0.54 (0.22 - 1.29) |
| | ICU Admission | 0.86 (0.60-1.24) | | Severe-COVID-19 | 1.70 (1.07 - 0.71) |
| | ARDS | 1.06 (0.66-1.68) | Meintrup et al.[57] | > 28-Day Mortality | 0.54 (0.35 - 0.86) |
| | Mechanical Ventilation | 0.93 (0.63-1.37) | Memel et al.[58] | > 28-Day Mortality | 0.54 (0.33 - 0.87) |
| | > 28-Day Mortality | 0.84 (0.53-1.32) | Masana et al.[56] | ICU Admission | 1.20 (0.96 - 1.60) |
| Israel et al.[46] | Hospitalization | 0.67 (0.60-0.76) | | Mechanical Ventilation | 1.23 (0.93 - 1.62) |
| Zhang et al.[83] | < 28-Day Mortality | 0.60 (0.45-0.83) | | Kidney Failure | 1.40 (1.10 - 1.80) |
| | Mechanical Ventilation | 0.51 (0.34-0.78) | | ARDS | 1.36 (1.11 - 1.67) |
| | ICU Admission | 0.80 (0.62-1.05) | Maric et al.[55] | > 28-Day Mortality | 0.92 (0.81 - 1.05) |
| | ARDS | 0.81 (0.5-1.16) | Mallow et al.[54] | > 28-Day Mortality | 0.54 (0.49 - 0.60) |
| | Kidney Failure | 0.78 (0.41-1.76) | Lohia et al.[52] | > 28-Day Mortality | 0.61 (0.42 - 0.90) |
| Yetmar et al.[82] | > 28-Day Mortality | 1.14 (0.64-2.03) | | Mechanical Ventilation | 0.61 (0.43 - 0.87) |
| Yan et al.[81] | Severe-COVID-19 | 1.78 (0.54-5.13) | | ICU Admission | 0.54 (0.36 - 0.80) |
| Wang et al.[84] | > 28-Day Mortality | 6.21 (1.37-39.77) | Lohia et al.[53] | > 28-Day Mortality | 0.66 (0.46 - 0.95) |
| | Hospitalization | 12.06 (2.78-76.13) | | Mechanical Ventilation | 0.80 (0.55 - 1.15) |
| Wander et al.[80] | Hospitalization | 1.00 (0.91-1.10) | | ICU Admission | 0.92 (0.66 - 1.29) |
| | ICU Admission | 0.91 (0.79-1.04) | Lee et al.[51] | > 28-Day Mortality | 0.64 (0.43 - 0.97) |
| | > 28-Day Mortality | 0.76 (0.66-0.88) | Lala et al.[50] | > 28-Day Mortality | 0.55 (0.45 - 0.68) |

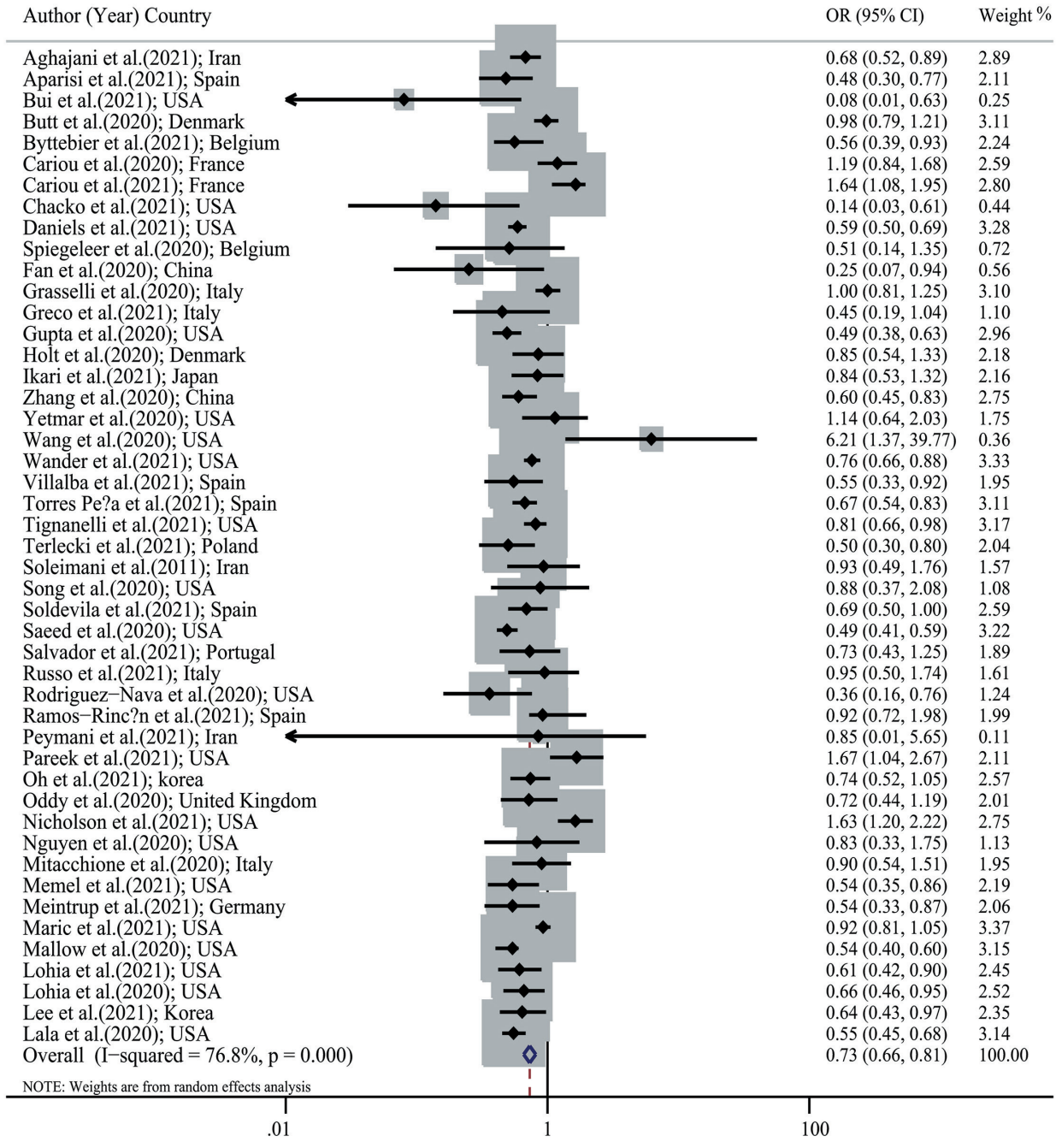


Figure 2. Forest plot for the association between statin therapy with odds of mortality in COVID-19 patients based on a random-effects model. Each study identifies by the first author (year) and country. Each line segment's midpoint shows the odds ratio estimate, length of line segment indicates 95% CI in each study, and diamond mark illustrates the pooled estimate of odds ratio.

odds of ventilation [pooled OR (95% CI): 0.85 (0.70 to 0.99)] but have no effects on the odds of ICU admission [pooled OR (95% CI): 0.93 (0.77 to 1.12)], oxygen therapy [pooled OR (95% CI): 0.85 (0.70 to 0.99)], recovery [pooled OR (95% CI): 1.85 (0.35 to 9.92)], kidney failure [pooled OR (95% CI): 1.01 (0.73 to 1.40)], hospitalization [pooled OR (95%

Table 3. Pooled odds ratio and corresponding 95% confidence interval of statins therapy for mortality and other clinical outcomes in COVID-19 patients

| Clinical outcomes | Number of studies [Heterogeneity indices] | Pooled OR (CI 95%) |
|---|---|---|
| Mortality | | |
| <28 day | N=6; [$I^2$=84.9%, P<0.001, $Tau^2$=0.166] | 0.79 (0.55 to 1.13) |
| >28 day | N=42; [$I^2$=74.4%, P<0.001, $Tau^2$=0.074] | 0.72 (0.64 to 0.80)* |
| Cross-sectional | N=5; [$I^2$=80.6%, P=0.001, $Tau^2$=0.134] | 1.05 (0.70 to 1.56) |
| Retrospective | N=41; [$I^2$=73.3%, P<0.001, $Tau^2$=0.066] | 0.69 (0.62 to 0.77)* |
| Prospective | N=5; [$I^2$=83.0%, P=0.003, $Tau^2$=0.290] | 0.88 (0.45 to 1.71) |
| Total | N=51; [$I^2$=76.8%, P<0.001, $Tau^2$=0.084] | 0.73 (0.66 to 0.81)* |
| ICU admission | N=12; [$I^2$=81.5%, P<0.001, $Tau^2$=0.073] | 0.93 (0.77 to 1.12) |
| Ventilation | N=16; [$I^2$=75.4%, P<0.001, $Tau^2$=0.080] | 0.85 (0.70 to 0.99)* |
| Severe COVID-19 | N=4; [$I^2$=0.0%, P=0.661, $Tau^2$= 0.010] | 1.32 (1.23 to 1.42)* |
| Recovery | N=2; [$I^2$=79.8%, P=0.026, $Tau^2$=1.215] | 1.85 (0.35 to 9.92) |
| Oxygen therapy | N=2; [$I^2$=62.9%, P=0.101, $Tau^2$=0.355] | 0.58 (0.22 to 1.57) |
| Kidney failure | N=4; [$I^2$=76.6%, P=0.005, $Tau^2$=0.077] | 1.01 (0.73 to 1.40) |
| Hospitalization | N=4; [I $I^2$=95.6%, P<0.001, $Tau^2$=0.182] | 1.45 (0.88 to 2.36) |
| Asymptomatic COVID-19 | N=2; [$I^2$=80.5%, P=0.024, $Tau^2$=1.259] | 1.33 (0.24 to 7.44) |
| ARDS | N=7; [I $I^2$=63.3%, P=0.012, $Tau^2$=0.067] | 1.15 (0.88 to 1.49) |

*Significance at 0.05
OR, Odds ratio; CI, Confidence interval; ARDS, Acute respiratory distress syndrome

CI): 1.45 (0.88 to 2.36)], asymptomatic disease [pooled OR (95% CI): 1.33 (0.24 to 7.44)], and ARDS [pooled OR (95% CI): 1.15 (0.88 to 1.49)]. Moreover, the results of the current meta-analysis showed that the use of statins overally was associated to severe COVID-19 [pooled OR (95% CI): 1.32 (1.23 to 1.42)]. In other word, in a COVID-19 patient under statins therapy, the odds of severe COVID-19 is 32% more than a COVID-19 patient who does not use statins during the disease.

## Heterogeneity and Meta-regression

The results of Cochran's Q test showed significant heterogeneity among the studies for all outcomes except for severe COVID-19 (Table 3). The heterogeneity source of mortality, the main outcome of the present studies, was evaluated by meta-regression. As shown in Table 3, the $I^2$ index for mortality was 79.8%. The results of the simple and multiple meta-regression showed in Table 4. The results of the simple meta-regression analysis showed that study design (coefficient: 0.231, 95% CI, p: 0.011) has a significant effect on the heterogeneity and this variable explains 22.96% in log odds ratio of mortality variation. It means the log odds ratio from cross-sectional to retrospective cohort or from retrospective cohort to prospective cohort increased about 0.23 units. Other variables including sample size (coefficient: -0.001, p: 0.994), mean of age (coefficient: -0.002, p: 0.880), and death time (coefficient: -0.131, p: 0.417) had no significant effects on the heterogeneity of mortality (Figure 3a and 3b).

The effects of variables, including study design,

Table 4. Simple and multiple meta-regression results for the identification of mortality heterogeneity determinants in the included studies

| Variables | Simple multiple meta-regression | | | Multiple meta-regression | | |
|---|---|---|---|---|---|---|
| | Coefficient (95%CI) | P-value | Adj-$R^2$ | Coefficient (95%CI) | P-value | Adj-$R^2$ |
| Study design | 0.231 (0.051 to 0.402) | 0.011* | 22.96% | 0.383 (0.090 to 0.676) | 0.013* | 45.93% |
| Sample size (number) | -0.001 (-0.001 to 0.001) | 0.994 | 0% | -0.001 (-0.001 to 0.001) | 0.174 | |
| Mean of age (yrs. old) | -0.002 (-0.26 to 0.241) | 0.880 | 0% | -0.026 (-0.053 to 0.001) | 0.056 | |
| Death (<28 vs > 28 day) | -0.131 (-0.480 to 0.201) | 0.417 | 1.29% | -0.201 (-0.707 to 0.304) | 0.418 | |

*Significance at 0.05
CI, Confidence interval;
Coding for study design: 1=Cross-sectional, 2=Retrospective cohort, 3=Prospective cohort

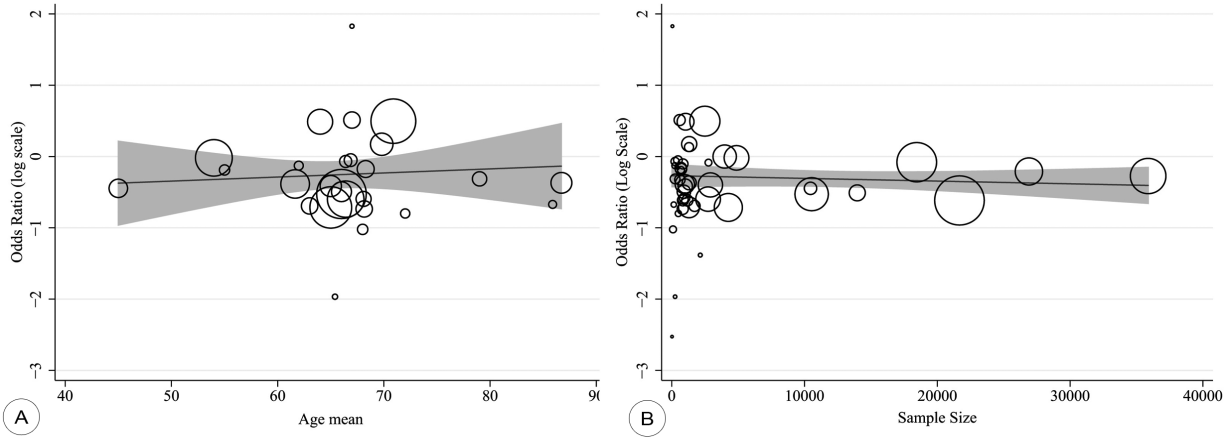


Figure 3. Association among age (A) and sample size (B) with the odds ratio of mortality for statin therapy (log scale) by means of meta-regression. The size of circles indicates the precision of each study.

sample size, mean of age and death time, on heterogeneity of mortality in multiple meta-regressions were also evaluated. As shown in Table 4, the study design remains significant effect on the heterogeneity of mortality (b: 0.383, p: 0.013) when adjusted for sample size, mean of age and death time. Although, the study design has a significant effect on the heterogeneity in the multiple model, but these four variables, in overall, explain about half of the mortality variance (Adj-$R^2$ = 45.93%).

## Publication Bias

The results of Egger's test showed no significant publication bias in the meta-analysis (coefficient: -0.051, p: 0.936). Figure 4 shows the funnel plot of mortality for statins therapy in the included studies.

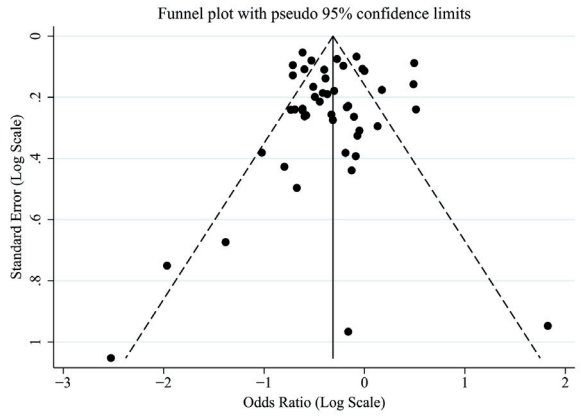


Figure 4. The funnel plot for publication bias assessment. The horizontal and vertical axes represent the odds ratio of mortality for statin therapy (in log scale) and the standard error of the odds ratio, respectively.

## Discussion

The present meta-analysis showed that statin therapy was associated with a reduced risk of mortality and ventilation in patients with COVID-19 but have had no effects on other clinical outcomes as compared to non-statin users. Statins have been traditionally used as lipid-lowering medications in patients with cardiovascular and cerebrovascular diseases, diabetes mellitus as well as other systemic disorders. Most studies have shown a reduced or a trend for decreased risk of death with statin use,[29, 30, 32-34, 36, 37, 39-41, 43, 45, 50-55, 57-60, 62, 63, 65-70, 72-74, 76-78, 80, 83] however, a few studies showed statins therapy were significantly associated with mortality.[28, 31, 38, 61, 64, 81, 82] Thus, conducting a meta-analysis in this regard is inevitable. In the current study, the results of the simple meta-regression analysis showed that study design have a significant effect on heterogeneity and random-effects model of meta-analysis was applied. These heterogeneities in the reported results may originate from the chronic and in-hospital use of statins and it is an important point of view to highlight. This suggests that prolonged exposure to statins would be required to manifest their beneficial consequences in patients with COVID-19. The presence of comorbidities in COVID-19 patients is associated with higher rates of severity and mortality, and patients with these chronic disorders are frequently prescribed statins before contracting and during COVID-19 infection.[85] Statins exert pleiotropic effects. High levels of cholesterol lead in the formation of atherosclerosis and accumulation of immune cells, including macrophages known as foam cells, which induce systemic inflammatory reactions, such as toll-like receptor and nuclear factor kappa-light- chain- enhancer of activated B cell (NF-κB) signaling[86-88] and in the main mechanism of action statins inhibit the HMG-CoA reductase in the cholesterol biosynthesis pathway. On the other hand, many pathways are required in the pathogenesis of COVID-19. SARS-CoV-2 enters into cells using ACE2, which is expressed with predominance in the lungs, heart, kidneys, and vascular system (89). ACE acts on angiotensin II to form angiotensin-(1 to 7), which has antifibrinolytic, anti-proliferative, anti-hypertrophic effects, vasodilating, and diuretic functions. Interestingly, statins can regulate ACE2 and have pleiotropic function against oxidative stress and inflammation.[12, 90] Moreover, it seems that statins up-regulate angiotensin-converting enzyme 2 receptor, which can facilitate SARS-CoV-2 cell entry.[91] In contrast, there is a potential mechanistic negative event of statins on COVID-19 infection from increasing ACE2 expression.[92] On contrary, statins alleviate major pathophysiological disorders of SARS-CoV-2 infection, including acute lung injury, endotheliitis and thrombo-inflammation.[90]

Besides, statins, especially pitavastatin, could cause a direct antiviral effect by interacting with the main protease enzyme of SARS-CoV-2.[20] The exaggerated immune response that lead to cytokine storm is thought to be the mechanism underlying the development of COVID-19-provoked complications, including ARDS, sepsis, dispersed intravascular coagulation and multiorgan failure.[85, 93] Some authors found that patients on statins therapy during hospitalization had lower[37, 83] but others showed higher rate of ARDS[56, 58] whereas, there is a potential mechanistic negative event of statins on COVID-19 infection from higher rates of ACE2 expression.[92] A recent study showed statins such as rosuvastatin significantly reduced SARS-CoV-2 hospitalization.[46] There were confounding factors that were not adequately reported or analyzed by the included studies that may contribute to the unexplained heterogeneity. Differences in statins types and dosage, as well as compliance, may affect the clinical outcomes. Some other studies indicated that the statins intake were significantly associated with hospitalization.[60] Randomized controlled trials are required for definite conclusion and there are several studies registered in clinical trials. Moreover, statin usage was significantly decreased the risk for intensive mechanical ventilation (IMV),[41, 74] whereas another study indicated that patients on statins during hospitalization had more rates of being on IMV than patients never on statin at 28 days.[58] A few authors showed patients on statin therapy had less kidney injuries.[78, 83] In contrast, some other studies demonstrated higher rates of kidney injuries.[56, 62] Statin therapy was not significantly related to other secondary outcomes such as acute kidney injury.[28] Therefore, statin may provoke many side effects such as myotoxicity and hepatotoxicity. Maybe myalgia (more common), increased creatine phosphokinase, rhabdomyolysis (rare) and consequently acute kidney injury, are the possible adverse events (94). However, liver injuries from statins are very rare, including COVID-19 patients.[36] In some patients, statins could cause elevated liver enzymes and rarely, liver injury in severe cases of COVID-19. Several authors have shown lower rates of ICU admission in participants taking statins[52, 53, 59, 62] but others found that patients on statins during hospitalization had higher rates of ongoing ICU admission.[34, 56, 58] However, the present meta-analysis showed that statin therapy was associated with a reduced risk of mortality and ventilation in patients with COVID-19 but have had no effects on other clinical outcomes. On other hand, there were some limitations to conduct the current study. First, due to the evaluation of observational studies, there is still a residual risk of confounding that can alter the results. Second, the heterogeneity of all estimates was high. Possible reasons for the heterogeneity include sample size, type, and timing of a heterogeneous population taking statins. Third, due to the lack of detailed information, there is a risk of misclassifying the timing of statin use (chronic versus hospitalized). Finally, some studies included outpatients and others only considered patients in the ICU. These differences in disease severity are possible sources of selection bias and may affect the estimate of the pooled effects.

## Conclusion

The present meta-analysis showed that statin therapy was associated with a reduced risk of mortality and ventilation in patients with

COVID-19 but have had no effects on other clinical outcomes.

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No.

**Conflicts of interests**

None declared.

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# Supplementary Material

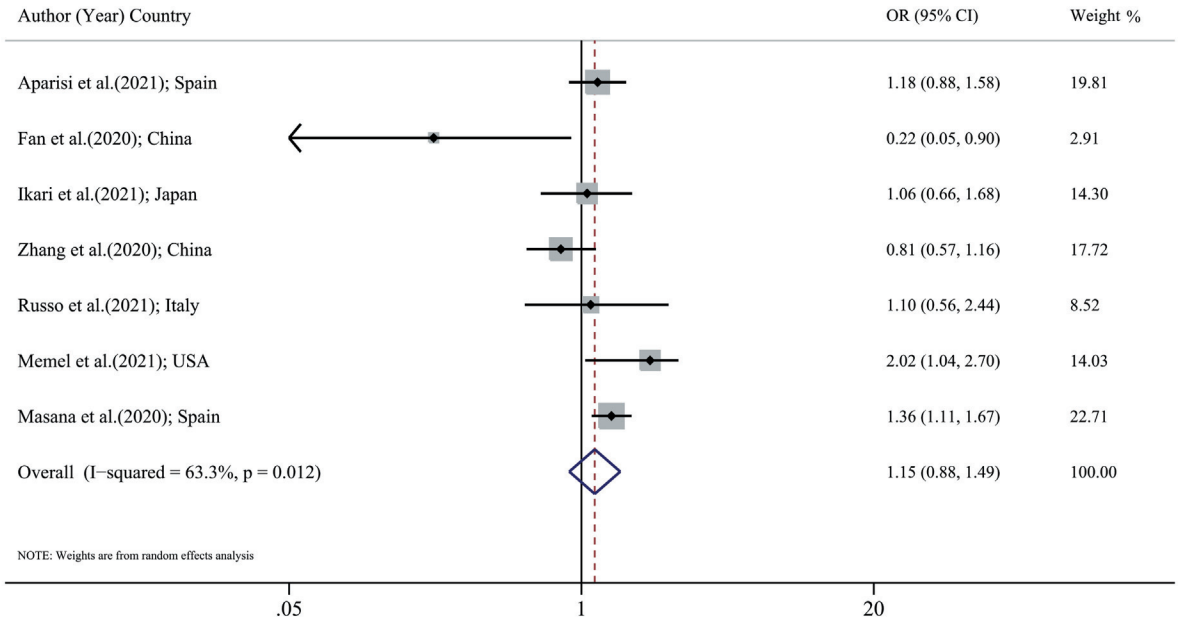


Figure 1. Forest plot for the association between statin therapy with odds of ARDS in COVID-19 patients based on a random-effects model. Each study identifies by the first author (year) and country. Each line segment's midpoint shows the odds ratio estimate, length of line segment indicates 95% CI in each study, and diamond mark illustrates the pooled estimate of odds ratio.

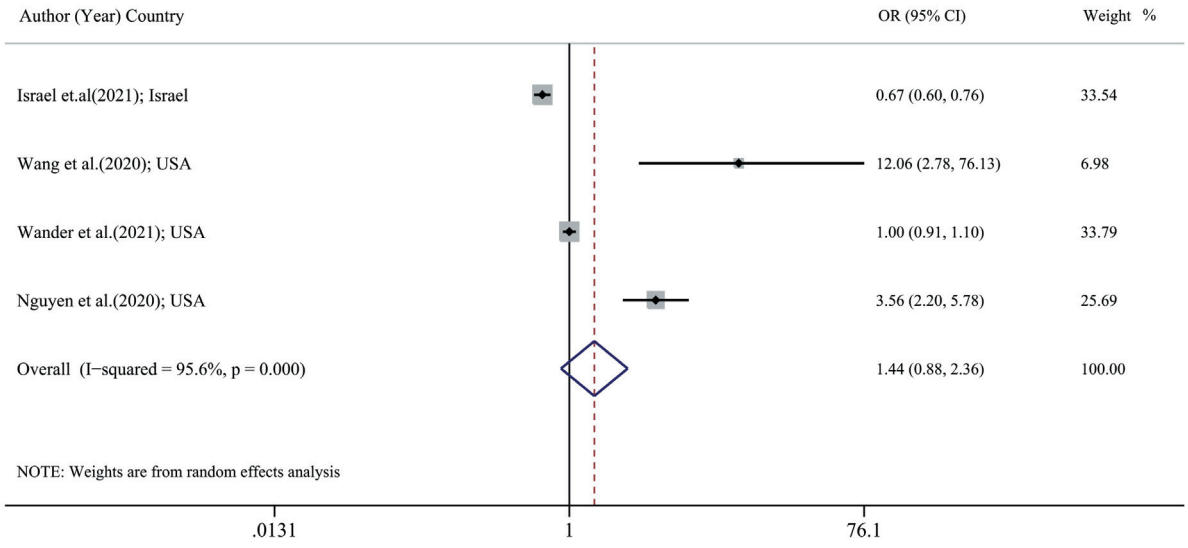


Figure 2. Forest plot for the association between statin therapy with odds of hospitalization in COVID-19 patients based on a random-effects model. Each study identifies by the first author (year) and country. Each line segment's midpoint shows the odds ratio estimate, length of line segment indicates 95% CI in each study, and diamond mark illustrates the pooled estimate of odds ratio.

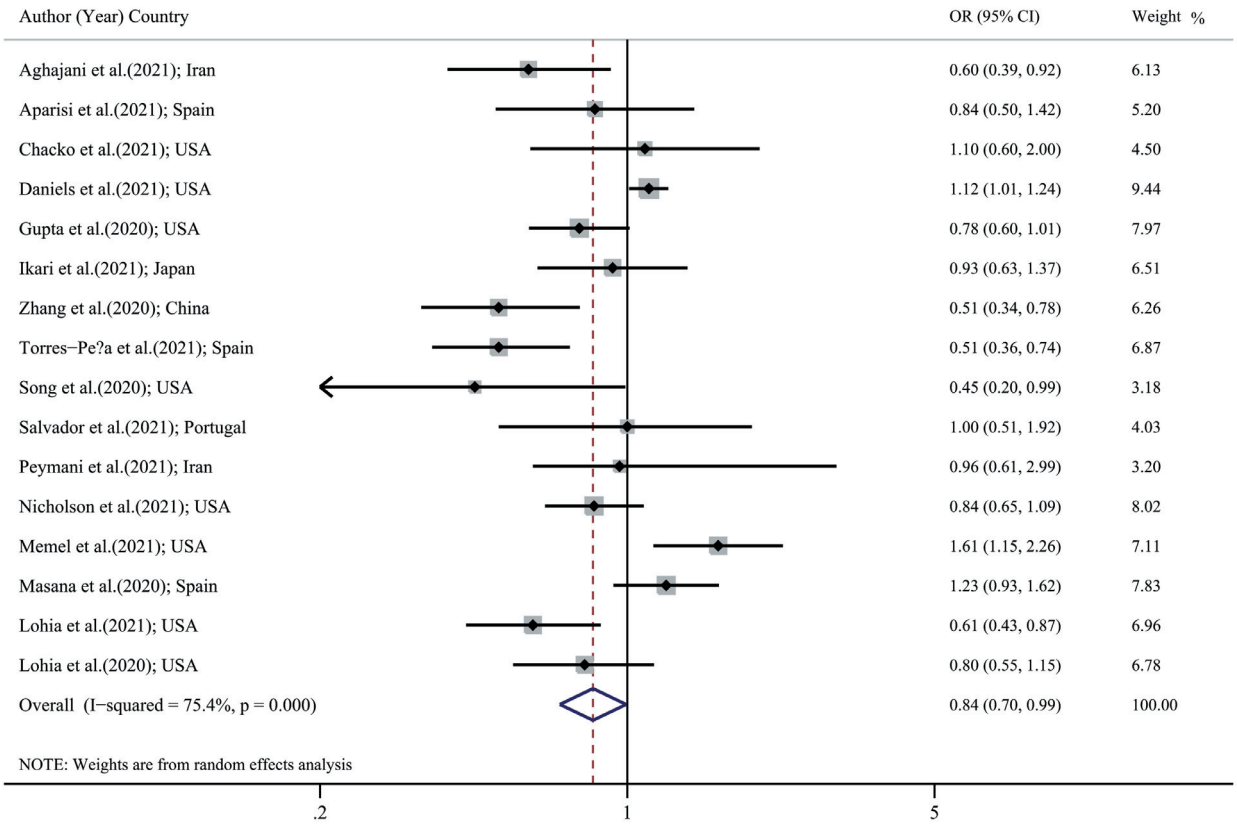


Figure 3. Forest plot for the association between statin therapy with odds of ventilation in COVID-19 patients based on a random-effects model. Each study identifies by the first author (year) and country. Each line segment's midpoint shows the odds ratio estimate, length of line segment indicates 95% CI in each study, and diamond mark illustrates the pooled estimate of odds ratio.

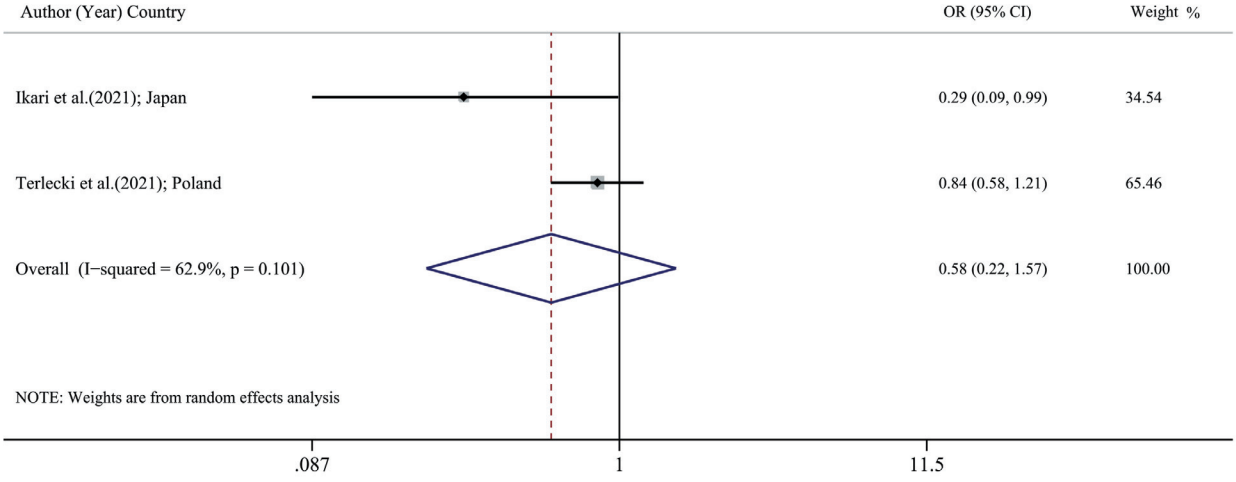


Figure 4. Forest plot for the association between statin therapy with odds of oxygen therapy in COVID-19 patients based on a random-effects model. Each study identifies by the first author (year) and country. Each line segment's midpoint shows the odds ratio estimate, length of line segment indicates 95% CI in each study, and diamond mark illustrates the pooled estimate of odds ratio.

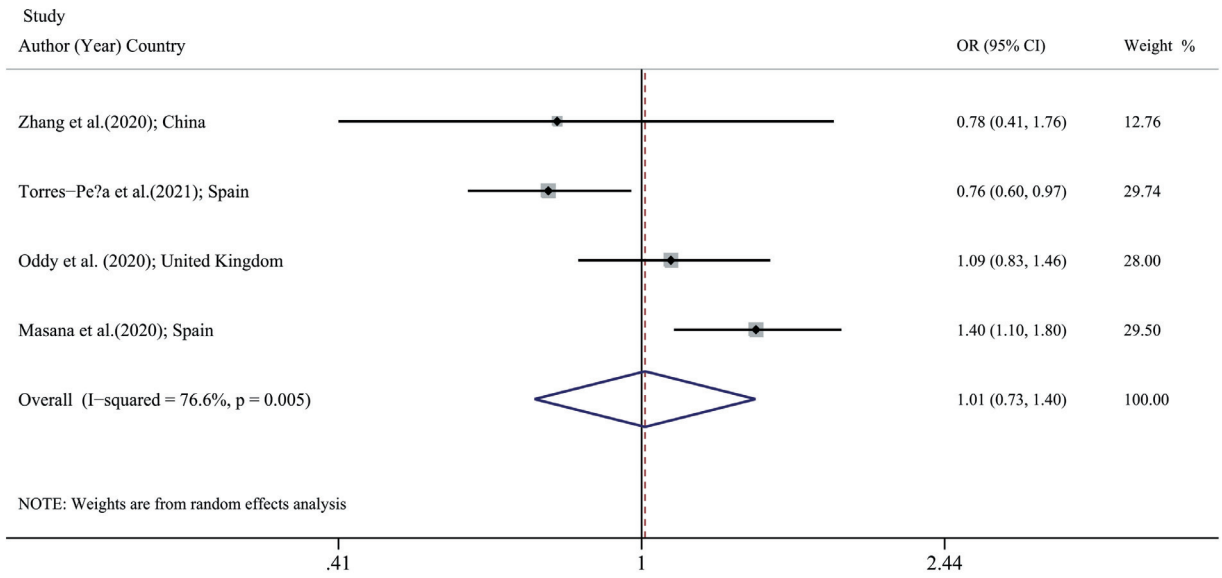


Figure 5. Forest plot for the association between statin therapy with odds of kidney failure in COVID-19 patients based on a random-effects model. Each study identifies by the first author (year) and country. Each line segment's midpoint shows the odds ratio estimate, length of line segment indicates 95% CI in each study, and diamond mark illustrates the pooled estimate of odds ratio.

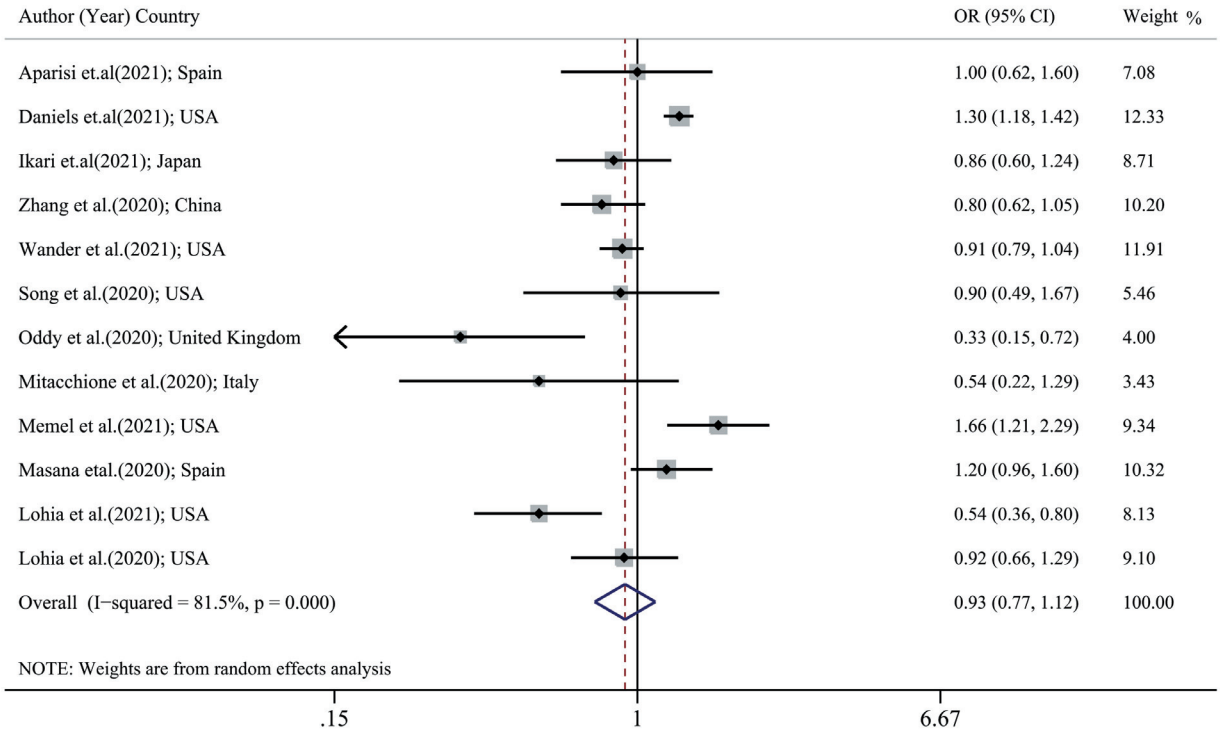


Figure 6. Forest plot for the association between statin therapy with odds of ICU admission in COVID-19 patients based on a random-effects model. Each study identifies by the first author (year) and country. Each line segment's midpoint shows the odds ratio estimate, length of line segment indicates 95% CI in each study, and diamond mark illustrates the pooled estimate of odds ratio.

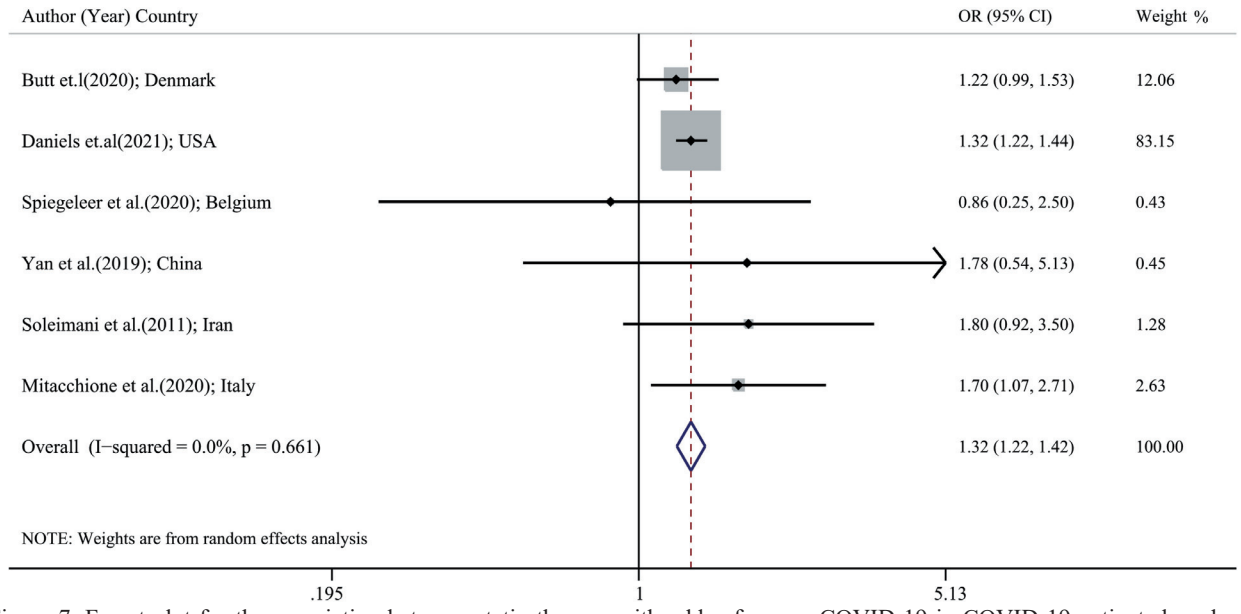


Figure 7. Forest plot for the association between statin therapy with odds of severe COVID-19 in COVID-19 patients based on a random-effects model. Each study identifies by the first author (year) and country. Each line segment's midpoint shows the odds ratio estimate, length of line segment indicates 95% CI in each study, and diamond mark illustrates the pooled estimate of odds ratio.

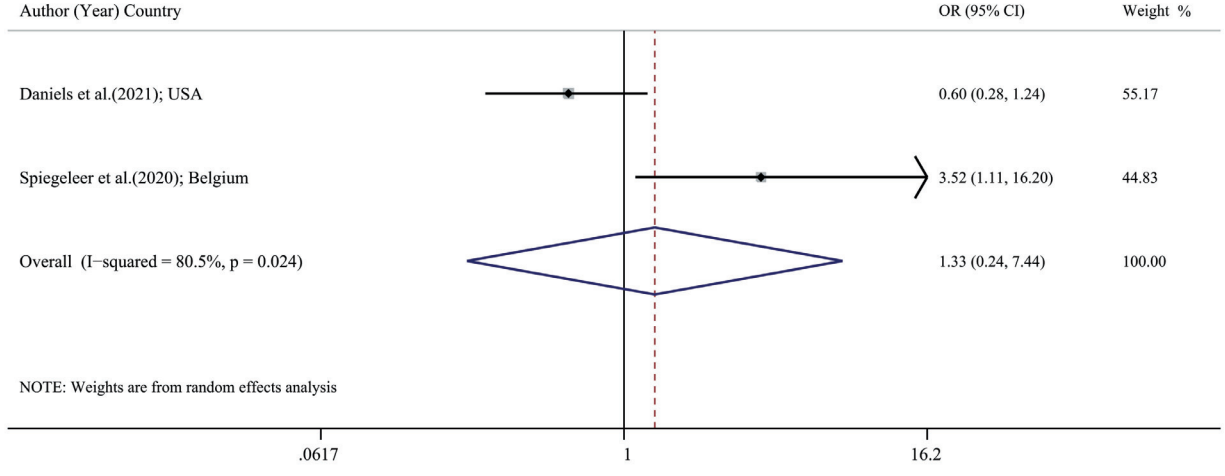


Figure 8. Forest plot for the association between statin therapy with odds of asymptomatic COVID-19 in COVID-19 patients based on a random-effects model. Each study identifies by the first author (year) and country. Each line segment's midpoint shows the odds ratio estimate, length of line segment indicates 95% CI in each study, and diamond mark illustrates the pooled estimate of odds ratio.