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ORIGINAL ARTICLE

Statin therapy and postoperative short-term mortality after rectal cancer surgery

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Abstract

Aim: This study aimed to assess the correlation between regular statin therapy and postoperative mortality following surgical resection for rectal cancer.

Method: This retrospective cohort study included all adult patients undergoing abdominal rectal cancer surgery in Sweden between January 2007 and September 2016. Data were gathered from the Swedish Colorectal Cancer Registry, a large population-based prospectively collected registry. Statin users were defined as patients with one or more collected prescriptions of a statin within 12 months before the date of surgery. The statin-positive and statin-negative cohorts were matched by propensity scores based on baseline demographics.

Results: A total of 11 966 patients underwent surgical resection for rectal cancer, of whom 3019 (25%) were identified as statin users. After applying propensity score matching (1:1), 3017 pairs were available for comparison. In the matched groups, statin users demonstrated reduced 90-day all-cause mortality (0.7% vs. 5.5%, $p < 0.001$) and also showed significantly reduced cause-specific mortality due to cardiovascular and respiratory events, as well as sepsis and multiorgan failure. The significant postoperative survival benefit of statin users was seen despite a higher rate of cardiovascular comorbidity.

Conclusion: Preoperative statin therapy displays a strong association with reduced postoperative mortality following surgical resection for rectal cancer. The results from the current study warrant further investigation to determine whether a causal relationship exists.

INTRODUCTION

Major abdominal surgery entails a high risk of postoperative complications, which occur in up to a third of all cases [1]. A fraction of these complications are presumed to be amplified by the immediate stress response initiated by the surgical trauma [2]. This may not only give rise to surgical complications but also adverse medical events of infectious, cardiovascular, respiratory and cerebral origin [3–6]. Such nonsurgical postoperative problems predispose this surgical patient group to a higher mortality rate. Previous scientific literature outlines rates of between 7.5% and 29.4% for such adverse outcomes [7].

Surgery for rectal cancer remains a high risk area for postoperative morbidity. Postoperative morbidity rates approach 40%, and 90-day mortality is around 3% [8]. A strong relationship between the release of proinflammatory cytokines after rectal surgery and worse outcomes

has previously been noted [9,10]. It is proposed that 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, also known as statins, may have postoperative anti-inflammatory and protective immunomodulatory effects [11]. Previous studies have investigated the potential impact of statin therapy on short-term postoperative outcomes following colorectal surgery. While some have found postoperative benefits in the form of decreased complication rates, [12–14] others have not been able to demonstrate any association [15–17]. Data on statin therapy and postoperative mortality isolated to rectal resection surgery for cancer are scarce [12].

The objective of this study is to assess the correlation between regular statin therapy and postoperative mortality following rectal cancer surgery by using patients from a large national registry.

What does this paper add to the literature?

Surgery for rectal cancer remains an area of high postoperative risk for adverse outcomes. Data are scarce regarding any postoperative protective effects of statin therapy after rectal cancer surgery. This study is the first to show an association between statin use and postoperative mortality. The results warrant a prospective randomized trial.

METHOD

Study setting

This retrospective cohort study, approved by the Regional Ethical Review Board (ref. 2018/400, Uppsala, Sweden), was conducted in line with the Declaration of Helsinki and STROBE guidelines. All adult patients (≥18 years) undergoing surgery for rectal cancer between 1 January 2007 and 22 September 2016 were identified from the Swedish Colorectal Cancer Registry (SCRCR), a prospectively recorded national registry with a coverage of 99.5% for all cases of colorectal cancer in Sweden [18]. It monitors surgical and oncological colorectal cancer treatment. The following patient demographic and outcome variables were extracted from the SCRCR: age, sex, American Society of Anesthesiologists (ASA) classification, cancer stage, type of surgical resection, surgical technique (open versus laparoscopic), neoadjuvant and adjuvant therapy, total length of hospital stay, 30-day and 90-day all-cause mortality. The SCRCR does not contain information regarding patient comorbidities. The Charlson Comorbidity Index (CCI) was therefore calculated using data from the National Patient Registry which contains all recorded diagnoses from both primary and secondary care settings. The National Patient Registry is maintained by the Swedish Board of Health and Welfare [19]. Information related to cause-specific mortality was gathered from the Swedish Death Registry, also maintained by the Swedish Board of Health and Welfare. All registries can be linked through unique national registration numbers (i.e. the Swedish 'personnummer') that are individually assigned to all Swedish residents. The primary and secondary outcomes of interest were 90-day all-cause mortality and 90-day cause-specific mortality, respectively.

Statin therapy

Data related to statin therapy were obtained from the national drug registry, which contains details on all medical prescriptions issued by physicians in Sweden. [20] It includes information on drug type, dosage, date of issue and date of collection. Statin users (ACT-code C10AA) were defined as patients with one or more collected prescriptions of a statin within 12 months before the date of surgery. Patients who did not collect their issued statin prescriptions were not regarded as statin users. Patients were subdivided into statin users and nonusers.

Statistical analyses

Descriptive statistical methods were used for the presentation of patient clinical characteristics and outcomes. Results are provided as either means ± standard deviations (SDs) for continuous variables, counts and percentages for categorical variables or medians and quartiles for ordinal variables wherever suitable. Statistical significance between groups was tested using Student's *t*-test for continuous variables or the chi-square test for categorical and ordinal data. Potential confounders were handled by the matching of statin users and nonusers in conformity with propensity scores, in which the following variables were considered: age, sex, ASA classification, CCI, cancer stage, type of rectal resection, surgical technique, neoadjuvant therapy and adjuvant therapy [21]. Statin users were matched with a 1:1 ratio to nonusers according to a caliper width of 0.2. Differences following propensity score matching for categorical and ordinal data were tested using the McNemar test with Bonferroni correction and paired Student's *t*-test for continuous variables. Further analysis, using conditional Poisson regression with a robust error variance, was carried out for the matched cohorts to control for differences in covariates in the model between the groups [22]. A two-tailed *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were conducted using the R statistical programming language, version 3.6.3 (R Core Team, 2020). Propensity score matching was performed with the MatchIt package [23].

RESULTS

During the study period, a total of 11 966 patients underwent surgical resection for rectal cancer in Sweden. Of these, 3019 (25%) were identified as statin users. The prevalence of statin exposure was equivalent to that of the general Swedish population within a similar age range [24]. Table 1 depicts differences in patient characteristics before and after propensity score matching. Statin users were significantly older (71 ± 8 years vs. 67 ± 11 years, $p < 0.001$), more likely to be men (68.4% vs. 57.7%, $p < 0.001$) and to have a worse preoperative health status assessed by the ASA

classification (ASA 3–4 38.2% vs. 17.4%, $p < 0.001$), as well as a higher CCI score when compared with non-users (CCI ≥7 27.5% vs. 15.8%, $p < 0.001$). There were no significant differences regarding the distribution of surgical procedures and techniques performed between the two groups. Furthermore, patients on statin therapy had less advanced disease (Stage 3 cancer seen in 33.6% vs. 34.6%, $p < 0.001$; Stage 4 cancer seen in 7.4% vs. 11.2%, $p < 0.001$) and were less likely to receive neoadjuvant (16.3% vs. 20.8%, $p < 0.001$) and adjuvant (2.4% vs. 5.3%, $p < 0.001$) therapy. Following propensity score matching, a total of 3017 patient pairs were available for comparison, with no statistical differences between the cohorts with regard to the abovementioned patient and clinical characteristics (Table 1).

After propensity matching, hypertension, myocardial infarction, peripheral vascular disease, cerebrovascular disease and diabetes remained significantly more common in the statin user cohort. The prevalence of dementia, liver disease and metastatic cancer (including other than colorectal cancer) was significantly lower in statin users in the matched cohort (Table 2).

Clinical outcomes following surgery are outlined in Tables 3 and 4. Following propensity score matching, statin users displayed statistically lower all-cause mortality rates at both 30 days (0.3% vs. 3.7%, $p < 0.001$)

TABLE 1 Patient demographics before and after propensity score matching

	Before matching			After matching		
Variable	**Statin − (*n* = 8947)**	**Statin + (*n* = 3019)**	***p*-value**	**Statin − (*n* = 3017)**	**Statin + (*n* = 3017)**	***p*-value**
Age (years) ± SD	67 ± 12	71 ± 8	<0.001	71 ± 11	71 ± 8	0.329
Sex						
Male	5164 (57.7%)	2066 (68.4%)	<0.001	2023 (67.1%)	2064 (68.4%)	0.223
Female	3783 (42.3%)	953 (31.6%)		994 (32.9%)	953 (31.6%)	
ASA classification						
1	2290 (25.6%)	143 (4.7%)	<0.001	152 (5.0%)	143 (4.7%)	1
2	4954 (55.4%)	1688 (55.9%)		1725 (57.2%)	1688 (55.9%)	
3	1495 (16.7%)	1093 (36.2%)		1,055 (35.0%)	1093 (36.2%)	
4	64 (0.7%)	60 (2.0%)		50 (1.7%)	58 (1.9%)	
5	144 (1.6%)	35 (1.2%)		35 (1.2%)	35 (1.2%)	
CCI						
≤4	4014 (44.9%)	669 (22.2%)	<0.001	694 (23.0%)	669 (22.2%)	1
5–6	3519 (39.3%)	1519 (50.3%)		1541 (51.1%)	1519 (50.3%)	
≥7	1414 (15.8%)	831 (27.5%)		782 (25.9%)	829 (27.5%)	
Cancer stage						
1	2300 (25.7%)	907 (30.0%)	<0.001	859 (28.5%)	905 (30.0%)	1
2	2546 (28.5%)	875 (29.0%)		902 (29.9%)	875 (29.0%)	
3	3100 (34.6%)	1015 (33.6%)		1041 (34.5%)	1015 (33.6%)	
4	1001 (11.2%)	222 (7.4%)		215 (7.1%)	222 (7.4%)	
Surgical procedure						
Anterior resection	4580 (51.2%)	1513 (50.1%)	0.075	1500 (49.7%)	1511 (50.1%)	1
Abdominoperineal resection	3293 (36.8%)	1096 (36.3%)		1105 (36.6%)	1096 (36.3%)	
Hartmann's operation	1074 (12.0%)	410 (13.6%)		412 (13.7%)	410 (13.6%)	
Surgical technique						
Open surgery	7611 (85.1%)	2521 (83.5%)	0.042	2521 (83.6%)	2519 (83.5%)	0.972
Laparoscopic surgery	1336 (14.9%)	498 (16.5%)		496 (16.4%)	498 (16.5%)	
Neoadjuvant therapy						
Yes	1859 (20.8%)	491 (16.3%)	<0.001	476 (15.8%)	491 (16.3%)	0.623
No	7088 (79.2%)	2,528 (83.7%)		2541 (84.2%)	2526 (83.7%)	
Adjuvant therapy						
Yes	473 (5.3%)	72 (2.4%)	<0.001	70 (2.3%)	72 (2.4%)	0.928
No	8474 (94.7%)	2947 (97.6%)		2947 (97.7%)	2945 (97.6%)	

Abbreviations: ASA, American Society of Anesthesiologists; CCI, Charlson Comorbidity Index.

TABLE 2 Patient comorbidities before and after propensity score matching

	Before matching			After matching		
Variable	Statin − (*n* = 8947)	Statin + (*n* = 3019)	*p*-value	Statin − (*n* = 3017)	Statin + (*n* = 3017)	*p*-value
Hypertension	1662 (18.6%)	1371 (45.4%)	<0.001	819 (27.1%)	1370 (45.4%)	<0.001
Arrhythmia	710 (7.9%)	441 (14.6%)	<0.001	414 (13.7%)	440 (14.6%)	0.336
Myocardial infarction	157 (1.8%)	483 (16.0%)	<0.001	109 (3.6%)	482 (16.0%)	<0.001
Congestive heart failure	263 (2.9%)	216 (7.2%)	<0.001	203 (6.7%)	215 (7.1%)	0.561
Peripheral vascular disease	142 (1.6%)	201 (6.7%)	<0.001	104 (3.4%)	201 (6.7%)	<0.001
Cerebrovascular disease	310 (3.5%)	364 (12.1%)	<0.001	198 (6.6%)	364 (12.1%)	<0.001
Dementia	92 (1.0%)	30 (1.0%)	0.95	63 (2.1%)	30 (1.0%)	0.001
COPD	389 (4.3%)	200 (6.6%)	<0.001	213 (7.1%)	199 (6.6%)	0.508
Rheumatic disease	145 (1.6%)	67 (2.2%)	0.038	75 (2.5%)	67 (2.2%)	0.545
Peptic ulcer	134 (1.5%)	63 (2.1%)	0.034	83 (2.8%)	63 (2.1%)	0.113
Liver disease	71 (0.8%)	14 (0.5%)	0.082	41 (1.4%)	14 (0.5%)	<0.001
Diabetes	460 (5.1%)	727 (24.1%)	<0.001	308 (10.2%)	726 (24.1%)	<0.001
Paraplegia	41 (0.5%)	38 (1.3%)	<0.001	35 (1.2%)	38 (1.3%)	0.81
Renal disease	95 (1.1%)	74 (2.5%)	<0.001	73 (2.4%)	73 (2.4%)	1
Metastatic carcinoma	803 (9.0%)	187 (6.2%)	<0.001	296 (9.8%)	187 (6.2%)	<0.001

Abbreviation: COPD, chronic obstructive pulmonary disease.

and 90 days (0.7% vs. 5.5%, $p < 0.001$) (Table 3). In the matched groups, statin users also demonstrated significantly lower incidences of cause-specific mortality due to cardiovascular (0.3% vs. 1.7%, $p < 0.001$) and respiratory events (0.0% vs. 0.9%, $p < 0.001$), as well as sepsis (0.0% vs. 0.4%, $p = 0.001$) and multiorgan failure (0.3% vs. 2.1%, $p < 0.001$). No difference was seen in deaths due to cerebrovascular events (Table 4). Further, the protective effects of statin on 90-day mortality remained significant with analysis by conditional Poisson regression model adjusting for all covariates in the matched cohort (adjusted incidence rate ratio 0.08, 95% CI 0.03–0.24, $p < 0.001$) (Table S1).

DISCUSSION

In this retrospectively analysed cohort of over 3000 matched patients undergoing abdominal resection for rectal cancer, statin use was significantly associated with a lower risk of 90-day all-cause mortality. Additionally, subgroup analysis of cause of death showed that nonusers were at higher risk of mortality from cardiovascular events, respiratory complications, sepsis and multi-organ failure.

Several extensive retrospective studies have demonstrated that statins decrease postoperative mortality in noncardiovascular surgery. However, these studies include a wide variety of surgical procedures, and studies focusing on just rectal cancer surgery are lacking [25,26]. The impact of statin therapy on early postoperative mortality following rectal cancer surgery has not previously been reported. To date only one study exists, conducted by Disbrow and colleagues, in which a subgroup analysis of rectal resections was carried out [12]. Their study compares 485 propensity score-matched patients who underwent surgery for rectal cancer, but their results failed to detect any statistical difference in 30-day postoperative mortality between statin users and nonusers, although a trend for better survival was noticed in the statin cohort (0.21% vs. 1.44%, $p = 0.076$). Furthermore, the same study reported postoperative

TABLE 3 Clinical outcomes before and after propensity score matching

	Before matching			After matching		
Variable	Statin − (*n* = 8947)	Statin + (*n* = 3019)	*p*-value	Statin − (*n* = 3017)	Statin + (*n* = 3017)	*p*-value
LOS						
Median (IQR)	9.0 (7.0–15.0)	10.0 (7.0–15.0)	0.002	10.0 (7.0–15.0)	10.0 (7.0–15.0)	0.064
Missing	73 (0.8%)	26 (0.9%)		27 (0.9%)	26 (0.9%)	
30-day mortality[a]	182 (2.0%)	8 (0.3%)	<0.001	112 (3.7%)	8 (0.3%)	<0.001
90-day mortality[a]	291 (3.3%)	20 (0.7%)	<0.001	166 (5.5%)	20 (0.7%)	<0.001

Abbreviations: IQR, interquartile range, LOS, length of stay.

[a]All-cause mortality.

TABLE 4 Ninety-day cause-specific mortality before and after propensity score matching

Variable	Before matching			After matching		
	Statin − (*n* = 8947)	Statin + (*n* = 3019)	*p*-value	Statin − (*n* = 3017)	Statin + (n = 3017)	*p*-value
Cardiovascular event	90 (1.0%)	8 (0.3%)	<0.001	50 (1.7%)	8 (0.3%)	<0.001
Respiratory event	41 (0.5%)	1 (0.0%)	<0.001	27 (0.9%)	1 (0.0%)	<0.001
Cerebrovascular insult	8 (0.1%)	2 (0.1%)	1	5 (0.2%)	2 (0.1%)	0.45
Sepsis	24 (0.3%)	0 (0.0%)	0.001	12 (0.4%)	0 (0.0%)	0.001
Multiorgan failure	109 (1.2%)	8 (0.3%)	<0.001	62 (2.1%)	8 (0.3%)	<0.001

advantages of reduced incidence of postoperative sepsis (2.89% vs. 6.60%, *P* = 0.01) and anastomotic failure (1.29% vs. 4.13%, *P* = 0.014) in patients on statin therapy. While complication rates were not analysed in our study, deaths due to sepsis were significantly lower in patients on statin therapy.

A Danish nationwide observational study by Fransgaard et al. investigating the relationship between preoperative statin use and postoperative outcomes after colorectal surgery did not find any risk reduction in 30-day postoperative mortality (hazard ratio 0.91, 95% CI 0.80–1.04, *p* = 0.16) [16]. However, the interpretation of their results is difficult since both colon and rectal resections were included, as well as elective and emergent procedures, without any subgroup analyses. The authors of the present study strongly believe that elective and emergency resections should be assessed separately since emergency cases frequently present with worse morbidity and carry much higher early mortality and less favourable oncological outcomes [27–29]. A similar large Danish registry-based study by Bisgård et al. showed no difference between groups in their univariate analysis of 30-day postoperative mortality [15]. Again, their study did not differ between colon and rectal cancers when comparing mortality rates. In contrast to the above-outlined studies, the current study design exclusively involved rectal cancer resections, which differ from colon cancer resections with regard to anatomy, the complexity of the surgical procedure and differences in associated neoadjuvant and adjuvant treatment modalities; in addition, rectal cancer resection is almost always an elective procedure. Therefore, patients undergoing rectal cancer surgery are more susceptible to adverse postoperative outcomes [15,30].

Several explanations for the observed beneficial effects of statin therapy present themselves. Statins have been shown to possess pleiotropic characteristics by which they can improve endothelial function, maintain plaque stability, prevent antithrombotic events and modulate inflammatory responses. These effects are believed to be mediated through inhibition of the conversion of HMG-CoA to mevalonate, which hampers the downstream synthesis of isoprenoids [31]. Endothelial and immunomodulatory effects are most likely to be of the greatest importance against the surgical stress response as such properties provide both cardiovascular and anti-inflammatory protection. The anti-inflammatory properties of statin therapy are manifested as lower postoperative bloodstream levels of proinflammatory cytokines. In a prospective randomized trial by Singh and colleagues, perioperative simvastatin therapy was evaluated in the context of colorectal surgery [17]. Although no significant differences in mortality were detected, lower plasma concentrations of interleukins 6 and 8 and tumour necrosis factor α were measured in patients receiving simvastatin. Other investigations have shown a clear association between the reduction of postoperative proinflammatory cytokines and improved patient outcomes after rectal resection [9,10]. Some of these mechanisms might explain our findings that the incidence of inflammatory-mediated specific causes of death, such as sepsis, multiorgan and respiratory failure, was significantly lower in the statin-user cohort.

Moreover, statin users displayed decreased deaths of cardiovascular origin despite having more cardiovascular comorbidities. This may be explained by the proposed reparative effects of statins on endothelial cells. There is a body of evidence in the literature to support this claim [4].

Statins have also been proposed to exhibit anticancer effects by inhibiting cell proliferation and tumour growth [32]. Meta-analyses have reported that statin use both before and after cancer diagnosis is associated with lower rates of all-cause and cancer-specific mortality in patients with colorectal cancer [33,34]. This observation strengthens the theory of a longitudinal antineoplastic effect provided by statins. In the present study, a lower prevalence of advanced stage cancer was observed in patients with ongoing statin therapy at the time of surgery. While no conclusions may be drawn, we suggest that this could be the result of a possible effect of statin therapy on rectal carcinoma proliferation. Previous studies have also suggested that statin users show complete response to neoadjuvant chemoradiation compared with nonusers, which further justifies the use of this drug as part of the overall optimization process of patients with rectal cancer who are planned for surgery [35,36]. At this point, however, there is insufficient evidence to implement statin treatment for all patients diagnosed with rectal cancer.

This study possesses several limitations. Firstly, despite the use of propensity score matching to generate similar baseline patient demographics between groups, with additional regression analyses to control for covariates in the model, there is a risk of residual confounding, as with all retrospective studies. Secondly, the inability to adjust for preadmission and in-hospital administration of statin therapy makes it difficult to distinguish whether beneficial results are due to pre- or postoperative use. Thirdly, the

pharmacological features of various types of statins might differ and have not been adjusted for in this study. However, differences in pleiotropic effects based on drug type have not been reported [37]. Finally, the authors recognize that many patients who are prescribed statins may have cardiovascular diseases that require medical treatment other than statins. Therefore, there may be other important drugs that have not been controlled for which may contribute to the observed protective effect of statins. Future studies may benefit from exploring the role of several cardiovascular drugs and whether any differences are seen in the context of rectal cancer surgery. The strengths of this study are based on the nationwide population-based design that minimizes selection bias since virtually all adult patients who underwent rectal cancer surgery in Sweden during the study period were included. Data were provided from a prospectively collected registry containing over 99.5% of all cases of rectal cancer surgery, as well as the use of the Swedish Board of Health and Welfare's national registries that have a 100% coverage rate concerning drug prescriptions. Additionally, this study only covers cases of surgical resection for rectal cancer from a nation with universal health care, offering a patient group that has, to a larger extent, undergone a standardized surgical treatment with a fairly extensive preoperative work-up to allow for preoperative optimization.

CONCLUSION

This cohort study shows a strong association between statin therapy and reduced postoperative mortality following surgical resection for rectal cancer. Prospectively controlled trials are warranted to determine whether a causal relationship exists.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare and have received no financial benefit in the execution of this study.

ETHICS APPROVAL

Ethical approval was obtained from the Regional Ethical Review Board (Ref. 2018/400, Uppsala, Sweden). The study was conducted in line with the Declaration of Helsinki and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines

AUTHOR CONTRIBUTIONS

Study design: SM, AP, RA, PM.
Data collection: SM, RA, GS, PM.
Analysis and interpretation of data: SM, AP, GS, YC, MPF.
Article draft: SM, AP, RA, GAB, PM.
All authors have critically revised and accepted the submitted article.

DATA AVAILABILITY STATEMENT

The data are available upon reasonable request from the editorial board.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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