Review Article

Effect of Statin on Mortality in Diabetic Patients with COVID-19: A Systematic Review and Meta-Analysis

Azin Alizadehasl[1], Davood Khoda Amorzideh[1], Nashmil Ghadimi[2], Hossein Hosseinifard[3], Sara Kaveh[2], Niloufar Akbari Parsa[4], Kamran Roudini[5]

[1]Cardio-Oncology Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, [2]Department of Health Management, Policy and Economics, School of Public Health, Tehran University of Medical Sciences, [4]Department of Echocardiography, Rajaei Cardiovascular, Medical and Research Center, [5]Department of Internal Medicine, Hematology and Medical Oncology Ward, Cancer Research Center, Cancer Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, [3]Department of Biostatistics, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran

Abstract

Context: It seems that the threat of death increases among diabetic patients with coronavirus infection disease-2019 (COVID-19). Statins have anti-inflammatory and anti-thrombogenic properties along with lowering blood cholesterol. Therefore, statins could be considered as an important factor in reducing the mortality rates in diabetic patients with COVID-19. This systematic review and meta-analysis study was performed to investigate the effect of statin on mortality in diabetic patients with COVID-19. **Evidence Acquisition:** This study was done based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Electronic databases such as PubMed, Embase, Scopus, Web of Science, and Cochrane Library were searched from December 2019 until the end of September 2022. Meta-analysis was used by the comprehensive meta-analysis software to combine the results. A funnel plot and Egger's regression test were used to investigate the publication bias. **Results:** Six studies were included in the meta-analysis. Nine thousand five hundred and thirty-three diabetic patients with COVID-19 were studied. The heterogeneity between studies was significant. According to the meta-analysis, using the random-effects model, we found that the rate of mortality due to COVID-19 in diabetic patients who used statins was 9% lower than other patients. Publication bias between studies included in the meta-analysis was not significant. **Conclusions:** In this study, there was no significant difference between the mortality rates of diabetic people with COVID-19 who used statins and individuals who did not consume statins – this difference was just 9%. Therefore, it could be said that more clinical trials are needed to ensure the clinical efficacy of statins among diabetic patients with COVID-19.

Keywords: Cardiovascular disease, coronavirus, COVID-19, diabetes mellitus, statin

Introduction

During the COVID-19 pandemic, people infected by SARS-CoV-2 (COVID-19) may show several problems. This infection may lead to immune system abnormalities, inflammation, and severe acute respiratory syndrome (SARS).[1,2] Although the recovery rate from this infectious disease was near 80%, COVID-19-related mortality still appears to have an upward trend, and the global number of deaths exceeds more than 6 million through June 2022.[2,3] There is a clearly recognizable relationship between disease severity and uncontrolled inflammation. Inflammatory markers including C-reactive protein, interleukin-6, and ferritin are elevated. The mentioned biomarkers are predictive of death during COVID-19.[4,5]

Most of COVID-19 patients have comorbid conditions and the most prevalent ones are diabetes, hypertension, and cardiovascular disease.[6] Soon after COVID-19 pandemic outbreak, diabetes was rapidly identified as a risk factor for poor outcome. The same can be said for patients infected by the

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Address for correspondence: Dr. Kamran Roudini, Department of Internal Medicine, Hematology and Medical Oncology Ward, Cancer Research Center, Cancer Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.
E-mail: roudini.k@gmail.com

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2009 H1N1 pandemic influenza or the Middle-East Respiratory Syndrome-related coronavirus.[5,7] Among these, diabetes consistently appeared as the high-ranked comorbidities associated with COVID-19. Moreover, diabetes is associated with a worse prognosis. Indeed, among patients admitted to the intensive care units, the prevalence of diabetes was two to three times higher compared with those with less severe disease and the mortality rate was consistently higher in patients with diabetes.[1,8-10]

Different types of medications are prescribed to patients with cardiovascular disease and diabetes. Statins, the most common prescribed ones, not only have anti-inflammatory and anti-thrombogenic properties but also can decrease blood cholesterol through the inhibition of β-hydroxy β-methylglutaryl-CoA (HMG-COA) reductase. Another feature of this medication group is the pleotropic effect which results in the reduction in reactive oxygen species and platelet reactivity. The acute administration of statins is contributed to survival improvement in pro-inflammatory states such as myocardial infarction. Moreover, the beneficial effects of statins in limiting viral endotheliitis have been implicated during COVID-19. This feature sets statins as a beneficial drug to alleviate host response to COVID-19.[1,4,5,9-11]

According to the studies done on the diabetic patients with COVID-19 who received statins, conflicting results were obtained regarding the association of statin use with the rate of mortality. Some studies suggested that statins intensify disease severity and some indicated reduced mortality.[12-14]

Objectives

This meta-analysis study investigates the effect of statin on mortality in diabetic patients with COVID-19.

Evidence Acquisition

Data sources and study selection

This meta-analysis was conducted and reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA).[15]

We performed an electronic search, including PubMed, Scopus, Embase, Cochrane Library, and Web of Science from December 2019 to the end of September 2022 using the following search terms: COVID-19, SARS-CoV-2, statin, simvastatin, atorvastatin, rosuvastatin, pitavastatin, lovastatin, fluvastatin, and mortality. Reference list of studies was reviewed for missing data through the strategy search. The language was limited to English only.

Inclusion criteria included (I) patients with COVID-19 who had diabetes type 1 or 2, (II) studies that had shown the number of patients treated with any statin before admission and nonstatins, (III) studies that had reported mortality as a result of COVID-19 in diabetic people, and (IV) types of clinical trial studies, retrospective, observational.

The exclusion criteria were as follows: (I) studies that had not been officially accepted and published and (II) studies that had not reported mortality.

Two investigators independently screened the articles entered in the endnote ×8. First, duplicate articles were removed. Then, the title and abstract of the articles were reviewed, and finally, the full text of the articles was reviewed according to the inclusion criteria. Any disagreements were solved through discussion with the third reviewer.

Data extraction

The following data were extracted from all included studies: type of study, year, country, population demographics such as age, type of diabetes, type of statin, the number of people using statin or nonstatin, mortality in 7 days, 28 days, total mortality, and outcome of heart disease.

Quality assessment

All studies were retrospective. Therefore, Newcastle–Ottawa Scale (NOS),[16] which is suitable for nonrandomized studies, was used for assessing the quality of eligible studies. The steps of data extraction and evaluation of the quality of the studies were done by two independent researchers, and any disagreements were resolved through the consensus of opinions with the third author. Table 1 shows the characteristics of the studies.

Quality of evidence assessment

The certainty of evidence in this study was assessed by the use of GRADE approach which indicates the quality by four GRADE score as follow: high-quality, moderate-quality, low-quality, or very low-quality evidences.[17] Various factors affect these scores, the factors that could enhance the score were plausible confounding, large effect, and dose–response gradient. On the other side, indirectness, publication bias,

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

Author	Year	Country	Sample size	Type of diabetes	Use of statins before admission		Mean age (years)	Study design
					Yes	No		
Cariou *et al*.	2020	French	2449	2	1192	1257	70.9	Retrospective, cohort
Saeed *et al*.	2020	USA	2266	2	983	1283	68	Retrospective, cohort
Wargny *et al*.	2021	France	2795	2	1283	1512	69.7	Retrospective, cohort
Lohia *et al*.	2021	USA	413	2	136	277	66	Retrospective, cohort
Ramos-Rincon	2020	Spain	790	2	415	375	86	Observational, multicenter
Ayeh *et al*.	2021	USA	4447	2	317	503	48.1	Retrospective, cohort

inconsistency, risk of bias, and imprecision may result in lowering the scores.[17]

Data analysis

In this study, the sample size in the two groups user statin and nonstatin was extracted along with the number of deaths in each group of studies. The odds of patient death were calculated for each study. I^2 index and Q statistics were used to evaluate the heterogeneity between studies. A meta-analysis was used to combine the results. In the absence of homogeneity, the random effect model was used in the meta-analysis. The funnel plot and Egger's regression test were used to evaluate the publication bias. $P < 0.05$ was used as a significant level in all analyzes. The comprehensive meta-analysis V.02 software was used to analyze the data.

Results

Study selection and characteristics

Among 326 initially identified articles, first, 201 duplicate studies were excluded. After reviewing the titles and abstracts of the studies, 176 articles were deleted and 25 articles were assessed to review the full text according to the inclusion criteria of the study. Finally, 6 studies were included in the meta-analysis [Figure 1]. Two of the studies had been conducted in France,[18,19] three studies had been conducted in the United States,[4,20,21] and one had be conducted in Spain.[22] In total, these studies had enrolled 9533 patients with diabetes type 2. The mean (standard deviation) age of the patients was 68.11 (7.97) years.

In NOS, 9 is considered as the maximum score. High-quality articles have a score of ≥7, while a score of <5 is for low-quality articles. An article score which is between the range of 5–7 shows moderate quality. Assessment with the Newcastle–Ottawa Scale revealed that two studies[4,20] are of high quality (8/9–8/9) and four studies[19,21-23] are of moderate quality (at least 6/9). None of the included studies are of poor quality.

Meta-analysis results

Six studies were included in the meta-analysis, which had assessed 9,533 diabetic patients with COVID-19. Four thousand three hundred and twenty-six patients used statins, while 5, 207 of them were nonstatins. On the other hand, five studies reported the number of deaths in the two groups which were 821 and 1037, respectively.[4,19,20,22,23] One study had not reported the number of mortality among patients.[21]

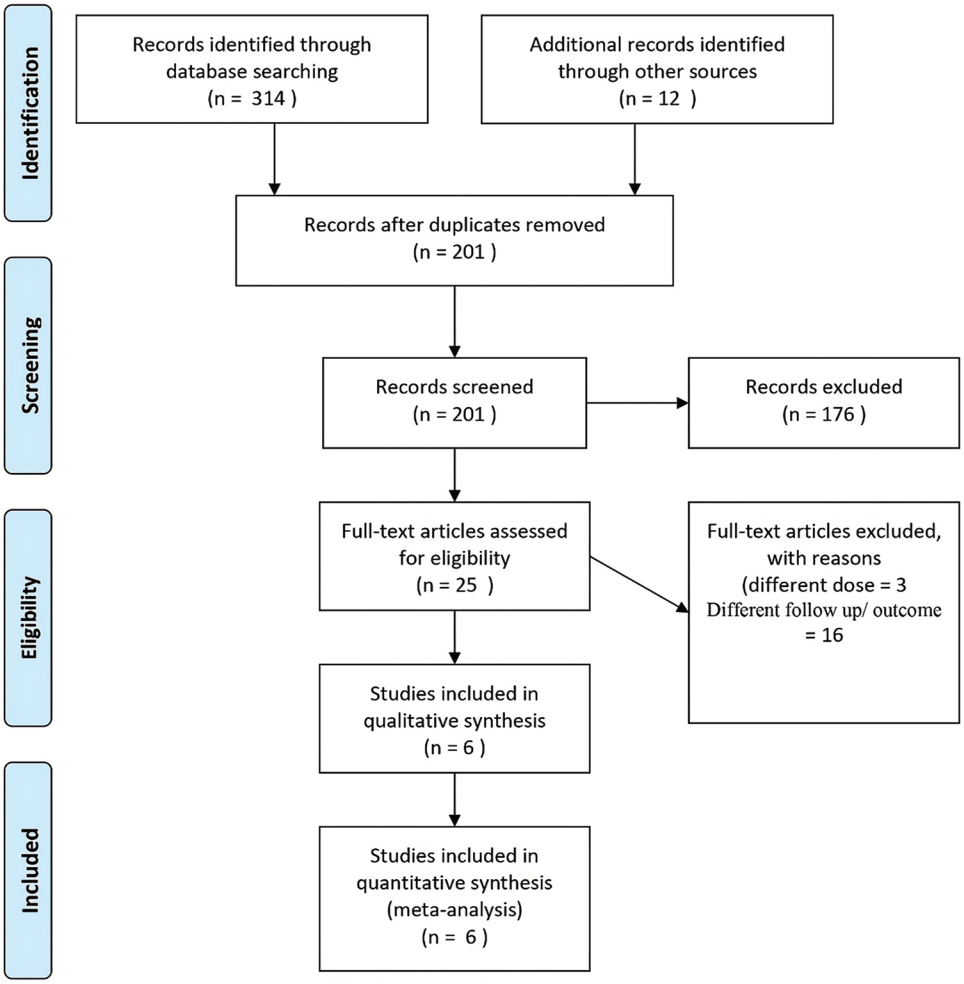

Figure 1: PRISMA flow diagram for study selection. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

Heterogeneity between studies was significant (Q = 82.09, df = 5, P < 0.001, I^2 = 93.91). According to the results of meta-analysis using random model effects, odds of death in diabetic patients with COVID-19 who used statin was 9% less than diabetic patients with COVID-19 who did not statin (pooled odds ratio [OR] =0.91, 95% confidence interval = 0.60–1.38, P = 0.68). Figure 2 shows the forest plot from the meta-analysis.

In another analysis, the prevalence of mortality due to COVID-19 in patients with diabetes was examined. In this analysis, five studies were evaluated, in which 8714 people had been studied, and the number of mortality due to COVID-19 in these studies was equal to 2293 people. Heterogeneity between studies was significant (Q = 981.78, df = 4, I^2 = 99.59). Based on the results of meta-analysis using a random-effects model, the prevalence of death in diabetic patients with COVID-19 artery was 31.7%. Figure 3 shows the forest plot from the meta-analysis.

Publication bias

In Figure 4, the funnel plot for the publication bias is shown. Based on the results of the Egger's regression test, there was no evidence of publication bias in the meta-analysis studies (t = 0.83, df = 4, P = 0.45).

Quality of evidence

The overall assessment of quality of evidence according to GRADE methodology for mortality in diabetic patients using statin/nonstatin and prevalence of COVID-19 mortality in patients with diabetes combined is summed up in Table 2. In summary, the evidence was judged to be moderate for OR of mortality in diabetic patients and very low for the prevalence of COVID-19 mortality in patients with diabetes.

Discussion

From the beginning of the SARS-CoV-2 pandemic, numerous studies have shown that people with comorbid conditions such as diabetes mellitus (DM),[24] hypertension, and cardiovascular disease have a worse prognosis with COVID-19.[22,23,25] Among these comorbidities, diabetes had the most significant impact on mortality.[20] People with diabetes face a higher risk of death and critical conditions due to COVID-19. Some studies have highlighted the importance of statins, due to their anti-inflammatory role and cytokines reduction, in lowering the risk of death from COVID-19 in DM.[26-28]

Studies on the effects of statins on the prevention of COVID-19 death have been performed systematically; however, none of these studies has been performed specifically in diabetic

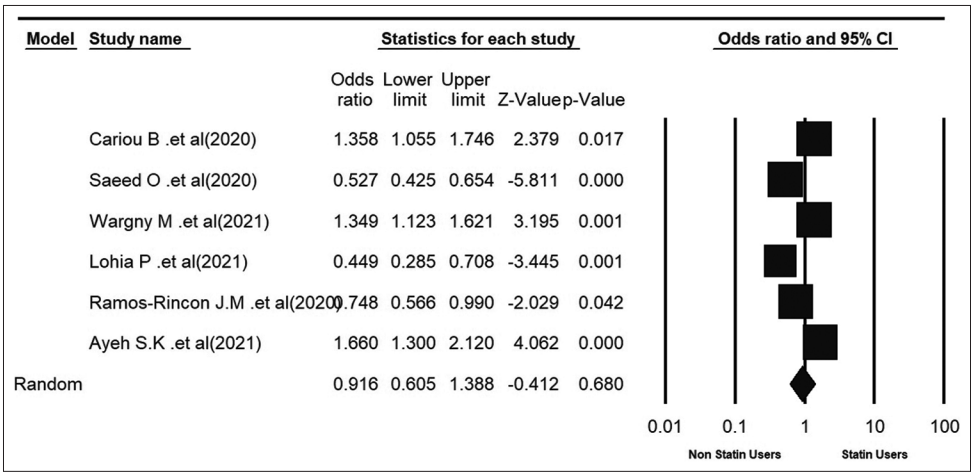

Figure 2: Forest plot from meta-analysis for COVID-19 of mortality in diabetic patients using statin/nonstatin

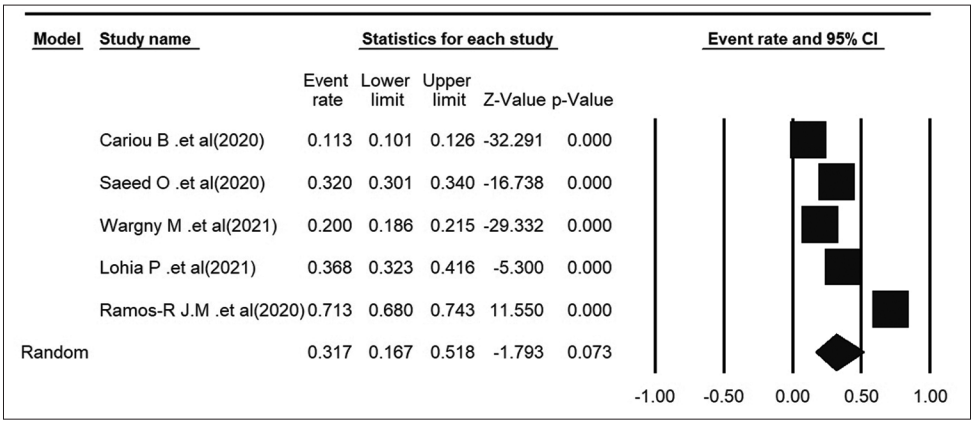

Figure 3: Forest plot from meta-analysis for the prevalence of COVID-19 mortality in patients with diabetes

Table 2: Quality of evidence assessment (grading of recommendations assessment, development, and evaluation)

	Certainty assessment							Number of patients		Effect OR/prevalence (95% CI)	Certainty
	Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Statin	Nonstatin		
Mortality in diabetic patients using statin/nonstatin	6	Observational studies	Not serious	Serious	Not serious	Not serious	None	4326	5207	OR 0.91 (0.60–1.38)	⊕⊕⊕○ moderate
Prevalence of COVID-19 mortality in patients with diabetes	5	Observational studies	Not serious	Serious	Not serious	Not serious	None	8714	-	0.317 (0.167–0.518)	⊕○○○ very low

OR: Odds ratio, CI: Confidence interval. The circles depicted in the table signify the degree of certainty associated with the calculated odds ratios

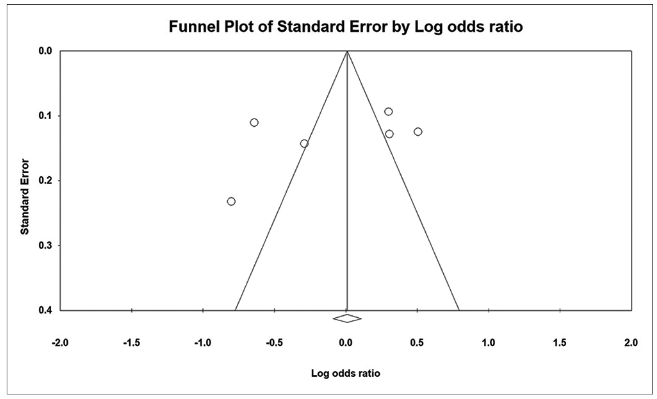

Figure 4: Funnel plot to investigate diffusion bias in meta-analysis

patients.[29-31] According to studies, the death rate due to coronary artery disease in diabetic patients is higher than in healthy people.[26] Therefore, this study was conducted to summarize the results of studies on the effect of statins on the death of diabetic patients with COVID-19.

Our meta-analysis of five studies[4,19,20,22,23] compared the chances of COVID-19 death in diabetic patients using statins with nonstatins and the prevalence of COVID-19 death in diabetic patients. This study was performed on 9533 diabetic patients with COVID-19. The chance of mortality from COVID-19 was 9% lower in diabetic patients using statins than in patients not using statins. The prevalence of COVID-19 death in diabetic patients was 31.7%.

Lohia *et al*.,[20] in a retrospective cohort study on hospitalized patients, examined the effect of statin (atorvastatin) on death and showed that mortality rates in patients who received statins were lower than those who did not. On the other hand, Cariou *et al*.[23] in an observational study of 2499 diabetic patients with COVID-19 showed that there were higher deaths of patients with COVID-19 between those taking statins compared with those who did not. The results of our study showed that the chance of mortality between statin users and nonstatin users was not statistically significant. These results were consistent with the results of the other studies.[23] The results of previous studies and the present study do not support the protective role of statins in patients with COVID-19. It can be said that to show the potential effects of statins on mortality due to COVID-19, we need to examine other influencing factors such as age, gender, and other laboratory factors. Holman *et al*.[6] examined a large number of data related to COVID-19 patients and found that there was a correlation between modifiable factors such as blood pressure, age, and hyperglycemia with COVID-19 mortality. Although modifying identified risk factors for mortality from COVID-19 in diabetic patients are not easy, there are interventions to improve glycated hemoglobin. One of the best ways to decrease the COVID-19-related mortality risk factors is to improve the recommendations and standard guidelines which aims to prevent the cardiovascular and microvascular complications. In a multicenter, case–control, retrospective, observational study on 338 diabetic patients

with COVID-19, Solerte *et al*.[32] recently showed that when sitagliptin had been added to patient standard care, they had less probability of mortality. Another point is that the timing of statin use could play a decisive role. As shown in Chow's meta-analysis,[29] people who take statins after identification of COVID-19 have a lower risk of death. In our meta-analysis, the prevalence of COVID-19 mortality in diabetic patients was 31.7%, which was almost similar to the results of Saha *et al*.[30] The prevalence of mortality among DM patients in that study was 28.0%.

The limitations of this study were as follows: first, randomized clinical trials were not included. This study design has the potential to provide robust evidence along with examining several influencing factors, such as age, body mass index, antecedent statin uses at home, the chronicity of DM, and complications resulting from DM (presence of microvascular and macrovascular complications from DM). Moreover, several factors such as the use of angiotensin inhibitors and aspirin can be controlled in the included patients. Second, in this study, we restricted articles to the English language ones, due to the COVID-19 pandemic, scholars around the world were striving to provide evidence about this topic. There may be eligible articles written in languages other than English which could be included in the present study. Finally, the generalizability should be done carefully as the population was limited to diabetic patients.

Conclusions

In regards to diabetes disease, the mortality rate was 9% lower among people with COVID-19 who took statins than those who did not. Therefore, it can be expected that statins could play a crucial role in reducing mortality. However, to establish the strength of clinical evidence, further investigation, especially by designing a clinical trial, is required.

Ethical clearance

No human or animal studies were involved in this study.

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Conflicts of interest

There are no conflicts of interest.

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