The association between the use of statins and clinical outcomes in patients with COVID-19: A meta-analysis

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Abstract

Purpose

Previously, we have reported clinical benefits with the use of statins in patients with COVID-19, in which our meta-analysis revealed a significantly reduced hazard for a fatal or severe course of illness with the use of statins, but the meta-analysis had been limited by a small number of studies included, with small heterogeneity among studies, due to unavailability of studies at the point of literature search. We aimed to perform an updated meta-analysis to summarize the existing evidence on the effect of statins on the clinical outcomes of patients with COVID-19.

Methods

Electronic databases including PubMed, Google Scholar, Scopus, and preprint servers were searched to identify studies investigating the association between the use of statins in patients with COVID-19 and the development of severe disease and/or mortality. Random-effects model meta-analyses were performed to calculate the pooled odds ratio (OR) or hazard ratio (HR) with 95% confidence intervals (95% CIs). The outcomes of interest were: (1) all-cause mortality and (2) a composite endpoint of the severe illness of COVID-19.

Results

Upon systematic literature search, we identified 21 studies, of which 18 studies reported the outcome of all-cause mortality and 11 studies reported the composite endpoint of the severe illness of COVID-19 between statins users with COVID-19 versus non-statins users with COVID-19. Our meta-analysis revealed adequate evidence that the use of statins was associated with significantly lower risk of all-cause mortality (HR = 0.70; 95% CI 0.58–0.84; n=21,127 and OR = 0.63; 95% CI 0.51–0.79; n=115,097) and composite endpoint of severe illness (OR = 0.80; 95% CI 0.73–0.88; n=10,081) in patients with COVID-19, compared to non-use of statins, at the current sample size.

Conclusion

Statin use is associated with a better prognosis in patients with COVID-19. Our findings provided a rationale to trial the use of statins among patients with COVID-19 on a larger scale trial.

Keywords: COVID-19; HMG-CoA reductase inhibitor; Mortality; Severity; Statin

Key Points

- The establishment of clinical benefits with the in-hospital use or pre-admission use of statins in patients with COVID-19 would have a significant clinical implication since it would provide another rationale for clinicians to ensure that this patient population where statin treatment is appropriately indicated should be receiving a statin with appropriate intensity
- The use of statins was associated with a significantly lower risk of all-cause mortality and the composite endpoint of severe illness in patients with COVID-19 compared to non-use of statins.

Introduction

The global spreading of the coronavirus disease 2019 (COVID-19) pandemic has called for the development of new pharmacological therapeutic interventions or repurposing of existing pharmacological therapeutic interventions to prevent disease progression and deaths in patients with COVID-19. Previously, we have reported clinical benefits with the use of statins in patients with COVID-19, in which our meta-analysis of four studies with over 9,000 patients with COVID-19 revealed a significantly reduced hazard for a fatal or severe course of illness with the use of statins compared to non-use of statins (pooled hazard ratio = 0.70; 95% confidence interval 0.53-0.94) [1]. However, our meta-analysis on the effect of statins in patients with COVID-19 had been limited by the small number of studies included, with small heterogeneity among studies, due to the unavailability of studies at the point of literature search.

The establishment of clinical benefits with the in-hospital use or pre-admission use of statins in patients with COVID-19 would have a significant clinical implication, not only in the management of patients with COVID-19 but also in the management of patients at high risk or with established cardiovascular disease who have not acquired COVID-19 as yet, since it would provide another rationale for clinicians to ensure that this patient population where statin treatment is appropriately indicated should be receiving a statin with appropriate intensity, particularly amid the COVID-19 pandemic [2,3]. In terms of management of patients with COVID-19, we have thus far struggling to achieve a significant breakthrough for life-saving therapeutic interventions except for systemic corticosteroids, with the latest announcement of findings from the World Health Organization's Solidarity Trial failed to show clinical benefits with the use of much-hyped remdesivir and other antiviral agents [4,5]. Therefore, if statin treatment could be proven to provide clinical benefits in patients with COVID-19, the lives of hundreds of thousands could be saved since statins are readily available and certainly are one of the most prescribed drugs worldwide [6].

Since the publication of our meta-analysis [1] on the effect of statins in patients with COVID-19, few [7-9] have commented on the reliability of our findings. With more studies available that reported the clinical outcomes on the use of statins in patients with COVID-19, we aimed to perform an updated meta-analysis to determine the overall effect of statins on the clinical outcomes of patients with COVID-19. In this article, we also discussed the comments [7-9] addressed in our previous meta-analysis.

Methods

Search strategy and selection criteria

The eligibility criteria for inclusion of studies included: (1) original research which investigated the association between the use of statins, regardless of type, dose, and duration, in patients with COVID-19 and development of severe disease and/or mortality, (2) cohort studies and case-control studies which provided measurement of association with adjustment of confounders (3) studies with any languages or sample size. Exclusion criteria included: (1) commentaries, editorials, reviews, *in vitro* and *in vivo* studies, and other irrelevant study designs and (2) cohort studies and case-control studies that provided measurement of association without adjustment of confounders.

We performed a systematic literature search in electronic databases including PubMed, Google Scholar, Scopus. We also hand-searched preprint servers (medRxiv, Research Square, SSRN) and reference lists of relevant reviews and included studies. We last updated our literature search on June 03, 2021. The search strategy was built based on the following keywords and their MeSH terms: "COVID-19", "statin", and "HMG-CoA reductase". Two investigators (CSK and SSH) independently performed literature screening to identify eligible studies, and disagreements were resolved through mutual discussion.

Data extraction and risk of bias assessment

The data extraction and risk of bias assessment were performed by the first investigator (CSK) and cross-checked by the second investigator (SSH). Data extracted from the included studies included the name of the first author, study design, study location, the total number of patients, patients' age, type of statins received, event numbers, and summary estimates of effect measures, including adjusted odds ratio (aOR) and adjusted hazard ratio (aHR). The quality of observational studies was evaluated using the Newcastle-Ottawa Scale [10].

The outcomes of interest were: (1) all-cause mortality and (2) a composite endpoint of the severe illness of COVID-19, which included the requirement of intubation/mechanical ventilation, admission into intensive care unit, and is categorized as severe/critical course of illness as defined by the authors. The definition of severe/critical disease varied across the included studies.

Data analysis

Pooled odds ratio (OR) or hazard ratio (HR) with 95% confidence intervals (CIs) was used as a summary relative effect measure. The random-effects model was used to perform the meta-analysis given the potential heterogeneity across the included studies. The statistical heterogeneity was determined

using the I^2 and Q statistics. Subgroup analyses were conducted to determine potential differences based on the regions where the included studies were performed. Sensitivity analyses were conducted to evaluate the robustness of the results by limiting to studies that included patients with laboratory-confirmed COVID-19 (instead of clinically or radiologically conformed COVID-19), studies that confirmed the continuation of statin therapy during hospitalization for COVID-19, and studies which the definition of severe illness is based on the requirement of mechanical ventilation or intubation. A funnel plot for asymmetry was visually inspected to evaluate the included studies for publication bias. All the analyses were performed using Meta XL, version 5.3 (EpiGear International, Queensland, Australia).

Results

Study selection and characteristics

We retrieved 965 records from the combination of two independent searches. After the removal of duplications and irrelevant literature, 56 full-text articles were assessed for eligibility. A total of 35 studies [11-45] (32 published studies [11-24,26-29,31-35,37-45] and 3 studies available as a preprint [25,30,36]) which corresponded to the inclusion and exclusion criteria were included in the meta-analyses (**Figure 1**).

All the included studies [11-45] are observational studies, reported in the study design of cohort/case-control or database review. All except seven studies [18,26,29,35,38,39] were based directly on the original hospital (or nursing home) medical records, and twelve of the included studies [13,20,22,23,25,31,33,36,41-44] are single-centered observational studies. These hospital- (or nursing home)-based studies [11-17,19-25,27,28,30-34,36,37,40-45] covered a moderate number of participants per study (median: 840.0, interquartile range: 286.5-1997.5). There are seven studies [18,26,29,34,35,38,39] that analyzed data from nation-level registries (retrospective database review), which included a range of 1,868 to 64,781 participants. The regions where the included studies were performed span Asia (China [n=4] [11,12,27,42], Iran [n=1] [31], and Korea [n=1] [39]), Europe (Italy [n=4] [14,23,28,37], United Kingdom [n=2] [25,30], Belgium [n=1] [15], France [n=1] [19], Spain [n=3] [24,35,40], Denmark [n=1] [26], Poland [n=1] [44], Sweden [n=1] [38], and Belgium [n=1] [32]), and North America (United States of America [n=14] [13,16-18,20-22,29,33,34,36,41,43,45]). Seven studies [15,19,32-34,38,42] (could have) included both laboratory-confirmed and clinically or radiologically confirmed patients with COVID-19, while the remaining studies [11-14,16-18,20-31,33-37,39-41,43-45] included only laboratory confirmed patients with COVID-19. Eleven studies [12,13,18,20,27,32,35,36,39,42,44] confirmed the continuation/de novo initiation of statins during hospitalization for COVID-19. **Table 1** summarizes the main characteristics of all the included studies.

Assessment with the Newcastle-Ottawa Scale revealed that other than three studies [11,19,20] which are of moderate quality (5/9 to 6/9), all studies [12-18,21-45] are of good quality (at least 7/9). None of the included studies are of poor quality.

Use of statins and all-cause mortality in patients with COVID-19

The outcome of all-cause mortality is available in 32 studies [12-14,16-21,23-45] comparing statins users versus non-statins users with COVID-19, of which ten studies [12-14,20,24,26,27,31,36,45] provided adjusted measures in hazard ratio, whereas twenty two studies [16-19,21,23,25,28-30,32-35,37-44] provided adjusted measures in odds ratio. The meta-analysis of studies with a hazard ratio which included 21,127 patients with COVID-19 revealed that the use of statins was associated with a significantly lower hazard of all-cause mortality in patients with COVID-19, compared to non-use of statins (**Figure 2(A)**; HR = 0.70; 95% CI 0.58–0.84). The pooled measure of the adjusted odds ratio is consistent with the pooled measure of adjusted hazard ratio (n=115,097), which demonstrated significantly reduced odds of all-cause mortality with the use of statin in patients with COVID-19, compared to non-use of statins (**Figure 2(B)**; OR = 0.63; 95% CI 0.51–0.79). Visual inspection of the funnel plot (**Figure 4(A)**) identified some degree of asymmetry.

Subgroup analyses with studies originated from Asia (HR = 0.56; 95% CI 0.42-0.75) [12,27,31], Europe (OR = 0.77; 95% CI 0.64-0.94) [19,23,25,28,30,32,35,37,38,40,44], and North America (OR = 0.62; 0.54-0.73) respectively [16-18,21,29,33,34,41,43], observed significantly reduced risks of mortality with the use of statin in patients with COVID-19, compared to non-use of statins. Findings from the sensitivity analyses with studies [12-14,16-18,20,21,23-31,33-37,39-41,43-45] included only laboratory-confirmed patients with COVID-19 (OR = 0.64; 95% CI 0.57–0.72 and HR = 0.70; 95% CI 0.58–0.84) and studies [12,13,20,27,32,35,36,39,42,44] which confirmed the continuation of statins during hospitalization for COVID-19 (OR = 0.61; 95% CI 0.52–0.73 and HR = 0.59; 95% CI 0.41–0.84) are consistent with the main analyses.

Use of statins and development of severe illness in patients with COVID-19

A total of fifteen studies [11,12,15-17,19,22,26-28,31,35-37,43] reported the composite endpoint of severe illness of COVID-19, and all except four studies [12,26,27,36] provided adjusted measures in odds ratio. The definition of severe illness varied across the seven studies: in the study by Yan et al. [11], the definition is based on that given in Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia by the Chinese National Health Commission; in the studies by Zhang et al. [12], Butt et al. [26], Fan et al. [27], and Mitacchione et al. [28], and Greco et al. [37], the definition is based on admission into intensive care unit or Pulmonology department; in the study by Spiegeleer et al. [15],

the definition is based on long-stay hospital admission or death; in the studies by Gupta et al. [16], Cariou et al. [19], Peymani et al. [31], the definition is based on the requirement of intubation/mechanical ventilation; in the study by Song et al. [17] and Lohia et al. [43], the definition is based on admission into intensive care unit or requirement of intubation; in the study by Daniels et al. [22] and Memel et al. [36], the definition is based on admission into intensive care unit or death; in the study by Torres-Peña et al. [35], the definition is based on development of acute respiratory distress syndrome.

The meta-analysis of studies [11,15-17,19,22,28,31,35,37,43] with odds ratio, which altogether included 10,081 patients with COVID-19, observed that the use of statins was associated with significantly lower odds of development of severe illness in patients with COVID-19, compared to non-use of statins (**Figure 3(A)**; OR = 0.80; 95% CI 0.73–0.88). The pooled measure of adjusted hazard ratio is consistent with the pooled measure of adjusted odds ratio (n=10,738), which demonstrated non-significantly reduced hazard of development of severe illness with the use of statin in patients with COVID-19, compared to non-use of statins (**Figure 3(B)**; HR = 0.80; 95% CI 0.56–1.14). Visual inspection of the funnel plot (**Figure 4(B)**) identified some degree of asymmetry.

Subgroup analyses with studies originated from Europe (OR = 0.79; 95% CI 0.71-0.89) [15,19,28,35,37] and North America (OR = 0.79; 0.59-1.05) respectively [16,17,22,43], observed reduced risks of mortality with the use of statin in patients with COVID-19, compared to non-use of statins. Sensitivity analyses with studies [11,16,17,22,28,31,35,37,43] included only laboratory-confirmed patients with COVID-19 (OR = 0.79; 95% CI 0.72–0.88), studies [12,27,36] which confirmed the continuation of statins during hospitalization for COVID-19 (HR = 0.71; 95% CI 0.55–0.92), and studies which the definition of severe illness is based on the requirement of mechanical ventilation or intubation [16,17,19,31,43] (OR = 0.81; 95% CI 0.69–0.96) also revealed consistent findings.

Discussion

Before the publication of our first meta-analysis [1] on the effect of statins in patients with COVID-19, the use of statins had already gained attention, in which some hypothesized that statins might assume clinical benefits in patients with COVID-19 based on their several mechanisms of action [45,46], and yet some postulated that statins might cause harms in patients with COVID-19, citing a risk for development of acute respiratory distress syndrome, amongst others [47-49]. We have in our meta-analysis [1] denied the possibility of harms with the use of statins in patients with COVID-19, and again in our updated meta-analysis with more studies and a larger cohort of patients included, we substantiated our previous findings where the use of statins could reduce the risk of development of a fatal course or a severe course of illness in patients with COVID-19.

Our findings that statins were beneficial to patients with COVID-19 had their biological plausibility. Nevertheless, the mechanisms by which statins exert beneficial effects are still not known with certainty due to their pleiotropic effects: statins could modulate inflammation and immune response, as well as exert direct antiviral effects, and improve endothelial function. It has been demonstrated that statins can inhibit the activity of transcription factors, including activator protein-1 and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which are involved in mediating inflammatory pathways of coronavirus infection such as interleukin-1β [50]. In addition, statin therapy has been shown to downregulate the expression of toll-like receptor-4 on immune cells, with subsequent downregulation of NF-κB activity, and therefore a decrease in the secretion of inflammatory cytokines and a reduced risk for the development of acute distress respiratory syndrome [51].

On the other hand, statins' direct antiviral effect involves a reduction in the percentage of cholesterol present in the plasma membrane and subsequent alteration of the assembly of viral receptors, thereby markedly reducing the possibility of entry of coronaviruses into host cells, since coronaviruses bind specific receptors (angiotensin-converting enzyme 2) which are concentrated at the areas of plasma membrane rich in cholesterol, also known as lipid rafts [52,53]. Furthermore, potential improvement in endothelial function by statins among patients with COVID-19 could be achieved through reduced platelet aggregation, increased thrombomodulin expression on endothelial cells, and decreased tissue factor expression [54]. This mechanism of statin is highly desirable since endothelial dysfunction is the common denominator of a range of clinical manifestations of a severe course of COVID-19 [55].

There are concerns that the use of statins in patients with COVID-19 may heighten the risk and severity of viral-induced myopathies. However, clinically significant myonecrosis with an elevation of serum level of creatine kinase more than 10 times normal in conjunction with muscle symptoms developed in less than 0.5% of patients receiving statin therapy in large-scale clinical trials [56-59]. Moreover, clinical rhabdomyolysis, defined as myonecrosis with myoglobinuria or acute renal failure, continues to be a very rare event during statin therapy, with an incidence of hospitalization for rhabdomyolysis about 0.44 per 10,000 patient-years [60]. While COVID-19-associated myositis is likely not the main clinical manifestation, patients with symptomatic or asymptomatic myonecrosis or clinical rhabdomyolysis should discontinue statin therapy immediately.

Since statins could assume benefits in patients with COVID-19, the dosing of statin therapy for the treatment of COVID-19 has become an important issue. Only two included studies [12,13] revealed the dosing regimen of statins received by the patients; Zhang et al. [12] reported a median atorvastatin

equivalent dose of 20 mg per day, whereas Rodriguez-Nava et al. [13] reported the use of atorvastatin at a dose of 40 mg per day. Nevertheless, there had been three studies [26,28,43] that evaluated the difference in outcomes between low-/moderate-intensity statin therapy and high-intensity therapy. Butt et al. [26] reported no significant difference in the risk of all-cause mortality (HR = 1.07; 95% CI 0.77–1.50), and the risk of severe disease (HR = 0.81; 95% CI 0.60–1.10) in patients who received low-/moderate-intensity statin therapy compared to those who received high-intensity statin therapy. Similarly, Mitacchione et al. [28] reported no significant difference in the risk of in-hospital mortality (OR = 1.17; 95% CI 0.77–1.76) in patients who received moderate-intensity statin therapy compared to their counterparts who received high-intensity statin therapy. In contrast, the study by Lohia et al. [43] revealed that moderate-intensity and high-intensity but not low-intensity statin therapy was associated with significantly lower risk of mortality (OR= 0.52; 95% CI 0.31–0.87 and OR=0.54; 95% CI 0.29-0.99) compared to no statin therapy, among propensity-matched patients with COVID-19.

Fedson [7] commented that we had in our previous meta-analysis considered studies regardless of whether the included patients received statin therapy either during hospitalization or as outpatients. Therefore, our estimate of the effect of statins was probably imprecise. Although the study design of the concerned studies did not allow proper confirmation that statin intake from outpatient was continued during hospital admission, it may be safe to assume that statin intake was not discontinued during hospitalization, since there was no directive or recommendation from any clinical guidelines to discontinue statins upon acquisition of COVID-19 despite speculations that statins may cause harms in patients with COVID-19; conversely, continued use is recommended in patients already receiving statins prior to the acquisition of COVID-19, since the established clinical benefits with the use of statins outweigh the possibility of harms in this patient population [3,61]. In addition, we have now performed a subgroup analysis with the inclusion of studies that confirmed the use of statins during the hospitalization of COVID-19.

Katsiki et al. [8] provided mechanisms that could explain the beneficial impact of statins in patients with COVID-19, other than those we have described in our previous meta-analysis. They hypothesized that statins could exert a protective effect on developing acute kidney injury and acute cardiac injury in patients with COVID-19, both of which are also predictors of mortality in this patient population. We agreed with their proposed mechanism, though we would caution that such an effect has yet to be conclusively proven. In the study by Zhang et al. [12], there was no significant protective effect of statins against the development of both acute kidney injury (adjusted HR = 0.72; 95% CI 0.51–1.01) and acute cardiac injury (adjusted HR = 1.16; 95% CI 0.98–1.37). More evaluation from other studies is needed. Katsiki et al. [8] also cautioned drug-drug interactions between statins and other pharmacological treatments with COVID-19, specifically azithromycin and ritonavir/lopinavir.

However, the use of both azithromycin and ritonavir/lopinavir in patients with COVID-19 is out of favor currently since available studies have failed to show their benefits in patients with COVID-19 [4,62-64].

Ganjali et al. [9] have commented that the findings in our previous meta-analysis were in contrast with another meta-analysis by Hariyanto et al. [65], which reported that the use of statins failed to improve clinical outcomes of hospitalized patients with COVID-19. However, it should be noted that the meta-analysis by Hariyanto et al. [65] pooled odds ratio directly from crude event numbers without consideration of potential confounders that might modify the association between the use of statins and mortality as well as the development of severe outcomes in patients with COVID-19. In contrast, we extracted and pooled only adjusted measures of effect, which increased the reliability of our findings, which demonstrated clinical benefits using statins in patients with COVID-19.

Our meta-analysis has several limitations. First, the included studies are retrospective/prospective observational studies. Although studies with retrospective/prospective design may not be ideal for investigating the causal relationships between interventions and outcomes, adjustment of potential confounders in the respective studies may reduce the risk of bias in the findings. Second, it was unclear if statin use was continued during hospitalization for COVID-19 in most of the included studies, but continued use could be safely assumed since no recommendation of discontinuation of statins in patients with COVID-19 thus far. In addition, we have performed subgroup analysis with studies [12,13,18,20,27,32,35,36,39,42,44] that confirmed the continuation of statins during hospitalization for COVID-19. Third, the regimen of statins used was not mentioned in most of the included studies, but based upon studies that provided such information, statin therapy of moderate-to-high intensity could be effective.

Conclusion

Thus far, there is adequate evidence from observational studies at the current sample size suggesting that the use of statins was associated with a significantly reduced risk of development of a fatal course or a severe course of illness in patients with COVID-19. Our findings provided a rationale to trial the use of statins among patients with COVID-19 on a larger-scale clinical trial. In the meantime, we await more data from prospective studies or randomized controlled trials to substantiate our findings of clinical benefits using statins in patients with COVID-19. In addition, future studies should segregate the analysis based on different types of statins (lipophilic statins versus hydrophilic statins) to determine if the mortality benefits represent a class effect or if only certain types of statins demonstrate clinical benefits in patients with COVID-19.

Disclosure of interest:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1: Characteristics of included studies

Study	Country	Design	Total number of patients	Age (mean [SD]/median [IQR])	Type of statin	Mortality			Severe illness[a]			Adjustment	NOS
						Statin users (n/N; %)	Non-statin users (n/N; %)	Adjusted estimate	Statin users (n/N; %)	Non-statin users (n/N; %)	Adjsuted estimate		
Yan et al [11]	China	Retrospective, multicenter, case-control study	610	48.8 (14.2)	N/A	-	-	-	5/15; 31.3	123/578; 20.7	OR=1.78 (0.54-5.13)	Age, sex, body mass index	5/9
Zhang et al [12]	China	Retrospective, multicenter, cohort study	4305	Statin= 66.0 (59.0–72.0) Non-statin=57.0 (45.0–67.0)	Atorvastatin, rosuvastatin, simvastatin, pravastatin, fluvastatin, pitavastatin	45/861; 5.2	325/3444; 9.4	HR=0.58 (0.43-0.80)	N/A	N/A	HR=0.69 (0.56-0.85)	Mortality: Age, gender, and oxygen saturation at admission Severity: Age, gender, blood pressure, pre-existing comorbidities, indicators of disease severity and organ injuries, low-density-lipoprotein-cholesterol increase, total cholesterol increase	8/9
Rodriguez-Nava et al [13]	USA	Retrospective, single center, cohort study	87	68 (58-75)	Atorvastatin	N/A	N/A	HR=0.38 (0.18-0.77)	-	-	-	Age, hypertension, cardiovascular disease, invasive mechanical ventilation, severity according to the National Institutes of Health criteria, number of comorbidities, and adjuvant therapies	7/9
Grasselli et al [14]	Italy	Retrospective, multicenter, cohort study	3988	63 (56-69)	N/A	N/A	N/A	HR=0.98 (0.81-1.20)	-	-	-	Age, gender, type of respiratory support, comorbidities, angiotensin-converting enzyme inhibitor therapy, angiotensin receptor blocker, diuretic, positive end-expiratory pressure at admission, fraction of inspired oxygen at admission, arterial partial pressure of oxygen/fraction of inspired oxygen at admission	7/9
Spiegeleer et al [15]	Belgium	Retrospective, multicenter, cohort study	154	85.9 (7.2)	N/A	-	-	-	6/31	31/123	OR=0.86 (0.25–2.50)	Age, sex, functional status, diabetes mellitus, hypertension, diagnosis method	7/9
Gupta et al [16]	USA	Retrospective, multicenter, cohort study	2626	Statin users: 70 (63-79) Non-statin users: 62 (49-76)	N/A	N/A	N/A	OR=0.56 (0.44-0.72)	N/A	N/A	OR=0.80 (0.64-1.02)	Age, sex, body mass index, ethnicity, insurance, New York City borough of residence, comorbidities, outpatient use of beta-blockers, ACEi, ARBs, oral	8/9

												anticoagulants, and P2Y12 receptor inhibitors	
Song et al [17]	USA	Retrospective, multicenter, cohort study	249	Statin users: 71.0 (60.0–79.0) Non-statin users: 54.5 (42.0–67.0)	N/A	N/A	N/A	OR=0.88 (0.37–2.08)	N/A	N/A	ICU admission: OR=0.90 (0.49–1.67) Intubation: OR=0.45 (0.20–0.99)	Age, sex, race, comorbidities	7/9
Mallow et al [18]	USA	Retrospective database review	21676	64.9 (17.2)	Atorvastatin, rosuvastatin, simvastatin, pravastatin, pitavastatin	N/A	N/A	OR=0.54 (0.49-0.60)	-	-	-	Age, sex, primary payer, Medicaid, comorbidities. use of ACEi, use of ARBs, bed size, hospital teaching status, geographic region	8/9
Cariou et al [19]	France	Retrospective, multicenter, cohort study	2449	Statin users: 71.7 (10.8) Non-statin users: 70.2 (13.9)	N/A	229/1192; 19.2	248/1257; 19.7	OR=0.92 (0.63-1.35)	283/1192; 23.7	229/1257; 18.2	OR=0.92 (0.63-1.35)	Age, sex, ethnicity, body mass index, comorbidities, macrovascular complications, use of co-medications,	6/9
Saeed et al [20]	USA	Retrospective, single center, cohort study	2266	Statin users: 69 (11) Non-statin users: 67 (14)	Atorvastatin, rosuvastatin, simvastatin, pravastatin	N/A	N/A	HR=0.87 (0.83-0.91)	-	-	-	Age, sex, body mass index, days of symptoms prior to admission, history of atherosclerotic heart disease, Charlson comorbidity index, presenting diastolic blood pressure, respiratory rate, pulse oximetry measurement, heart rate, laboratory measurements, use of co-medications, troponin level and intravenous antibiotics during hospitalization	6/9
Nicholson et al [21]	USA	Retrospective, multicenter, cohort study	1042	64 (53-75)	N/A	122/511; 23.9	88/531; 16.6	OR=0.47 (0.24-0.92)	N/A	N/A	N/A	Age, sex, comorbidities, oxygen saturation to fraction of inspired oxygen ratio, body mass index, neutrophil to lymphocyte ratio, platelet count, procalcitonin level	8/9
Daniels et al [22]	USA	Retrospective, single center, cohort study	170	59 (19)	N/A	-	-	-	20/46; 43.4	70/124; 56.5	OR=0.29 (0.11-0.71)	Age, sex, comorbidities. use of ACEi, use of ARBs	8/9
Bifulco et al [23]	Italy	Retrospective, single center, cohort study	541	Statin users: 72.9 (10.9) Non-statin users: 63.0 (14.5)	N/A	N/A	N/A	OR=0.75 (0.26-2.17)	-	-	-	Age, sex, smoking habit, comorbidities, indicators of disease severity, organ injuries, blood biomarkers	7/9

Masana et al [24]	Spain	Retrospective, multicenter, cohort study	1162	Statin users: 73 (65-80) Non-statin users: 74 (64-84)	N/A	115/581; 19.8	148/581; 25.4	HR=0.58 (0.39-0.89)	-	-	-	Age, sex, smoking habit, comorbidities, use of co-medications, lipid profile before admission	7/9
Philipose et al [25]	UK	Retrospective, single center, cohort study	466	Disharged: 67 (26) Died: 77 (17)	N/A	79/164; 48.1	120/302 39.7	OR=1.03 (0.71-1.45)	-	-	-	Age, sex	8/9
Butt et al [26]	Denmark	Retrospective database review	4842	Statin users: 73 (63-79) Non-statin users: 50 (37-65)	Atorvastatin, rosuvastatin, simvastatin, pravastatin	311/3999; 7.8	177/843; 21.0	HR=0.96 (0.78-1.18)	419/3999; 10.5	204/843; 24.2	HR=1.16 (0.95-1.41)	Age, sex, ethnicity, education, income, use of comorbidities, comedications	7/9
Fan et al [27]	China	Retrospective, multicenter, cohort study	412	Statin users: 64 (57-72) Non-statin users: 66 (57-73)	N/A	3/206; 1.5	10/206; 4.9	HR=0.25 (0.07-0.92)	9/206; 4.4	17/206; 8.3	HR=0.38 (0.16-0.92)	Age, sex, comorbidities, type of hospital, use of ACEis/ARBs, use of glucocorticoids, neutrophil count, D-dimer level, total cholesterol level, triglyceride level, LDL-C level, procalcitonin level, creatine kinase–MB level, troponin level, brain natriuretic peptide level	8/9
Mitacchione et al [28]	Italy	Retrospective, multicenter, cohort study	290	Statin users: 71 (64-79) Non-statin users: 72 (61-80)	Atorvastatin, rosuvastatin, simvastatin	38/145; 26.2	41/145; 28.3	OR=0.90 (0.54-1.51)	6/145; 4.1	11/145; 7.6	OR=0.53 (0.19-1.46)	Age, sex, comorbidities	8/9
Rosenthal et al [29]	USA	Retrospective database review	64781	56.1 (19.9)	N/A	2426/12233; 19.8	4929/52548; 9.4	OR=0.60 (0.56-0.65)	-	-	-	Age, sex, race, ethnicity, payer type, type of admission, admission point of origin, geographic region, geographic size, rural/urban status, teaching status, comorbidities, complications, comedications, use of supplements during index hospitalization	8/9
Xiang et al [30]	UK	Prospective, multicenter, cohort study	3858	68.1 (8.1)	N/A	N/A	N/A	OR=2.48 (0.99-6.19)	-	-	-	Age, sex, ethnicity, comorbidities, blood measurement, number of medications taken, number of non-cancer illnesses, body mass index, Townsend Deprivation index, smoking status	7/9

Peymani et al [31]	Iran	Retrospective, single center, cohort study	150	Statin users: 63.6 (13.2) Non-statin users: 61.7 (15.8)	Atorvastatin, rosuvastatin, simvastatin	N/A	N/A	HR=0.76 (0.16-3.72)	N/A	N/A	OR=0.96 (0.61-2.49)	Age, comorbidities, disease stage, disease duration, comedications, blood pressure, oxygen saturation, lymphocyte count, international normalized ratio, serum creatinine level, hematocrit, requirement of mechanical ventilation	8/9
Byttebier et al [32]	Belgium	Retrospective, multicenter, case control	959	69.2	N/A	47/297; 15.8	103/662; 15.6	OR=0.56 (0.39-0.93)	-	-	-	Age, sex, hospital size, comorbidities	8/9
Ramachandran et al [33]	USA	Retrospective, single center, cohort study	295	PPI users=67.0 (57.3-76.5) Non-PPI users=65.0 (54.0-74.0)	N/A	N/A	N/A	OR=1.59 (0.84-3.02)	-	-	-	Charlson's comorbidity Index, body mass index, use of PPI	8/9
Yetmar et al [34]	USA	Retrospective database review	1295	Statin users: 65 (57-73) Non-statin users: 55 (43-65)	N/A	35/500; 7.0	24/795; 3.0	OR=1.14 (0.64-2.03)	-	-	-	Charlson comorbidity index, sex, clinical trial enrollment, aspirin use	8/9
Torres-Peña et al [35]	Spain	Retrospective database review	1868	Statin users: 72 (10) Non-statin users: 73 (11)	N/A	192/934; 20.6	258/934; 27.6	OR=0.67 (0.54-0.83)	333/934; 35.7	407/934; 43.6	OR=0.78 (0.69-0.89)	Age, sex, comorbidities, treatment with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, qSOFA category, C-reactive protein, D-dimer, lymphocyte count, serum creatinine	7/9
Memel et al [36]	USA	Retrospective, single center, cohort study	1179	Statin users: 69 Non-statin users: 52	Atorvastatin, rosuvastatin, and other statins	108/777; 13.9	46/402; 11.4	HR=0.57 (0.37-0.86)	N/A	N/A	HR=0.85 (0.60-1.19)	Age, sex, race, active smoker, BMI⩾30), comorbidities, ACEI use at presentation to care, number of days from March 1st, 2020 to the date of hospitalization to account for era effect, prior statin usage	7/9
Greco et al [37]	Italy	Retrospective, multicenter, cohort study	501	Statin users: 76 (10) Non-statin users: 71 (17)	N/A	15/51; 29.4	140/450; 31.1	OR=0.63 (0.29-1.35)	16/51; 31.4	113/450; 25.1	OR=1.00 (0.47-2.14)	Age, sex, Charlson Comorbidity Index, comorbidities	8/9
Ahlström et al [38]	Sweden	Retrospective database review	1544	61 (52-69)	N/A	110/275; 40	236/923; 25.6	OR=0.95 (0.81-1.12)	-	-	-	Comorbidities, use of co-medications	7/9

Oh et al [39]	Korea	Retrospective database review	7780	N/A	N/A	N/A	N/A	OR=0.74 (0.52-1.05)	-	-	-	Age, sex, income level, area of residence, disability, comorbidities, use of co-medications	7/9
Aparisi et al [40]	Spain	Retrospective, multicenter, cohort study	840	Statin users: 73.5 (10.1) Non-statin users: 65.7 (15.9)	N/A	64/295; 21.7	107/545; 19.6	OR=0.48 (0.30-0.77)	-	-	-	Age, sex, comorbidities, use of co-medications	8/9
Chacko et al [41]	USA	Retrospective, single center, cohort study	255	Statin users: 69.0 (10.6) Non-statin users: 62.4 (17.7)	N/A	21/116; 18.1	32/139; 23.0	OR=0.14 (0.03-0.61)	-	-	-	Age, sex, comorbidities, neutrophil to lymphocyte ratio, use of mechanical ventilation, body mass index, serum creatinine at admission, use of ACEIs/ARBs, use of antiplatelets	8/9
Luo et al [42]	China	Retrospective, single center, cohort study	283	Metformin users=63.0 (55.8-68.3) Non-metformin users=65.0 (57.5-71.0)	N/A	N/A	N/A	OR=2.98 (0.65-13.76)	-	-	-	Use of co-medications	7/9
Lohia et al [43]	USA	Retrospective, single center, cohort study	1014	Statin users: 67 (60-74) Non-statin users: 61 (47-72)	Atorvastatin, rosuvastatin, simvastatin, pravastatin, lovastatin	138/454; 30.4	159/560; 28.4	OR=0.64 (0.47-0.87)	ICU admission: 163/454; 35.9 Intubation: 120/454; 26.4	ICU admission: 174/560; 31.1 Intubation: 130/560 23.2	ICU admission: OR=0.92 (0.66–1.29) Intubation: OR=0.80 (0.55–1.15)	Age, sex, race, body mass index, insurance, comorbidities	8/9
Terlecki et al [44]	Poland	Retrospective, single center, cohort study	1729	63 (50-75)	N/A	32/269; 11.9	191/1460; 13.1	OR=0.54 (0.33-0.84)	-	-	-	Age, sex, comorbidities, use of co-medications	8/9
Lala et al [45]	USA	Retrospective, multicenter, cohort study	2736	66.4	N/A	N/A	N/A	HR=0.57 (0.47-0.69)	-	-	-	Age, sex, body mass index, race, ethnicity, comorbidities, use of ACEIs/ARBs, CURB-65 score at hospital admission	8/9

ACEi: angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; HR=hazard ratio; IQR=interquartile range; N/A=not available; NOS=Newcastle-Ottawa Scale; OR=odds ratio; SD=standard deviation; USA=United States of America

[a]The definition of severe illness varied across the included studies: in the study by Yan et al. [11], the definition is based on that given in Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia by the Chinese National Health Commission; in the studies by Zhang et al. [12], Butt et al. [26], Fan et al. [27], and Mitacchione et al. [28], the definition is based on admission into intensive care unit; in the study by Spiegeleer et al. [15], the definition is based on long-stay hospital admission or death; in the studies by Gupta et al. [16], Cariou et al. [19], Peymani et al. [31], the definition is based on requirement of intubation/mechanical ventilation; in the study by Song et al. [17], the definition is based on admission into intensive care unit or requirement of intubation; and in the study by Daniels et al. [22], the definition is based on admission into intensive care unit or death.

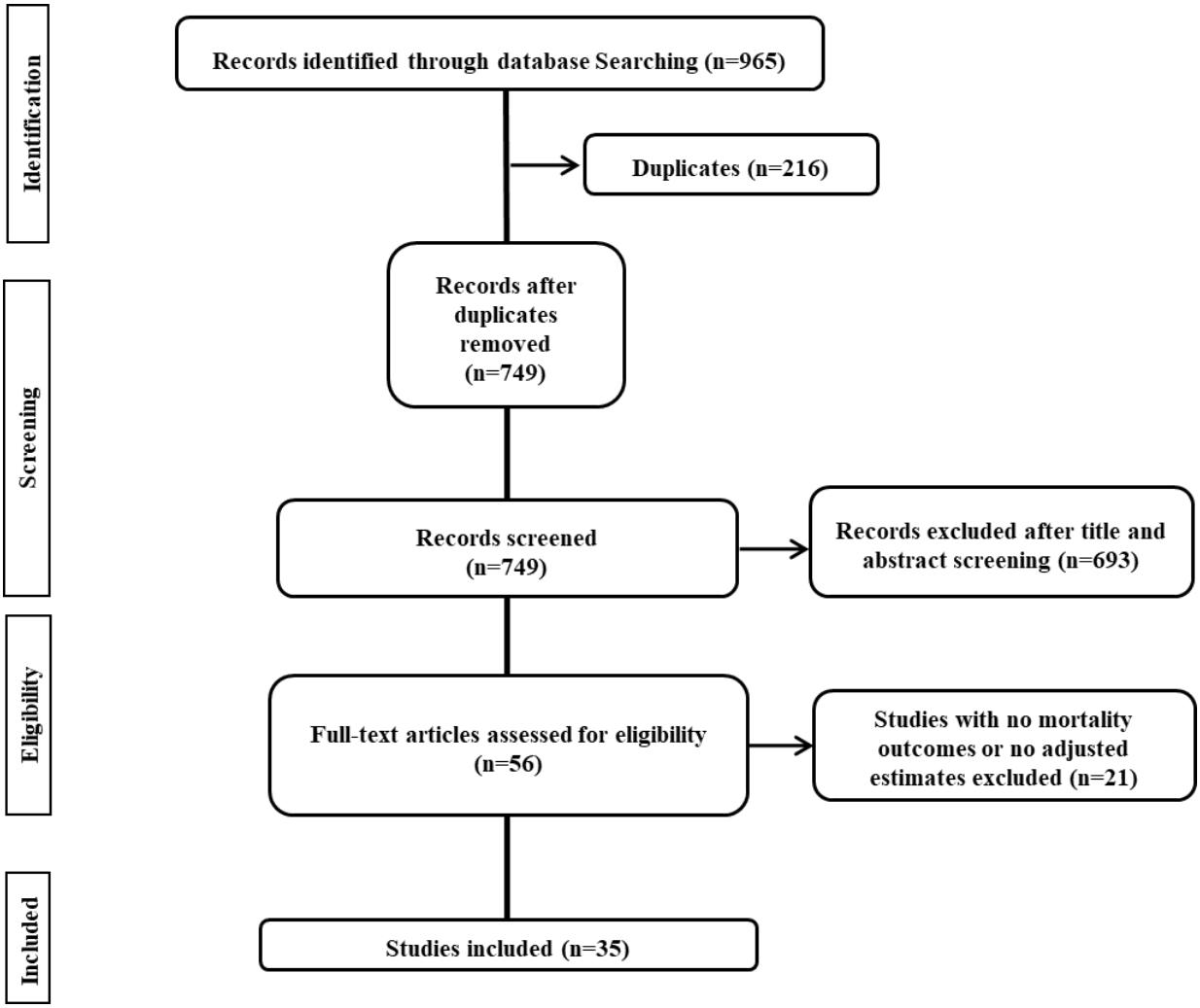

Figure 1: Flow diagram of the study selection

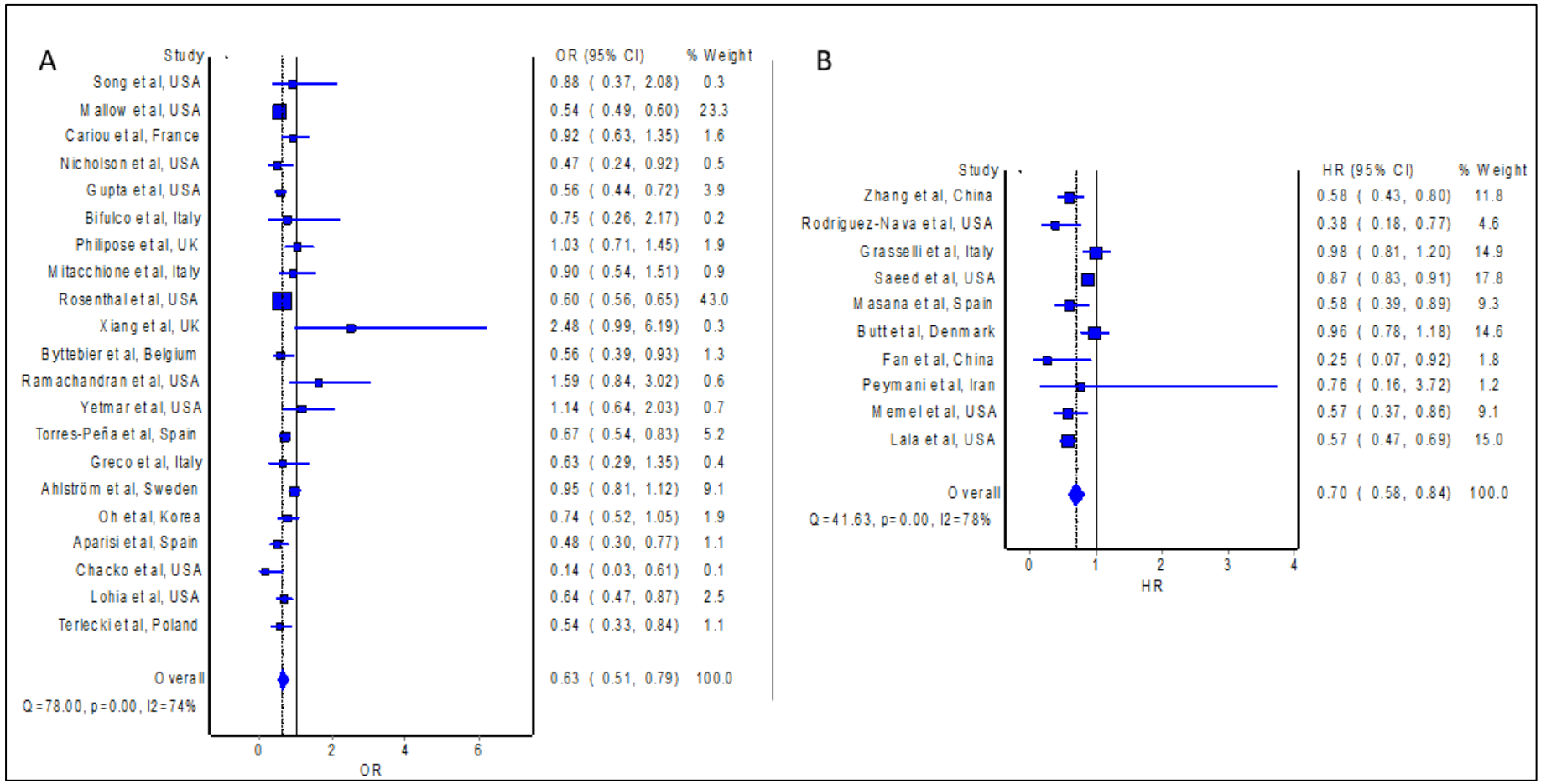

Figure 2: (A) Forest plot showing the pooled hazard ratio of mortality between statins users with COVID-19 and non-statins users with COVID-19 (B) Forest plot showing the pooled odds ratio of mortality between statins users with COVID-19 and non-statins users with COVID-19

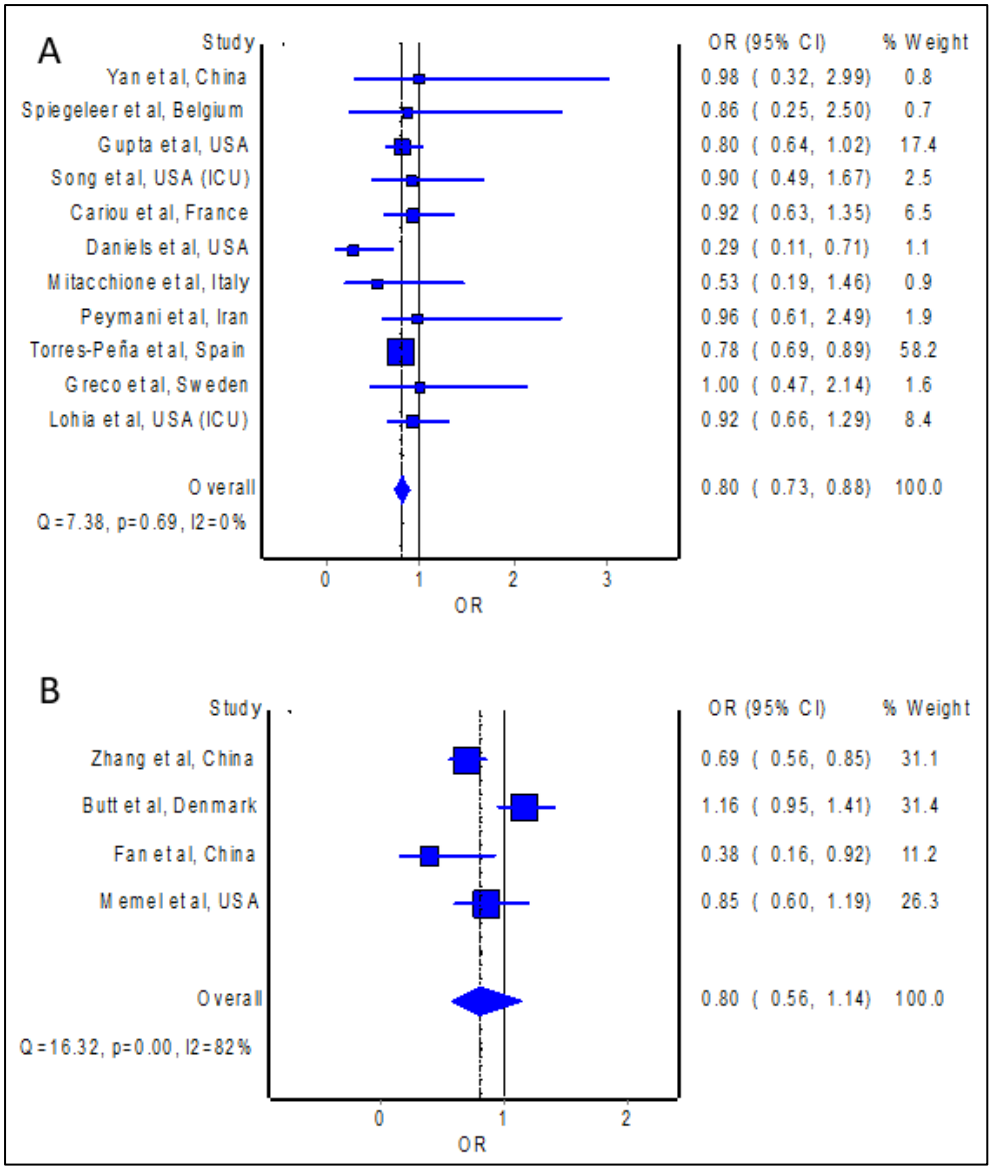

Figure 3: (A) Forest plot showing the pooled odds ratio of severe illness between statins users with COVID-19 and non-statins users with COVID-19 (B) Forest plot showing the pooled hazard ratio of severe illness between statins users with COVID-19 and non-statins users with COVID-19

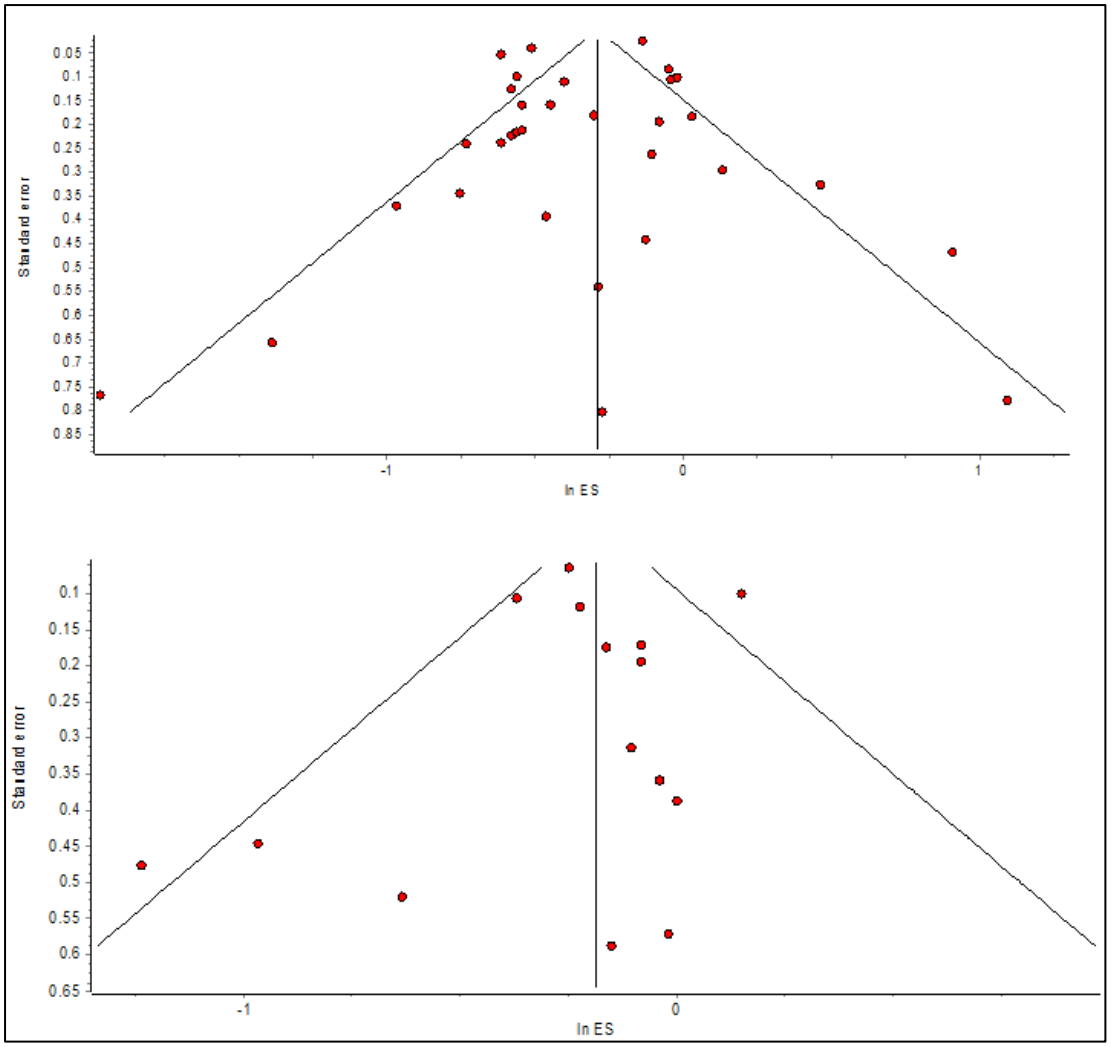

Figure 4: (A) Funnel plot of publication bias with studies reporting outcomes on mortality (B) Funnel plot of publication bias with studies reporting outcomes on severe illness