The association between statin use and survival of esophageal cancer patients

A systematic review and meta-analysis

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Abstract

Whether statin use has any impact on survival of esophageal cancer patients remains controversial. Therefore, we conducted a meta-analysis focusing on current topic for the first time.

We systematically searched the following databases for relevant studies comparing survival between statin users and non-users among esophageal cancer patients up to March 16, 2019: Pubmed, Embase, and Web of Science. We extracted data of hazard ratio (HR) with 95% confidence interval (CI) of all-cause and cancer-specific mortality for analysis. We used the STATA 12.0 software to perform this meta-analysis.

We finally included a total of 4 cohort studies involving a total of 20,435 esophageal cancer patients (5319 statin users and 15116 non-users). Our meta-analysis found that statin use after diagnosis of esophageal cancer was significantly correlated to decreased all-cause (random effects: HR = 0.81, 95%CI: 0.75–0.89, P < .001; F = 68.1%) and cancer-specific mortality (fixed effects: HR = 0.84, 95%CI: 0.78–0.89, P < .001; F = 46.6%) in esophageal cancer patients. When stratified by pathological subtypes, the protective effect of statin use after diagnosis of esophageal cancer was observed in both esophageal adenocarcinoma patients and esophageal squamous cell carcinoma patients. Moreover, statin use before diagnosis of esophageal cancer was also confirmed to have favorable survival benefit for esophageal cancer patients.

Statin use was significantly correlated to lower mortality risk of esophageal cancer patients regardless of the time when statins were taken and pathological subtypes of esophageal cancer. Statins may serve as promising adjunctive anticancer agents for treating esophageal cancer.

Abbreviations: CI = confidence interval, EA = esophageal adenocarcinoma, HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A, HR = hazard ratio, NOS = the Newcastle-Ottawa Scale, RCT = randomized controlled trial, SCC = esophageal squamous cell carcinoma.

Keywords: esophageal cancer, HMG-CoA reductase inhibitors, meta-analysis, mortality, statins

1. Introduction

Esophageal cancer still remains to be a heavy disease burden worldwide, with 455,800 new esophageal cancer cases and 400,200 deaths occurring in 2012.[1] In pathology, esophageal cancer mainly consisted of esophageal adenocarcinoma (EA) and esophageal squamous cell carcinoma (SCC).[2] Despite of the advancement of therapeutic strategies, the prognosis of esophageal cancer still remains dismal with a 5-year survival rate of about 15% to 34%.[3] Therefore, investigation on novel potential medications that have anticancer effects for esophageal cancer seems to be greatly important, which might help improve the survival of esophageal cancer patients.

Statins, as the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, have been widely utilized for the primary and secondary prevention of atherosclerotic cardiovascular disease, with more than 200 million people taking them worldwide.[4] However, recent evidence has showed that statins might have the anticancer effects such as antiproliferation and proapoptosis[5] and as a results, more and more studies have focused on the impact of statins on both risk and prognosis of various cancers. Previously, statins has been shown to lower the risk of esophageal cancer among people taking them, especially the risk of esophageal adenocarcinoma in patients with Barrett esophagus.[6] However, as for the impact of statins on survival of esophageal cancer patients, previous studies have drawn conflicting conclusions due to various biases.[7–10] Some studies found that statin use was significantly correlated with decreased all-cause and cancer-specific mortality in esophageal cancer patients with both EA and esophageal SCC[9] while others found that statin use had little evidence of cancer-specific mortality.
reduction in esophageal cancer patients. Moreover, some even found that statin use could only reduce the all-cause and cancer-specific mortality in patients with EA but not in patients with esophageal SCC. Therefore, the impact of statin use on prognosis of esophageal cancer remains unclear. Hence, in this study, we tried to conduct a systematic review and meta-analysis focusing on the impact of statin use on long-term survival of esophageal cancer patients by pooling all these up-to-date evidence together. To our knowledge, this is the first meta-analysis focusing on the correlation between statin use and survival of esophageal cancer patients.

2. Methods and materials

2.1. Literature search

We performed a comprehensive literature search in the following online databases systematically: PubMed, Embase, and Web of Science and the time period was up to March 16, 2019. We used the following search terms: ((statin) OR statins) OR hydroxymethylglutaryl coenzyme reductase inhibitors) OR HMG CoA reductase inhibitors)) AND ((esophageal OR oesophageal OR esophagus) OR oesophagus) OR esophageal) AND (((cancer) OR carcinoma) OR tumor) OR neoplasm). We also manually searched the reference lists of relevant studies for potential study retrieval.

2.2. Study inclusion and exclusion

We would include either randomized controlled trials (RCTs) or observational studies that met the following inclusion criteria:

1. exploring the effects of statins on survival of esophageal cancer patients by comparing statin users and non-users among esophageal cancer patients;
2. providing sufficient data of hazard ratio (HR) with 95% confidence interval (CI) for all-cause mortality or cancer-specific mortality;
3. if studies were conducted from the same population, only the most recent one was included.

We would exclude studies that met the following exclusion criteria:

1. including patients with other types of cancer apart from esophageal cancer;
2. no sufficient data for meta-analysis;
3. not published in English language;
4. reviews, case reports, conference abstracts, experimental studies.

2.3. Data extraction and the assessment of risk of bias

In order to minimize potential analyzing bias, we developed a standardized data collection form, which was utilized for data extraction from 2 of our authors independently. The data collected from these included studies consisted the following baseline characteristics: first author name, year of publication, country of origin, age, statin use status, total sample size, treatment strategies, follow-up information, sample size in statin user group and non-user group, and study design. Our main outcomes for analysis included all-cause mortality and cancer-specific mortality, which were expressed as HR with 95% CI comparing survival between statin users and non-users. For quality assessment and risk of bias analysis of each study, we would apply the Jadad scale to evaluate the quality of RCTs, which consisted of randomization (0–2 points), blinding of the studies (0–2 points), and withdrawals (0–1 point). For observational studies, we would use the Newcastle-Ottawa Scale (NOS) for risk of bias analysis. In this scale, it consisted of 3 factors: patient selection, comparability of the study groups, and assessment of outcome and a score of 0 to 9 (allocated as stars) would be assigned to each observational study based on the score. And a high-quality study was defined as one with a quality score of no less than 7.

2.4. Data synthesis and statistical analysis

We performed our meta-analysis by applying the STATA 12.0 package (StataCorp, College Station, TX, USA) in accordance with the PRISMA guidelines. We extracted HRs with 95% CI directly from the text of original study for comparison of all-cause mortality and cancer-specific mortality between statin users and non-users among esophageal cancer patients. Here we explored the impact of statin use on survival of esophageal cancer patients by not only focusing on these taking statins after the diagnosis of esophageal cancer but also these before the diagnosis. Moreover, we also conducted subgroup analysis based on pathological subtypes of esophageal cancer. We used the $\chi^2$-based Q statistics and I² test for assessing the between-study heterogeneity and defined a high heterogeneity as $P < .1$ or $I^2 > 50\%$. If we encountered high heterogeneity during analysis, we would use the random effects models. If no high heterogeneity was observed, the fixed effects models would be applied for analysis. To test the stability of our results, we also conducted a sensitivity analyses by removing each study sequentially. Finally, we applied a funnel plot as tested by Begg and Egger tests to evaluate potential publication bias. Statistical significance was as a two-sided $P$ value of less than .05.

3. Results

3.1. Search results

After careful searching in above online databases, we initially retrieved a total of 429 papers. Our process for study evaluation was presented in Figure 1. After excluding these duplicate papers, we had a total of 269 papers for evaluation. After evaluation of the titles and abstracts of these paper, we excluded these unrelated studies, conference abstracts, and studies not published in English. As a result, we had a total of 7 papers for further evaluation of full text. One systematic review focusing on all types of cancers was excluded and another 2 studies exploring the impact of statin use on either short-term outcomes or cost-utility effects in surgically treated esophageal cancer patients were also excluded. Finally, we included a total of 4 cohort studies involving a total of 20,435 esophageal cancer patients (3319 statin users and 15116 non-users) for meta-analysis.

3.2. Characteristics of the included studies

We presented the baseline characteristics of each included study in Table 1. All studies included patients with esophageal cancer.

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**Figure 1:** Flowchart of study selection process.
treated with surgery, chemotherapy, or radiotherapy. The follow-up was actually relatively long even though the absolute time of follow-up time was not given out in some studies. All studies had a relatively large sample size and appropriate adjustment for comparing survival between statin users and non-users. The main data for meta-analysis extracted from each included study were presented in Table 2. Two studies reported HRs of mortality for all esophageal cancers as well as EA and esophageal SCC individually, while 1 study only reported for all esophageal cancers without subgroup data for EA and esophageal SCC individually and another 1 only reported HRs for EA and esophageal SCC individually.

3.3. Quality assessment and risk of bias analysis

Because there was no RCTs available for analysis, we could only include above cohort studies for meta-analysis. Therefore, we used the NOS to evaluate the quality and risk of bias of these studies. The results of quality assessment were listed in Table 1. All these included studies yielded a quality score of no less than 7, which suggested a low risk of bias in our meta-analysis.

3.4. The impact of statin use after diagnosis on mortality of esophageal cancer patients

All studies reported HRs of mortality for comparing survival between statin users and non-users among esophageal cancer patients either stratified by pathological subtypes or not. Our meta-analysis found that statin use after diagnosis of esophageal cancer was significantly correlated to decreased all-cause mortality (random effects: HR = 0.81, 95% CI: 0.75–0.89, P < .001; I² = 68.1%) in esophageal cancer patients (Fig. 2A). Moreover, statin use after diagnosis of esophageal cancer was also found to be significantly correlated to decreased cancer-specific mortality (fixed effects: HR = 0.84, 95% CI: 0.78–0.89, P < .001; I² = 46.6%) in esophageal cancer patients (Fig. 2B). However, significant heterogeneity was observed during the analysis.

3.5. Subgroup analysis based on pathological subtypes of esophageal cancer

Because of significant heterogeneity observed above, considering the innate difference of EA and esophageal SCC, we conducted the subgroup analysis based on different pathological subtypes of esophageal cancer. However, our meta-analysis still found that statin use after diagnosis of esophageal cancer was significantly correlated to decreased all-cause mortality in both patients with EA (fixed effects: HR = 0.79, 95% CI: 0.74–0.85, P < .001; I² = 31.5%) and those with esophageal SCC (fixed effects: HR = 0.83, 95% CI: 0.73–0.94, P = .003; I² = 0%) (Fig. 3A). And statin use after diagnosis of esophageal was also found to be significantly correlated to decreased cancer-specific mortality in both patients with EA (fixed effects: HR = 0.81, 95% CI: 0.74–0.89, P < .001; I² = 31.1%) and those with esophageal SCC (fixed effects: HR = 0.82, 95% CI: 0.76–0.89, P < .001; I² = 39.7%).
## Table 1
Characteristics of the included studies in this meta-analysis.

| Authors        | Country      | Patients                                                                 | Age (ranges, years) | Follow-up                  | Sample size (N) | Statin users (N) | Non-users (N) | Study design | Adjustment                                                                 | Quality assessment |
|----------------|--------------|---------------------------------------------------------------------------|---------------------|-----------------------------|-----------------|-----------------|---------------|----------------|--------------------------------------------------------------------------------|-------------------|
| Alexandre, 2016| United Kingdom| Patients with esophageal cancer treated with surgery, chemotherapy, or radiotherapy | Mean: 70.8          | NA                          | 1530            | 219             | 1311          | Cohort study | age, gender, body mass index, smoking status, cardiovascular diseases, diabetes, surgery, pre-diagnosis statin use, and post-diagnosis use of other medications | NOS: 7 stars       |
| Cardwell, 2017 | United Kingdom| Patients with esophageal cancer treated with surgery, chemotherapy, or radiotherapy | NA                  | Mean: 24 months (range: 6–60 months) | 1921            | 651             | 1270          | Cohort study | sex, age, year of diagnosis, deprivation, cancer treatment within 6 months, comorbidities, and aspirin use | NOS: 8 stars       |
| Nguyen, 2018   | United States | Patients with esophageal cancer treated with surgery, chemotherapy, or radiotherapy | NA                  | NA                          | 11750           | 2821            | 8929          | Cohort study | age, sex, race, body mass index, alcohol use, smoking status, stage, grade, treatment, pre-diagnosis statin use, and post-diagnosis aspirin use | NOS: 7 stars       |
| Lacroix, 2019  | Belgium      | Patients with esophageal cancer treated with surgery, chemotherapy, or radiotherapy | NA                  | Median: 2.39 years          | 5234            | 1628            | 3606          | Cohort study | age, sex, year of diagnosis, stage, cancer treatment, morphology, and comorbidities | NOS: 7 stars       |

NA = not available, NOS = Newcastle–Ottawa Scale.
**Table 2**

| Authors      | Comparison                                | All-cause mortality | Cancer-specific mortality |
|--------------|-------------------------------------------|---------------------|--------------------------|
|              | Statin users VS non-users after diagnosis of esophageal cancer | Hazard ratio | 95% Confidence interval | Hazard ratio | 95% Confidence interval |
| Alexandre, 2016 | All esophageal cancers                     | 0.67                 | 0.58–0.77               | 0.62            | 0.44–0.86            |
|              | Esophageal SCC                            | 0.63                 | 0.43–0.92               | 0.61            | 0.38–0.96            |
|              | Esophageal SCC                            | 0.78                 | 0.41–1.50               | 0.65            | 0.29–1.46            |
| Cardwell, 2017 | All esophageal cancers                     | 0.94                 | 0.82–1.07               | 0.93            | 0.81–1.07            |
|              | Esophageal SCC                            | NA                   | NA                      | 0.90            | 0.75–1.08            |
| Nguyen, 2018   | All esophageal cancers                     | 0.80                 | 0.74–0.86               | 0.79            | 0.70–0.88            |
|              | Esophageal SCC                            | 0.83                 | 0.74–0.95               | 0.77            | 0.65–0.92            |
| Lacroix, 2019  | All esophageal cancers                     | 0.84                 | 0.77–0.92               | 0.87            | 0.78–0.97            |
|              | Esophageal SCC                            | NA                   | NA                      | NA              | NA                   |

**Legend:**
- EA = esophageal adenocarcinoma
- NA = not available
- SCC = squamous cell carcinoma

**Figure 2.** Forest plots of (A): all-cause mortality and (B): cancer-specific mortality demonstrating the impact of statin use after diagnosis of esophageal cancer on all esophageal cancer patients. NOTE: Those studies with the same author and year of publication were extracted from the same article analyzing subgroup based on different pathological subtypes; therefore, they shared the same identification code.

**Figure 3.** Forest plots of (A): all-cause mortality and (B): cancer-specific mortality demonstrating the impact of statin use after diagnosis of esophageal cancer on esophageal cancer patients stratified by pathological subtypes. SCC = squamous cell carcinoma.
0.71–0.95, \( P = .009; I^2 = 0\%\) (Fig. 3A). Moreover, no significant heterogeneity was observed during subgroup analysis.

3.6. The impact of statin use before diagnosis on mortality of esophageal cancer patients

Three studies reported the impact of statin use before diagnosis of esophageal cancer on mortality of esophageal cancer patients. Our meta-analysis found that statin use before diagnosis of esophageal cancer was still significantly correlated to decreased all-cause mortality (fixed effects: HR = 0.86, 95% CI: 0.81–0.90, \( P < .001; I^2 = 0\%\)) in esophageal cancer patients (Fig. 4A). Moreover, statin use before diagnosis of esophageal cancer was also found to be significantly correlated to decreased cancer-specific mortality (fixed effects: HR = 0.85, 95% CI: 0.79–0.91, \( P < .001; I^2 = 0\%\)) in esophageal cancer patients (Fig. 4B). Moreover, no significant heterogeneity was observed during analysis.

3.7. Sensitivity analysis and publication bias

For sensitivity analysis, we removed each study sequentially to test the stability of our results based on the analysis of all-cause and cancer-specific mortality. Sensitivity analysis showed that omitting each study sequentially did not change our primary results regarding the effects of statin use on mortality of esophageal cancer patients (Fig. 5). Moreover, we drew a funnel plot to evaluated publication bias based on all-cause mortality, which showed a symmetrical appearance, and no statistical significance was observed (Begg test: \( P = 1.00\); Egger test: \( P = .91\)), indicating a very low publication bias (Fig. 6).

4. Discussions

Statins, as the HMG-CoA reductase inhibitors, which could inhibit the endogenous mevalonate pathway and thus inhibit the downstream cholesterol biosynthesis and numerous isoprenoid metabolites,\(^{[18]}\) are commonly used as cholesterol-lowering agents in cardiovascular diseases.\(^{[19]}\) However, previous evidence has shown that apart from their cholesterol-lowering effects, statins also exhibited pleiotropic effects such as antiproliferative, pro-apoptotic, and anti-invasive effects in cancer cells.\(^{[19,20]}\) Therefore, more and more studies have been carried out to explore the impact of statin use on survival of cancer patients.\(^{[15]}\) Overwhelming evidence has shown that statin use was
was also significantly correlated to decreased mortality of patients with various cancers, such as prostate cancer,[21] breast cancer,[22] and lung cancer.[23] However, only a few studies[7–10] have focused on the impact of statin use on survival of esophageal cancer patients with conflicting conclusions because of different sample size as well as statistical methods and different adjustment for confounding factors. Therefore, the impact of statin use on survival of esophageal cancer patients remains unclear. Hence, in this study, we conducted the first comprehensive systematic review and meta-analysis to figure out the actual effects of statin use on esophageal cancer patients.

In this meta-analysis, we included only a total of 4 cohort studies involving a total of 20,435 esophageal cancer patients (5319 statin users and 15,116 non-users). Our meta-analysis found that statin use after diagnosis of esophageal cancer was significantly correlated to decreased all-cause mortality (HR = 0.81, 95% CI: 0.75–0.89, P < .001) and cancer-specific mortality (HR = 0.84, 95% CI: 0.78–0.89, P < .001). Moreover, statin use before diagnosis of esophageal cancer was also significantly correlated to decreased all-cause mortality (HR = 0.86, 95% CI: 0.81–0.90) and cancer-specific mortality (HR = 0.85, 95% CI: 0.79–0.91, P < .001) in esophageal cancer patients. Therefore, our studies proved that statin use could significantly decrease the mortality risk of esophageal cancer patients regardless of the time when statins were taken or pathological subtypes of esophageal cancer.

Preclinical studies have shown that statins could exert their anticancer effects via both HMG-CoA reductase-dependent and HMG-CoA reductase-independent signal pathways.[6] In the HMG-CoA reductase-dependent pathways, statins inhibit the HMG-CoA reductase and subsequently block the conversion of HMG-CoA into mevalonate, thus decreasing the downstream effects of overcoming radioresistance of esophageal cancer.[30] As a result, it is reasonable to find that statin use was significantly correlated lower risk of esophageal cancer.[6] Moreover, in esophageal cancer patients undergoing esophagectomy, statin use could significantly decrease inflammation biomarkers and pulmonary epithelial and systemic endothelial injury, which may lead to improved perioperative outcomes.[16] Adjuvant statin therapy was also found to yield lower costs and better quality-adjusted life years in EA patients and it was a promising cost-saving treatment.[17] Therefore, taken our results together, we believe that statin use may improve the prognosis of esophageal cancer patients. As a result, statins may serve as promising adjunctive anticancer agents in treating esophageal cancer patients. Therefore, our meta-analysis highlighted the need of well-conducted RCTs to verify the efficacy of statins in treating esophageal cancer.

However, several limitations existed in our meta-analysis. First, we could only include 4 observational studies for analysis, which might decrease the validity of our results. Second, potential heterogeneity was observed during analysis. Even though we conducted subgroup analyses, the sample size in each subgroup analysis remained relatively small. Therefore, well-conducted RCTs exploring the anticancer effects of statins in esophageal cancer patients are required.

5. Conclusions

We conducted the first meta-analysis to investigate the impact of statin use on survival of esophageal cancer patients. We found that statin use was significantly correlated to decreased all-cause and cancer-specific mortality of esophageal cancer patients. Statins may serve as adjunctive anticancer agents in treating esophageal cancer. Further well-designed anticancer agents in treating esophageal cancer. Further well-designed RCTs are badly needed to confirm and update our conclusions.

Author contributions

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