



Do statins improve the survival time after esophagectomy? — a propensity score matching study

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Background: The purpose of this study was to evaluate the impact of statins (HMG-CoA reductase inhibitors) on the prognosis of patients undergoing esophagectomy in a high incidence area.

Methods: This study retrospectively analyzed the database of patients underwent esophagectomy in the First Affiliated Hospital of Zhengzhou University. Preoperative application of statins for more than one year as the grouping factor. A propensity score matching (PSM) analyses was conducted to reduce heterogeneity and increase the comparability of the two groups, then compared the survival time of the matched groups through the Kaplan-Meier method. All P values were 2-sided and P<0.05 was statistically significant.

Results: 738 of 1,378 esophageal cancer patients with complete medical records (including 27 statins users) were selected in the study. Variables of the two matched groups in the male (sex), age, type II diabetes, cardiovascular comorbidity, differentiation of tumor and staging of tumor were no statistical difference after PSM. After 40 months of follow-up, there is no difference between the two groups regarding overall survival with P values of Breslow test (P=0.816).

Conclusions: Statins use do not improve the survival time of patients after esophagectomy in a high incidence area of China.

Keywords: Esophageal cancer; statins; hydroxymethylglutaryl-CoA reductase inhibitor; survival time

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Introduction

Esophageal cancer is the 8th common malignant tumor and the 6th common cancer-related cause death worldwide, especially in undeveloped regions (1,2). Esophageal squamous cell carcinoma (ESCC) is the most common type and male is about twice as likely as women (3). Esophagectomy combined with radiotherapy or/and chemotherapy is the main treatment, especially in the rapid development of minimally invasive esophagectomy (MIE) (4), however the prognosis is far from satisfaction,

and the five-year survival rate of esophageal cancer is still 18.4% (5). Studies suggested statins (HMG-CoA reductase inhibitors) improve the prognosis of esophageal cancer patients (6-8). We reviewed and compared the prognosis of 27 statins users with that of 711 non-users in our database using propensity score matching analyses.

Methods

Patients data were retrospectively collected from the HIS (Hospital Information System, Version 5.0, Neusoft

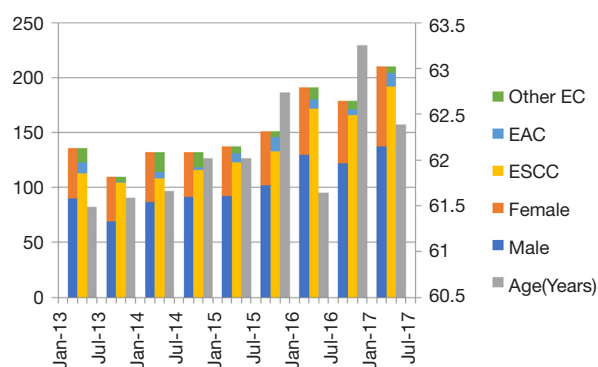


Figure 1 Characteristics of 1,378 patients underwent EC surgery from January 2013 to June 2017.

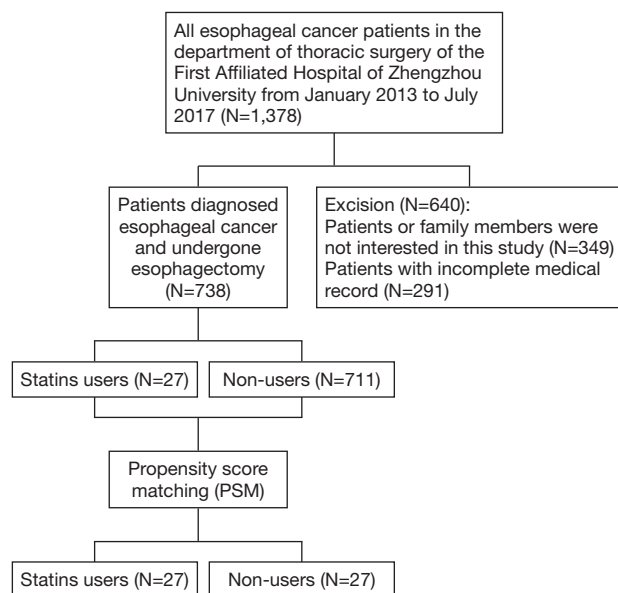


Figure 2 The screening progress of this study.

Co., Ltd, ShenYang, China) and the survival information was acquired by the patient returned to the hospital for postoperative reviews or telephone interviews based on a well-constructed questionnaire. The staging criteria is referred to the eighth edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual for epithelial cancers of the esophagus and esophagogastric junction (9). Inclusion criteria includes patients with a primarily confirmed pathological diagnosis of esophageal cancer and underwent esophagectomy from January 2013 to June 2017, however patients with previous stomach surgery and/or with distant metastasis were excluded. The variables (sex, age, BMI, type II diabetes, cardiovascular

comorbidity) were collected from medical records, other variables (tumor type, differentiation, cTNM) were searched from the pathologic reports from professors of pathology.

Statistical methods

All statistical analyses were operated with IBM SPSS Statistics 24.0 statistical software program (IBM SPSS Inc. Chicago, IL, USA). Continuous variables (age and BMI) were summarized as mean (SD) if normally distributed, otherwise median (IQR), moreover, T-test for normally distributed continuous variables and Wilcoxon signed-rank test for non-normally distributed variables. Categorical variables (type II diabetes, lymph node metastasis, cardiovascular comorbidity, tumor type, differentiation and cTNM) were compared using Chi-square test. Based on sex, age, BMI, type II diabetes, cardiovascular comorbidity, tumor type, differentiation and cTNM, a propensity score matching (PSM) analysis between 27 statins users and 711 non-users were conducted using SPSS. After PSM, the survival curves of the two matched groups (statins users and non-users) were plotted using Kaplan-Meier method and analyzed using Breslow test with SPSS.

Results

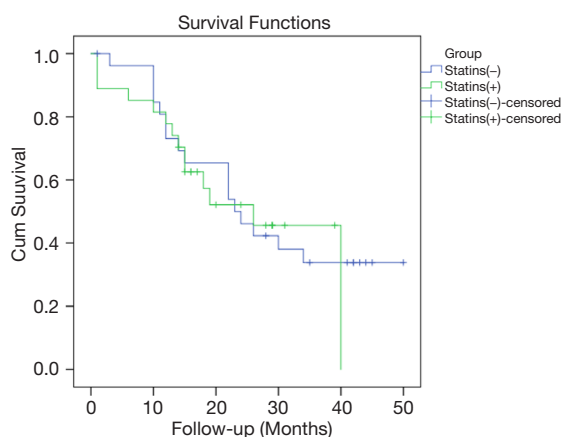
We retrospectively reviewed the data of 1,378 patients who underwent esophagectomy from January 2013 to June 2017 in our department. The characteristics of our patients were in line with that of previously reported, ESCC accounting for about 90% of the cases with a sex ratio of 2:1 (Male: Female) (3,10,11). The histological type and male-female ratio of patients with esophageal cancer did not change obviously, however, there were growth trends in the number and age of them (Figure 1).

After excluding 349 patients missing (patients or family members are not interested in this experiment and refuse to participate at the telephone conversations) and 291 patients with incomplete medical record, 738 patients were eligible for further analyses, including 27 cases of statins users. Finally, 27 pairs esophageal cancer patients were matched after PSM analyses (Figure 2).

Before PSM, the sex (male), age, type II diabetes and cardiovascular comorbidity of statins users group (N=27) and non-users group (N=711) were statistically different, and there were no statistical differences between all control variables in the two groups after PSM (Table 1).

Table 1 The differences of the two groups before and after propensity score matching

Variables	Before matching		P value	After matching		P value
	Stains users, N=27	Non-users, N=711		Stains users, N=27	Non-users, N=27	
Male (%)	24 (88.89%)	477 (67.09%)	0.017	24 (88.89%)	24 (88.89%)	1.000
Age [IQR] or (SD)	66.00 [62.00, 72.00]	63.00 [58.00, 68.00]	0.025	66.04 (6.86)	65.48 (6.89)	0.768
BMI (SD)	24.38 (3.94)	23.67 (3.42)	0.289	24.38 (3.94)	24.57 (3.47)	0.849
Type II diabetes (%)	5 (18.52%)	40 (5.63%)	0.019	5 (18.52%)	4 (14.81%)	1.000
Cardiovascular comorbidity (%)	27 (100%)	108 (15.19%)	0.000	27 (100%)	27 (100%)	1.000
Lymph node metastasis (%)	11 (40.74%)	221 (31.08%)	0.289	11 (40.74%)	12 (44.44%)	0.783
Type of tumor			0.121			1.000
ESCC	23 (85.19%)	660 (92.83%)		23 (85.19%)	22 (81.48%)	
EAC	4 (14.81%)	37 (5.20%)		4 (14.81%)	5 (18.52%)	
Others	0 (0%)	14 (1.97%)		0 (0%)	0 (0%)	
Differentiation of tumor (%)			0.061			0.958
Low	2 (7.41%)	178 (25.04%)		2 (7.41%)	2 (7.41%)	
Middle	15 (55.56%)	370 (52.04%)		15 (55.56%)	16 (59.26%)	
High	10 (37.04%)	163 (22.93%)		10 (37.04%)	9 (33.33%)	
cTNM (%)			0.297			0.970
0	2 (7.41%)	103 (14.49%)		2 (7.41%)	2 (7.41%)	
I	3 (11.11%)	114 (16.03%)		3 (11.11%)	2 (7.41%)	
II	11 (40.74%)	333 (46.84%)		11 (40.74%)	12 (44.44%)	
III	11 (40.74%)	160 (22.50%)		11 (40.74%)	11 (40.74%)	
IV	0 (0%)	1 (0.14%)		0 (0%)	0 (0%)	

**Figure 3** The survival analysis of the two groups after propensity score matching. Statins (+): statins use for more than 1 year before patients diagnosis esophageal cancer; Statins (-): patients in the control group; Censored: patients missing or still alive at the end of the follow-up.

After PSM, we followed the 27 pairs patients by the questionnaire through telephone and compared survival data. With the follow-up time of 14–50 months, the survival analysis and comparison of the two matched groups were showed in *Figure 3*. The survival curves were preformed using Kaplan-Meier method and there is no statistical difference between the two matched groups regarding overall survival with P values of 0.816 via Breslow (Generalized Wilcoxon) test, in other words, our data showed statins use for more than one year before esophagectomy do not improve their survival time in our center (*Figure 3*).

Discussion

After PSM, all statins use patients were matched with non-users and the variables of the matched groups were no

statistical difference. After 50 months of follow-up, the survival analysis showed that statins use for more than one year before esophagectomy does not improve the survival time in esophageal cancer patients.

Statins are effective in regulating lipids, anti-platelet aggregation, anti-inflammation, immunosuppression and improving vascular endothelial function through competitively inhibiting the HMG-CoA reductase (12,13). Some studies reported statins use may benefit the prognosis esophageal cancer patients. A retrospective investigation in 2016 from Alexandre and colleagues (6) reported that statins reduce the esophageal cancer-specific mortality (HR 0.61, CI: 0.38–0.96) and all-cause mortality (HR 0.63, CI: 0.43–0.92). Another retrospective study in 2017 from Cardwell and colleagues (7) showed that statins use for more than one year before diagnosis, resulting in reducing the esophageal cancer-specific mortality (HR 0.88, CI: 0.79–0.99). Recently, a retrospective study in 2018 from Nguyen and colleagues (8) found that statins use reduce the cancer-related mortality (HR 0.79, CI: 0.70–0.88) and all-cause mortality (HR 0.80, CI: 0.74–0.86) in esophageal cancer patients.

Undeniably, statins users group in our study have many great differences than general non-users group patients. There is very few patients applying statins and only about 2% esophageal cancer patients in our data use statins for more than one year before esophagectomy. Importantly, all statins users have clear cardiovascular complications in statins users group and the average age in statins users is older than general esophageal cancer patients, and these factors may lead to a worse prognosis. Although our data indicated that statins use for more than one year before esophagectomy does not improve the postoperative survival, we cannot deny that our retrospective analyses have significant limitations. Since we are a relatively high-volume center for esophagectomy, we will spare no efforts to perform further researches, determining the effects of statins in esophageal cancer.

Conclusions

Limited data showed patients use statins for more than one year before esophagectomy does not improve the postoperative survival time.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2020.03.51>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This is a retrospective observational study. Our research has been ethically reviewed, and our research met the requirements of the Ethics Committee of the First Affiliated Hospital of Zhengzhou University.

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