Association between the Use of Statins and Mortality in COVID-19 Patients: A Meta-Analysis

Sahar Vahdat [1*]

1- Isfahan Kidney Diseases Research Center, Khorshid Hospital, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

***Corresponding Author**: Sahar Vahdat, Isfahan Kidney Diseases Research Center, Khorshid Hospital, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
Email: s.vahdat11@yahoo.com

Abstract

Background: Since the start of COVID-19 pandemic, efforts have been made for finding efficient and effective drugs for the treatment and management of COVID-19 patients. As various comorbidities including cardiovascular diseases increase the risk of mortality in COVID-19 patients, the use of statin has been suggested to be associated with decreased risk of mortality due to its pleiotropic and cardioprotective characteristics.

Objectives: This meta-analysis study aims at evaluating the association of statin use and mortality in COVID-19 patients in current literature.

Methods and Materials: A systematic literature search was conducted on PubMed, Scopus, and Web of Science data bases until 31 September, 2021. Studies that reported adjusted odds (aOR) or hazard ratios (aHR) for statin use and mortality in COVID-19 patients were included. A meta-analysis of the aOR or aHR were performed using the inverse variance weighted method with a common fixed effect model.

Results: Of the 25 included studies, 7 had reported adjusted hazard ratios and 18 reported aOR. The pooled aOR revealed that the use of statin significantly reduces the risk of mortality in COVID-19 patients (pooled odds ratio (OR) = 0.8224, 95% CI [0.7893; 0.8569], p-value < 0.0001). Although the pooled aHR suggests protective effect of statin use on mortality of COVID-19 patients, it was not statistically significant (pooled hazard ratio (HR) = 0.9043, 95% CI [0.8082; 1.0119], p-value = 0.075). No publication bias was observed.

Conclusion: Use of statin significantly reduces the risk of mortality in COVID-19 patients. This conclusion should not be misinterpreted into a clinical indication for statin administration in COVID-19 patients during or prior to hospitalization.

Keywords: stain, COVID-19, cardiovascular disease, mortality, hospitalization

Tob Regul Sci.™ 2021;7(6-1): 6764-6779
DOI: doi.org/10.18001/TRS.7.6.1.8

1. Introduction

COVID-19 patients who suffer from comorbidities such as hypertension, cardiovascular diseases, diabetes mellitus, respiratory diseases, immunodeficiency disorders, chronic kidney disease, and other co-existing infections have a higher risk of mortality (1-5). Older patients with higher frailty scores, also, have more severe outcomes (6). From the start of COVID-19 pandemic nearly two years ago, efforts have been made for finding the most efficient and effective treatment course for this novel infection. It should be noted that these COVID-19 patients with comorbidities, receive various drugs for the treatment of their chronic condition (7). Hence, the effect of these drugs on outcomes of this infection is of utmost importance.

Statins are widely prescribed for patients with hypercholesterolemia, hypertriglyceridemia, and hyperlipoproteinemia (8). As the drugs lowers total cholesterol concentration and increases high-density lipoproteins (HDL), it primarily acts as a cardioprotective agent which reduces the risk of myocardial infarction, atherosclerosis, and stroke in these patients (8, 9). However, it has been found that due to its immunomodulatory and pleiotropic properties, statins have anti-inflammatory effects (10-12). Hence, studies have investigated the effect of this drug on outcome of COVID-19 infection (13-18). This meta-analysis aims at elucidating the association between the use of statins and mortality in hospitalized patients suffering from COVID-19 infection.

2. Methods and Materials

2.1. Search Strategy, Study Selection, and Data Extraction

A systematic search of literature was performed on PubMed, Scopus, and Web of Science data bases using the keywords '("coronavirus 2019" OR "2019-nCoV" OR "SARS-CoV-2" OR "COVID-19" OR COVID OR COVID19) AND (statin* OR atorvastatin OR rosuvastatin OR simvastatin OR pitavastatin OR pravastatin OR fluvastatin OR lovastatin) AND (mortality OR death OR fatal)'.

Two authors have subsequently screened the results based on the title and abstract of the articles. Afterwards, the eligibility of the remaining articles was assessed according to the inclusion and exclusion criteria. The inclusion criteria were (1) studies which have investigated the effect of statin use on mortality outcome of COVID-19 patients; (2) cohort and case-control studies with adjusted odds or hazard ratios. Exclusion criteria were (1) studies without adjusted odds or hazard ratios (2) other types of studies such as commentaries or in vitro and in vivo studies.

The data regarding the name of the first author, total number of patients, number of mortality events among statin users, total number of statin users, number of mortality events among non-statin users, total number of non-statin users, odds or hazard ration, 95% confidence interval, study design, and type of statin were extracted by one author and cross-checked by another author.

The intervention group was defined as all those patients that received statin while the control group was defined as those patients who did not receive statin. Mortality was defined as the measured outcome and the effect estimate is reported as odds or hazard ratios.

2.2 Statistical Analysis

The data analysis was performed using R statistical software (version 4.0.5) and *meta* package (19). The pool estimate of adjusted odds and hazard ratios of the studies were calculated with their 95% confidence interval (CI) using the logarithm of odds and hazard rations and their standard error according to the inverse variance-weighted meta-analysis method. The Cochran's Q test and I^2 statistics were used for assessment of heterogeneity; values greater than 50% were considered as statistically significant. Also, p-values lower than 0.05 were considered as statically significant. Due to low heterogeneity of the studies, the fixed effect model was used (20). The pooled odds and hazard ratios of the association between the use of statin and mortality outcome of COVID-19 patients is reported with the 95% CI. The result of the conducted meta-analysis is presented for each individual studies using a forest plot. Also, visual inspection of the funnel plot of odds and hazard ratios was used to determine publication bias.

3. Results

Of the 433 retrieved studies, 88 duplicates were primarily removed. 345 records have been then screened, among which 54 full-texts were assessed for eligibility. 30 studies were excluded and 25 studies (21-45) which fully met the eligibility criteria were included in the meta-analysis. (Figure 1)

The all-cause mortality outcome of statin and non-statin users COVID-19 patients was available in all the included studies, of which 18 studies (21-38)have reported adjusted odds ratios and 7 studies (39-45) have reported adjusted hazard ratios. 17 studies were multi-centred observational cohort study (21, 25-27, 30-34, 36-38, 40-42, 44, 45), 7 studies were single-centred observational cohort study (23, 24, 28, 29, 35, 39, 43), and 1 study was a multi-centred case-control study (22).

The meta-analysis of the 7 studies that reported hazard ratio, with 24,088 number of patients, indicates that use of statin did not significantly reduce the hazard of mortality in COVID-19 patients in comparison with those COVID-19 patients who did not receive statin (pooled hazard ratio (HR) = 0.9043, 95% CI [0.8082; 1.0119], p-value = 0.075). However, the pooled odds ratio is not consistent with the pooled hazard ratio. The meta-analysis of the 18 studies that reported odds ratio, with 94,023 number of patients, indicate that the use of statin significantly reduced the odds of mortality in COVID-19 patients in comparison with the patients who did not receive statin (pooled odds ratio (OR) = 0.8224, 95% CI [0.7893; 0.8569], p-value < 0.0001). The forest plots of ORs and HRs are available in figure 2 and 3, respectively. Figure 4 and 5 are the funnel plots of OR and HR, respectively. Visual inspection of these figures did not indicate any asymmetries. Hence, no publication bias has been observed.

4. Discussion

This meta-analysis of observational multi/single-centred cohort or case-control studies has shown that statin significantly reduces the odds of mortality in hospitalized patients with COVID-19 infection. Although the pooled hazard ratio also suggests a protective effect of statin on mortality, however, the result was not statistically significant (p-value > 0.05).

It is widely known now that cardiovascular diseases increase the risk of more severe outcomes among COVID-19 patients (46). Hence, hospitalized statin users who have been infected with COVID-19 suffer from more severe forms of cardiovascular diseases and have a higher risk of mortality. Also, systemic inflammation and ischemic and non-ischemic myocardial injuries are among the severe complications of COVID-19 infection (47). Thus, these factors should be noted prior to the assessment of statin use and its effect on in-hospital mortality of COVID-19 patients. Although the pooled OR and HR showed decreased risk of mortality among the statin users, however, the pooled HR was not statistically significant. Among the studies that reported OR and HR for statin use and mortality, 6 studies indicated that statin use does not significantly reduce the risk of mortality among COVID-19 patients (23, 31, 37, 38, 40, 43). However, in 4 of these studies, the prevalence of comorbidities among statin users was higher in comparison with non-statin users (31, 38, 40, 43). In one observational study in France, conducted by Cariou et al, tracheal intubation and/or death was more prevalent among the statin users, however, no data was available regarding other comorbidities or cardiovascular profile (23).

The precise mechanism of statin's action and effect on COVID-19 infection is not fully clear, however, statin has pleiotropic characteristics that help us to explain its mechanism of action to some extent. Statin reduces the expression of NF-κB pathway which subsequently decreases the expression level of pro-inflammatory cytokines. It also impedes T-cell and toll like receptors activation (48, 49). Due to its anticoagulative properties and by upregulating the production of nitric oxide it enhances the function of vascular and endothelial system (50). The cardioprotective characteristics of this drug in reducing the risk of cardiac injuries is another important factor in mortality risk reduction of COVID-19 patients (51). However, there is no consensus in the literature regarding the effect of statin on cell entry of SARS-COV-2. SAR-COV-2 binds to the angiotensin converting enzyme 2 (ACE-2) on the membrane surface of human cells, which higher concentration of cholesterol and sphingomyelin enhances this process (52). Hence, depletion and reduction of these lipids on the surface of cellular membranes conversely hinder this process. However, the effect of statin on membranous lipids is the point of discussion here. Although some studies indicate that statin reduces the intracellular synthesis of cholesterol and reduce the cholesterol level on cellular membrane surface (53), other studies suggest that by the increase in the expression of low density lipoprotein receptors (LDL-rs) on cellular membrane surface, circulating cholesterol uptake increases (54). Another important effect of statin is on ACAT (acyl-coenzyme A cholesterol acyl-transferase) enzyme. ACAT is an integral membrane protein in endoplasmic reticulum (ER), which plays a crucial role in cholesterol metabolism, and depletes cholesterol from cellular membrane surface. It has been recently

discovered that SARS-COV-2 can activate ACAT through certain mechanism. This decreases the cholesterol level of cellular membrane and thus impedes binding of SAR-COV-2 spike proteins with membrane receptors (55, 56). It should be noted that statin can intercept ACAT activation and increase viral entry (50). Another point of debate, is the effect of statin on ACE-2 expression and its effect on cell entry of SARS-COV-2. Some studies suggest that, due to the upregulation ACE-2 expression by this drug, statin may facilitate the process of infection and cell entry of this virus (57, 58). On the contrary, other studies indicate that by transformation of angiotensin II into angiotensin I-VII, facilitated by ACE-2, lung injury has been reduced in COVID-19 patients (59). Further studies should elucidate the precise cellular and molecular interaction of statin use and COVID-19 infection.

Some limitations of our meta-analysis study should be noted prior to interpretation of the results. While randomized clinical trials are the study design of choice for evaluation of treatment effects, our study included observational cohort and case-control studies, since the number of randomized trials is scarce. However, consistency is found among the results of the included studies. More importantly, the precise drug dosing regimen was not available in the included studies. Also, the type statin was not mentioned in most of the studies and in some studies statin was taken along with other ACE inhibitors and blockers. The severity of comorbidities among COVID-19 patients, radiographic images, and polymerase chain reaction test results were also not mentioned in most of the studies. It is unclear whether statin was administered at the time of or prior to hospital admission. Ultimately, it should be noted that this study does not suggest prescription of statin for COVID-19 patients prior to or during hospital admission. Further randomized trials should investigate the efficacy of statin use for treatment and management of severe outcomes of COVID-19.

5. Conclusion

Overall, the findings of this meta-analysis study support the association between the use of statin and decrease risk of mortality among COVID-19 patients. Although the cardioprotective, anti-inflammatory, anti-thrombotic, and pleiotropic characteristics of statin are potential explanations for its mechanism of action, however, further studies should investigate the precise pathophysiological interactions of statin, human cell, and SARS-COV-2. Finally, it should be taken into account that the findings of this study do not indicate initiation of statin administration for COVID-19 patients.

References

1. Yonas E, Alwi I, Pranata R, Huang I, Lim MA, Gutierrez EJ, et al. Effect of heart failure on the outcome of COVID-19 - A meta analysis and systematic review. Am J Emerg Med. 2021;46:204-11.
2. Pranata R, Supriyadi R, Huang I, Permana H, Lim MA, Yonas E, et al. The Association Between Chronic Kidney Disease and New Onset Renal Replacement Therapy on the Outcome

of COVID-19 Patients: A Meta-analysis. Clin Med Insights Circ Respir Pulm Med. 2020;14:1179548420959165.
3. Pranata R, Huang I, Lim MA, Wahjoepramono EJ, July J. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19-systematic review, meta-analysis, and meta-regression. J Stroke Cerebrovasc Dis. 2020;29(8):104949.
4. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia - A systematic review, meta-analysis, and meta-regression. Diabetes Metab Syndr. 2020;14(4):395-403.
5. Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, et al. Comorbidity and its Impact on Patients with COVID-19. SN Compr Clin Med. 2020:1-8.
6. Pranata R, Henrina J, Lim MA, Lawrensia S, Yonas E, Vania R, et al. Clinical frailty scale and mortality in COVID-19: A systematic review and dose-response meta-analysis. Arch Gerontol Geriatr. 2021;93:104324.
7. Zein A, Sulistiyana CS, Khasanah U, Wibowo A, Lim MA, Pranata R. Statin and mortality in COVID-19: a systematic review and meta-analysis of pooled adjusted effect estimates from propensity-matched cohorts. Postgrad Med J. 2021.
8. Bakhai S, Bhardwaj A, Sandhu P, Reynolds JL. Optimisation of lipids for prevention of cardiovascular disease in a primary care. BMJ Open Qual. 2018;7(3):e000071.
9. Toth PP, Banach M. Statins: Then and Now. Methodist Debakey Cardiovasc J. 2019;15(1):23-31.
10. Davignon J. Beneficial cardiovascular pleiotropic effects of statins. Circulation. 2004;109(23 Suppl 1):Iii39-43.
11. Liao JK, Laufs U. Pleiotropic effects of statins. Annu Rev Pharmacol Toxicol. 2005;45:89-118.
12. Oesterle A, Laufs U, Liao JK. Pleiotropic Effects of Statins on the Cardiovascular System. Circ Res. 2017;120(1):229-43.
13. Peymani P, Dehesh T, Aligolighasemabadi F, Sadeghdoust M, Kotfis K, Ahmadi M, et al. Statins in patients with COVID-19: a retrospective cohort study in Iranian COVID-19 patients. Transl Med Commun. 2021;6(1):3.
14. Sadeghipour P, Talasaz AH, Rashidi F, Sharif-Kashani B, Beigmohammadi MT, Farrokhpour M, et al. Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality among Patients with COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial. JAMA - Journal of the American Medical Association. 2021;325(16):1620-30.
15. Vahedian-Azimi A, Rahimibashar F, Najafi A, Kidde J, Shahriary A, Shojaei S, et al. Associastion of In-hospital Use of Statins, Aspirin, and Renin-Angiotensin-Aldosterone Inhibitors with Mortality and ICU Admission Due to COVID-19. Advances in Experimental Medicine and Biology2021. p. 205-14.
16. Choi D, Chen QZ, Goonewardena SN, Pacheco H, Mejia P, Smith RL, et al. Efficacy of Statin Therapy in Patients with Hospital Admission for COVID-19. Cardiovascular Drugs and Therapy.

17. Ma Y, Zhang Y, Li S, Yang H, Li H, Cao Z, et al. Sex Differences in Association Between Anti-Hypertensive Medications and Risk of COVID-19 in Middle-Aged and Older Adults. Drugs and Aging. 2021.
18. Sathekge M, Byttebier G, De Spiegeleer B, Saxberg B, Ueckermann V, Belmans L, et al. Adjunctive use of statins for COVID-19. Journal of Clinical Medicine. 2021;10(7).
19. Harrer M, Cuijpers P, Furukawa TA, Ebert DD. Doing Meta-Analysis With R: A Hands-On Guide. 1st ed. Boca Raton, FL and London: Chapman & Hall/CRC Press; 2021 2021.
20. Bell A, Fairbrother M, Jones K. Fixed and random effects models: making an informed choice. Quality & Quantity. 2019;53(2):1051-74.
21. Ahlström B, Frithiof R, Hultström M, Larsson IM, Strandberg G, Lipcsey M. The swedish covid-19 intensive care cohort: Risk factors of ICU admission and ICU mortality. Acta Anaesthesiologica Scandinavica. 2021;65(4):525-33.
22. Byttebier G, Belmans L, Alexander M, Saxberg BEH, De Spiegeleer B, De Spiegeleer A, et al. Hospital mortality in COVID-19 patients in Belgium treated with statins, ACE inhibitors and/or ARBs. Human Vaccines and Immunotherapeutics. 2021;17(9):2841-50.
23. Cariou B, Goronflot T, Rimbert A, Boullu S, Le May C, Moulin P, et al. Routine use of statins and increased COVID-19 related mortality in inpatients with type 2 diabetes: Results from the CORONADO study. Diabetes and Metabolism. 2021;47(2).
24. Chacko SR, DeJoy R, Lo KB, Albano J, Peterson E, Bhargav R, et al. Association of Pre-Admission Statin Mortality in COVID-19. American Journal of the Medical Sciences. 2021;361(6):725-30.
25. Daniels LB, Ren JT, Kumar K, Bui QM, Zhang J, Zhang XL, et al. Relation of prior statin and anti-hypertensive use to severity of disease among patients hospitalized with COVID-19: Findings from the American Heart Association's COVID-19 Cardiovascular Disease Registry. Plos One. 2021;16(7).
26. Greco S, D'Amuri A, Giorgini E, Luciani F, Lopreiato M, Fortunato V, et al. Role of Statins in Coronavirus-Related Disease (COVID-19): A Retrospective Cohort Study in Northern Italy. High Blood Pressure and Cardiovascular Prevention. 2021;28(4):355-64.
27. Ikari Y, Matsue Y, Torii S, Hasegawa M, Aihara K, Kuroda S, et al. Association between statin use prior to admission and lower coronavirus disease 2019 (COVID-19) severity in patients with cardiovascular disease or risk factors. Circulation Journal. 2021;85(6):939-43.
28. Lohia P, Kapur S, Benjaram S, Cantor Z, Mahabadi N, Mir T, et al. Statins and clinical outcomes in hospitalized COVID-19 patients with and without Diabetes Mellitus: a retrospective cohort study with propensity score matching. Cardiovascular Diabetology. 2021;20(1).
29. Lohia P, Kapur S, Benjaram S, Mir T. Association between antecedent statin use and severe disease outcomes in COVID-19: A retrospective study with propensity score matching. Journal of Clinical Lipidology. 2021;15(3):451-9.
30. Meintrup D, Borgmann S, Seidl K, Stecher M, Jakob CEM, Pilgram L, et al. Specific Risk Factors for Fatal Outcome in Critically Ill COVID-19 Patients: Results from a European Multicenter Study. Journal of Clinical Medicine. 2021;10(17).

31. Mitacchione G, Schiavone M, Curnis A, Arca M, Antinori S, Gasperetti A, et al. Impact of prior statin use on clinical outcomes in COVID-19 patients: data from tertiary referral hospitals during COVID-19 pandemic in Italy. Journal of Clinical Lipidology. 2021;15(1):68-78.
32. Nicholson CJ, Wooster L, Sigurslid HH, Li RH, Jiang W, Tian W, et al. Estimating risk of mechanical ventilation and in-hospital mortality among adult COVID-19 patients admitted to Mass General Brigham: The VICE and DICE scores. EClinicalMedicine. 2021;33.
33. Ramos-Rincón JM, Pérez-Belmonte LM, Carrasco-Sánchez FJ, Jansen-Chaparro S, De-Sousa-Baena M, Bueno-Fonseca J, et al. Cardiometabolic therapy and mortality in very old patients with diabetes hospitalized due to COVID-19. Journals of Gerontology - Series A Biological Sciences and Medical Sciences. 2021;76(8):E102-E9.
34. Rosenthal N, Cao Z, Gundrum J, Sianis J, Safo S. Risk Factors Associated with In-Hospital Mortality in a US National Sample of Patients with COVID-19. JAMA Network Open. 2020;3(12).
35. Terlecki M, Wojciechowska W, Klocek M, Olszanecka A, Stolarz-Skrzypek K, Grodzicki T, et al. Association between cardiovascular disease, cardiovascular drug therapy, and in-hospital outcomes in patients with COVID-19: Data from a large single-center registry in Poland. Kardiologia Polska. 2021;79(8):773-80.
36. Torres-Pena JD, Perez-Belmonte LM, Fuentes-Jimenez F, Carmona MDL, Perez-Martinez P, Lopez-Miranda J, et al. Prior Treatment with Statins is Associated with Improved Outcomes of Patients with COVID-19: Data from the SEMI-COVID-19 Registry. Drugs. 2021;81(6):685-95.
37. Wargny M, Potier L, Gourdy P, Pichelin M, Amadou C, Benhamou PY, et al. Predictors of hospital discharge and mortality in patients with diabetes and COVID-19: updated results from the nationwide CORONADO study. Diabetologia. 2021;64(4):778-94.
38. Yetmar ZA, Challener DW, Tleyjeh IM, Sohail MR, Cerhan JR, Badley AD, et al. Association Between Chronic Statin Use and 30-Day Mortality in Hospitalized Patients With COVID-19. Mayo Clin Proc Innov Qual Outcomes. 2021;5(2):442-6.
39. Aghajani MH, Moradi O, Tehrani HA, Amini H, Pourheidar E, Hatami F, et al. Promising effects of atorvastatin on mortality and need for mechanical ventilation in patients with severe COVID-19; a retrospective cohort study. International Journal of Clinical Practice. 2021;75(9).
40. Butt JH, Gerds TA, Schou M, Kragholm K, Phelps M, Havers-Borgersen E, et al. Association between statin use and outcomes in patients with coronavirus disease 2019 (COVID-19): A nationwide cohort study. BMJ Open. 2020;10(12).
41. Fan Y, Guo T, Yan F, Gong M, Zhang XA, Li C, et al. Association of Statin Use With the In-Hospital Outcomes of 2019-Coronavirus Disease Patients: A Retrospective Study. Frontiers in Medicine. 2020;7.
42. Lee HY, Ahn J, Park J, Kyung Kang C, Won SH, Wook Kim D, et al. Beneficial Effect of Statins in COVID-19-Related Outcomes-Brief Report: A National Population-Based Cohort Study. Arteriosclerosis, Thrombosis, and Vascular Biology. 2021:E175-E82.

43. Rey JR, Merino Llorens JL, Iniesta Manjavacas ÁM, Rodríguez SOR, Castrejón-Castrejón S, Arbas-Redondo E, et al. Influence of statin treatment in a cohort of patients admitted for COVID-19. Medicina Clinica. 2021.
44. Villalba GC, Amat-Santos IJ, Dueñas C, Otero DL, Catalá P, Aparisi Á, et al. Impact of the presence of heart disease, cardiovascular medications and cardiac events on outcome in covid-19. Cardiology Journal. 2021;28(3):360-8.
45. Zhang XJ, Qin JJ, Cheng X, Shen L, Zhao YC, Yuan Y, et al. In-Hospital Use of Statins Is Associated with a Reduced Risk of Mortality among Individuals with COVID-19. Cell Metabolism. 2020;32(2):176-87.e4.
46. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives.
47. Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. Am J Emerg Med. 2020;38(7):1504-7.
48. Lefer DJ. Statins as potent antiinflammatory drugs. Circulation. 2002;106(16):2041-2.
49. Yuan X, Deng Y, Guo X, Shang J, Zhu D, Liu H. Atorvastatin attenuates myocardial remodeling induced by chronic intermittent hypoxia in rats: partly involvement of TLR-4/MYD88 pathway. Biochem Biophys Res Commun. 2014;446(1):292-7.
50. Minz MM, Bansal M, Kasliwal RR. Statins and SARS-CoV-2 disease: Current concepts and possible benefits. Diabetes Metab Syndr. 2020;14(6):2063-7.
51. Kollias A, Kyriakoulis KG, Kyriakoulis IG, Nitsotolis T, Poulakou G, Stergiou GS, et al. Statin use and mortality in COVID-19 patients: Updated systematic review and meta-analysis. Atherosclerosis. 2021;330:114-21.
52. Glende J, Schwegmann-Wessels C, Al-Falah M, Pfefferle S, Qu X, Deng H, et al. Importance of cholesterol-rich membrane microdomains in the interaction of the S protein of SARS-coronavirus with the cellular receptor angiotensin-converting enzyme 2. Virology. 2008;381(2):215-21.
53. Moeller R, Zapatero-Belinchon FJ, Lasswitz L, Kirui J, Brogden G, Gunesch AP, et al. Effect of statins on SARS-CoV-2 infection. medRxiv. 2020.
54. Shrestha SK. Statin drug therapy may increase COVID-19 infection. Nepalese Medical Journal. 2020;3(1):326-7.
55. Chang TY, Li BL, Chang CC, Urano Y. Acyl-coenzyme A:cholesterol acyltransferases. Am J Physiol Endocrinol Metab. 2009;297(1):E1-9.
56. Wang S, Li W, Hui H, Tiwari SK, Zhang Q, Croker BA, et al. Cholesterol 25-Hydroxylase inhibits SARS-CoV-2 and other coronaviruses by depleting membrane cholesterol. Embo j. 2020;39(21):e106057.
57. Fedson DS, Opal SM, Rordam OM. Hiding in Plain Sight: an Approach to Treating Patients with Severe COVID-19 Infection. mBio. 2020;11(2).
58. Castiglione V, Chiriacò M, Emdin M, Taddei S, Vergaro G. Statin therapy in COVID-19 infection. Eur Heart J Cardiovasc Pharmacother. 2020;6(4):258-9.
59. Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev Res. 2020;81(5):537-40.

Figure 1: Flow diagram of the selected studies

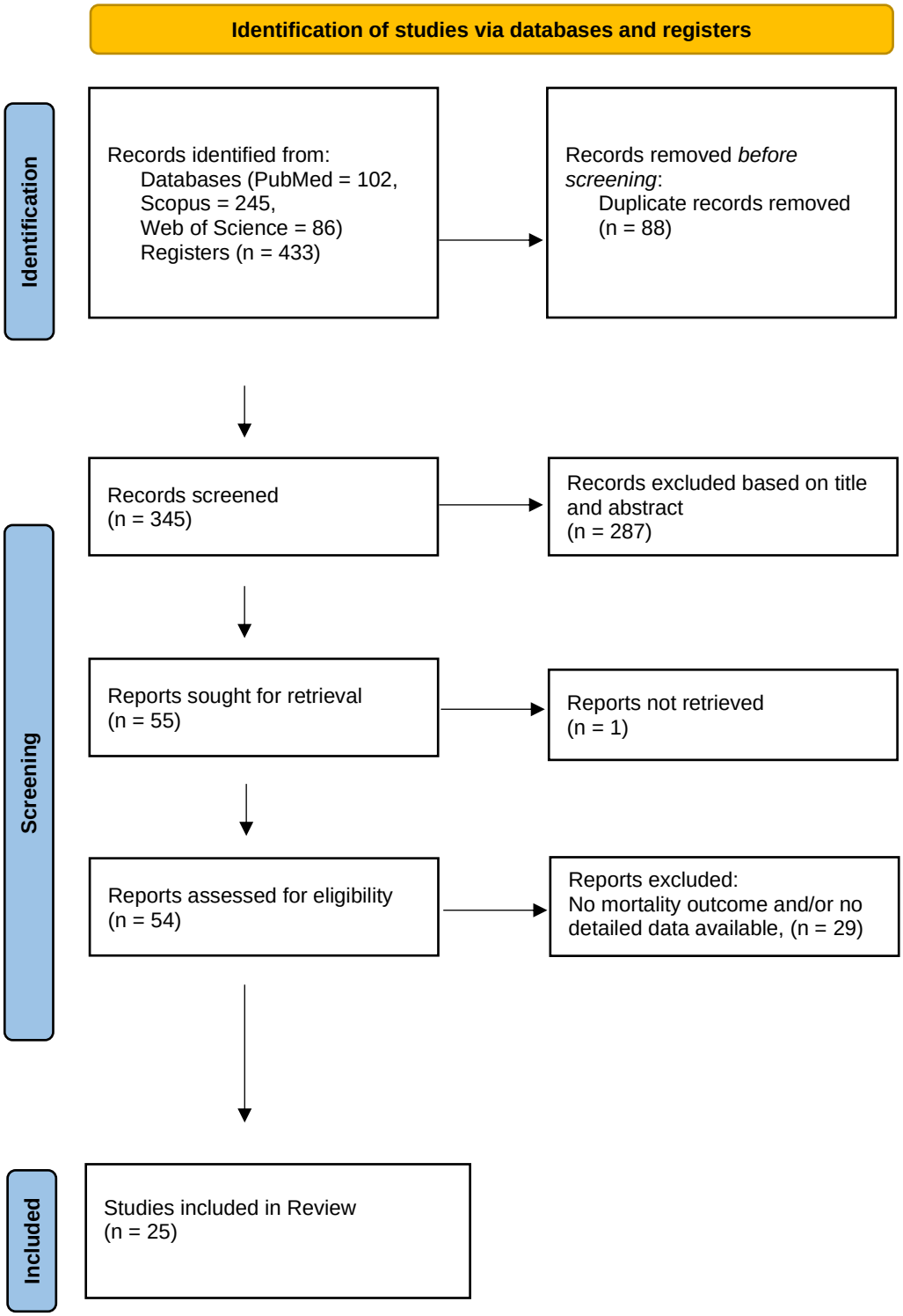
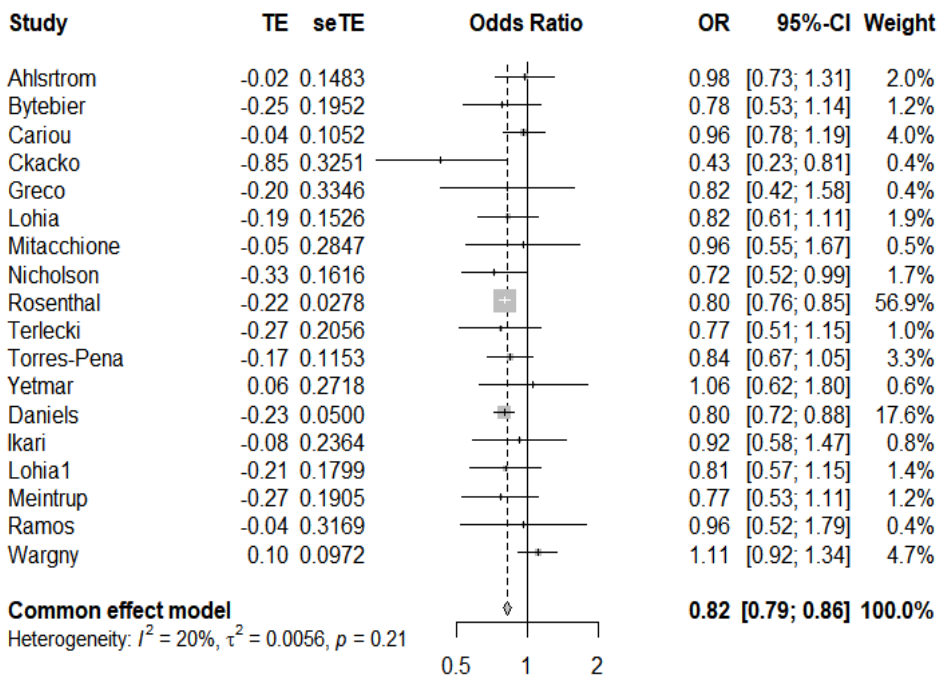
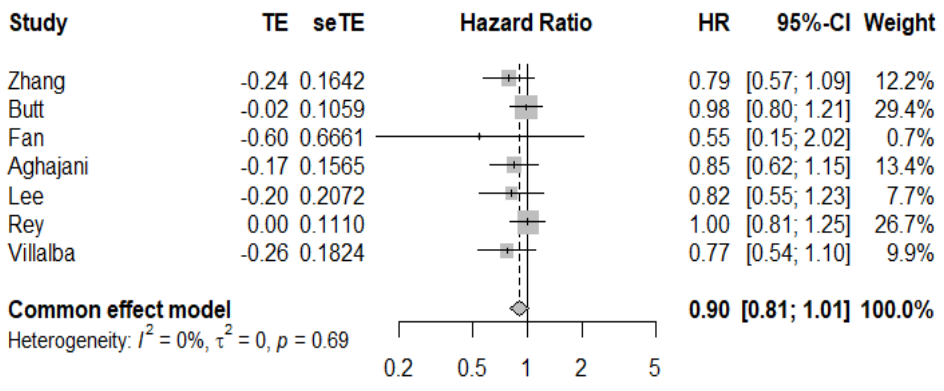


Figure 2: The forest plot of pooled OR of mortality outcome between statin users and non-users



TE = treatment effect values; seTE = standard error of treatment effect values; OR = odds ratio

Figure 3: The forest plot of pooled HR of mortality outcome between statin users and non-users



TE = treatment effect values; seTE = standard error of treatment effect values; HR = hazard ratio

Figure 4: The funnel plot of studies reporting OR

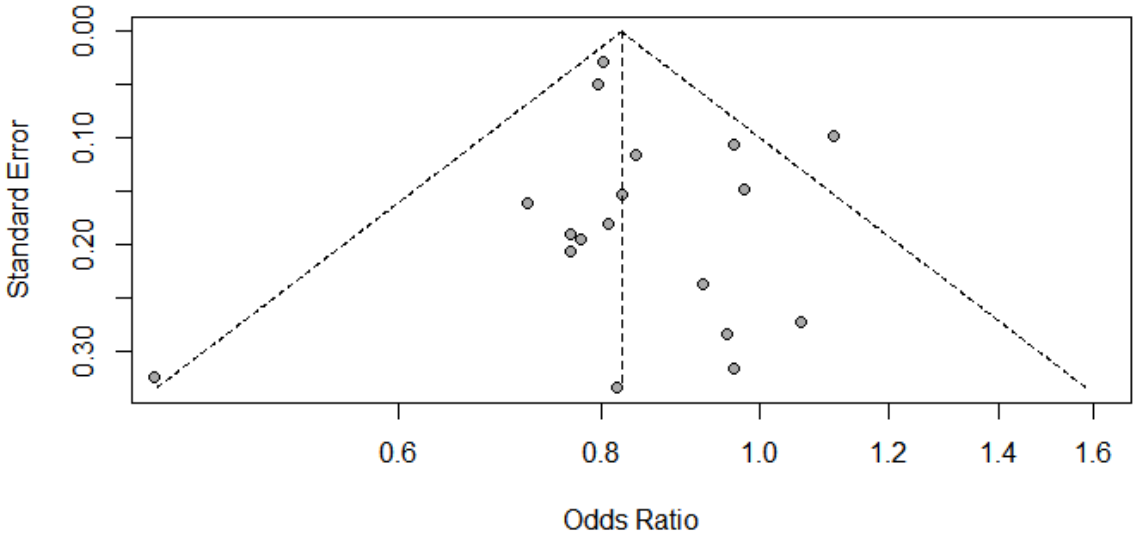


Figure 5: The funnel plot of studies reporting HR

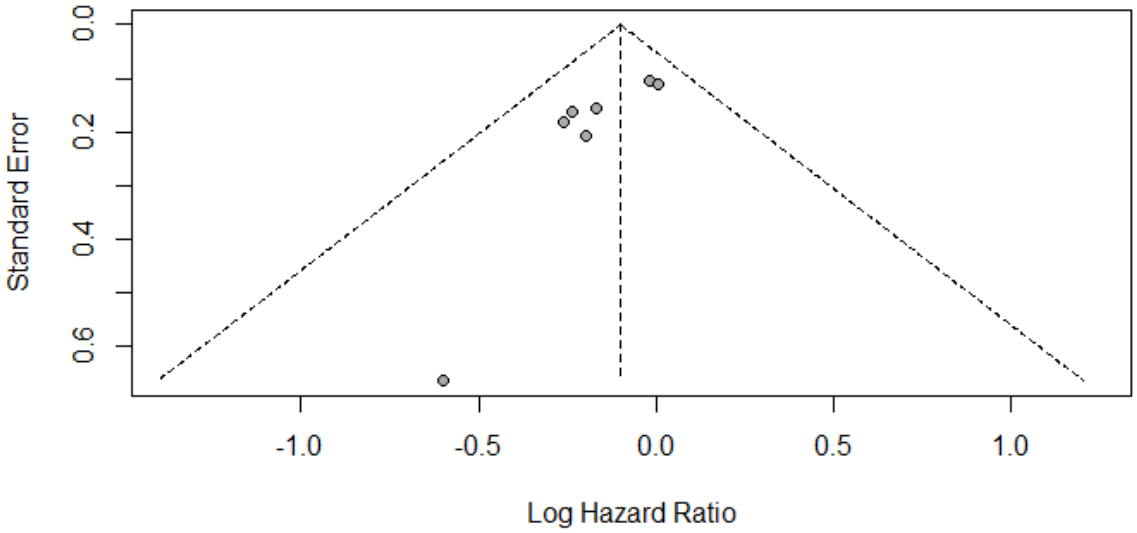


Table 1: Summary of the findings of the included studies

Author	TNP	Age	Se	St	non-Se	non-St	aOR/aHR	95% CI		study design	type of statin
								lower	upper		
Ahlsrtrom	1544	61 (52–69)	110	375	236	923	0.95	0.81	1.12	multi-centre retrospective cohort study	..
Bytebier	959	69.2	47	297	103	662	0.56	0.39	0.93	multi-centre retrospective case-control study	..
Cariou	2266	Statin users: 71.7 (10.8) / Non-statin users: 70.2 (13.9	229	1192	248	1257	0.92	0.63	1.35	single-centre retrospective cohort study	..
Ckacko	255	Statin users: 69.0 (10.6)/ Non-statin users: 62.4 (17.7)	21	116	32	139	0.14	0.03	0.61	single-centre retrospective cohort study	..
Greco	501	Statin users: 76 (10), Non-statin users: 71 (17)	15	61	140	450	0.63	0.29	1.35	multi-centre retrospective cohort study	..
Lohia	1014	Statin users: 67 (60–74)/ Non-statin users: 61 (47–72)	138	454	159	560	0.64	0.47	0.87	single-centre retrospective cohort study	Atorvastatin, rosuvastatin, simvastatin, pravastatin, lovastatin
Mitacchione	290	Statin users: 71 (64–79)/	38	145	41	145	0.9	0.54	1.51	multi-centre retrospective cohort study	Atorvastatin, rosuvastatin,

		Non-statin users: 72 (61–80)									simvastatin
Nicholson	1042	64 (53–75)	122	511	88	531	0.47	0.24	0.92	multi-centre retrospective cohort study	..
Rosenthal	64781	56.1 (19.9)	2426	12233	4929	52548	0.6	0.56	0.65	single-centre retrospective cohort study	..
Terlecki	1729	63 (50–75)	32	269	191	1460	0.54	0.33	0.84	single-centre retrospective cohort study	..
Torres-Pena	1868	Statin users: 72 (10) Non-statin users: 73 (11)	192	934	258	934	0.67	0.54	0.83	single-centre retrospective cohort study	..
Yetmar	1295	Statin users: 65 (57–73)/ Non-statin users: 55 (43–65)	35	500	24	795	1.14	0.64	2.03	single-centre retrospective cohort study	..
Daniels	10541	…	1027	4449	1185	6092	0.59	0.5	0.69	multi-centre retrospective cohort study	..
Ikari	693	Statin users: 67.8±12.9/ Non-statin users: 68.5±15.6	30	214	77	479	0.83	0.531	1.322	multi-centre retrospective cohort study	..
Lohia	922	Statin users: 66 (59–75)/ Non-statin users:	69	250	224	672	0.61	0.42	0.9	single-centre retrospective cohort study	…

		65 (54–73)									
Meintrup	739	…	72	345	75	394	0.54	0.33	0.87	multi-centre retrospective cohort study	…
Ramos	790	survivors: 85.8 (82.7-88.9)/ Non survivors: 86 (82.7-88.9)	188	385	227	405	0.917	0.723	1.978	multi-centre retrospective cohort study	…
Wargny	2794	survivors: 67.9 ± 13.0/ Nonsurvivors:76.8 ± 11.3	299	1282	278	1512	1.27	1.05	1.54	multi-centre retrospective cohort study	…
Zhang	4305	66.0 (59.0–72.0)	45	816	325	3119	0.58	0.43	0.8	multi-centre retrospective cohort study	Atorvastatin, rosuvastatin, simvastatin, pravastatin, fluvastatin, pitavastatin
Butt	4842	Statin users: 73 (63–79), Non-statin users: 50 (37–65)	311	3688	177	666	0.96	0.78	1.18	multi-centre retrospective cohort study	Atorvastatin, rosuvastatin, simvastatin, pravastatin
Fan	412	Statin users: 64 (57–72), Non-statin users: 66	3	203	10	196	0.25	0.07	0.92	Retrospective, multicenter, cohort study	..

		(57–73)									
Aghajani	991	Statin users: 65.46 ± 14.94 Non-statin users: 58.82 ± 17.88	113	308	143	427	0.679	0.517	0.89	retrospective cohort study, single center	atrovastatin
Lee	10488	Statin users: 65.53 (12.17) Non-statin users: 43.75 (19.53)	28	505	200	9715	0.637	0.425	0.953	multicenter retrospective cohort study	…
Rey	2191	68,0 ± 17,8	294	533	303	1001	1.01	0.78	1.3	single center retrospective cohort study	…
Villalba	859	68.1	66	229	110	454	0.551	0.329	0.921	multicenter retrospective cohort study	…

TNP: total number of patients; Se: number of mortality in statin users; St: total number of statin users; non-Se: number of mortality in non-statin users; non-St: total number of statin users; aOR: adjusted odds ratio; aHR; adjusted hazard ratios; CI: confidence interval;