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ORIGINAL ARTICLE

Statins and metachronous recurrence after endoscopic resection of early gastric cancer: a nationwide Korean cohort study

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Abstract

Background Statins have shown to reduce the risk of various cancers. However, their effects on metachronous recurrence (MR) after endoscopic resection (ER) for early gastric cancer (EGC) are unknown. We evaluate their effects on MR development after ER for EGC.

Methods We selected 11,568 patients who received ER for EGC from 2002 to 2011 from the Korean National Health Insurance database and classified into 2 groups: control and statins using propensity score matching. Metachronous recurrence was defined as the second ER or gastrectomy performed 6 months after the first ER.

Results Mean follow-up period was 8.8 ± 3.1 years. Statins showed a significantly lower incidence of MR than the control group (12.5% vs 2.2%, respectively, $P < 0.01$). After conducting competing risk analyses and time-dependent cox regression analysis considering immortal time bias, statins still showed a lower incidence rate of MR compared to that observed in the control group. For the multivariate analysis, statins remained significant (HR 0.17; 95% CI 0.13–0.24, $P < 0.01$). In the dose–response analysis, an inverse dose–response relationship was identified between MR and statins ($P < 0.01$).

Conclusion Statins was significantly associated with a reduced risk of MR after ER for EGC with an inverse dose–response relationship.

Keywords Medication · Recurrence · Stomach neoplasm · Endoscopic treatment

Abbreviations

ADDD	Average DDD
BMI	Body mass index
CI	Confidence intervals
DDD	Defined daily dose
EGC	Early gastric cancer
EMR	Endoscopic mucosal resection
ER	Endoscopic resection
ESD	Endoscopic submucosal dissection
H. pylori	*Helicobacter pylori*
HR	Hazard ratio
ICD-10	International classification of disease 10th revision
KCCR	Korean Central Cancer Registry
NHIS	National Health Insurance Service
MR	Metachronous recurrence
OR	Odds ratio
PSM	Propensity score-matching
SD	Standard deviation

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Introduction

Endoscopic resection (ER), including endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR), are widely used treatments for gastrointestinal

neoplasia. ER is safe, less invasive, and effective for early gastric cancer (EGC); however, the risk of metachronous recurrence (MR) is higher in patients who undergo ER than in those who undergo surgery [1–4]. The 5-year MR rate after ER for EGC varies from 3.6 to 16% [2, 3, 5–8], and known risk factors are old age, cigarette smoking, male sex, multiple initial EGCs, mucosal atrophy, intestinal metaplasia, and failure of *Helicobacter pylori* (*H. pylori*) eradication [5, 6, 9–11].

Recently, Statins have attracted widespread attention for their potential anti-cancer and/or anti-inflammatory effects in cancers, such as renal, colon, lung, skin, prostate, non-Hodgkin's lymphoma, and hepatocellular carcinoma [12–14]. Statins, in particular, have shown to reduce gastric cancer risk [15–18].

However, to the best of our knowledge, no studies have investigated statins' protective effects on MR after ER for EGC.

The aim of this retrospective, population-based cohort study is to clarify the potential protective effects of statins on the incidence of MR after ER for EGC using information from the Korean National Health Insurance Service (NHIS) database.

Materials and methods

Data sources

The NHIS is a mandatory universal health insurance system and the only one available in Korea; it has provided comprehensive medical care to more than 98% of all Korean citizens since 1999 [19, 20]. The NHIS database contains information on Qualification, Claim, Health check-up, and death; therefore, the NHIS database can be used to conduct population-based, nationwide studies for various diseases [21]. Moreover, the Korean Central Cancer Registry (KCCR), which is a part of the NHIS database and used in this study, is very accurate and the completeness of cancer incidence data was estimated to be 97.8% [22]. This registry is regularly managed and verified by multiple national government agencies such as the Ministry of Health and Welfare, Ministry of Strategy and Finance, and Statistics Korea, because the registered patients receive benefits to only pay 5% of the total medical expenses for 5 years after cancer registration [23].

The detailed information on the NHIS database and list of publications using this database could be obtained from the NHIS website [21].

We evaluated general health check-up, lifetime transition period health check-up, and cancer check-up from the Health check-up database. All examinees were requested to have biannual health check-ups. The proportion of complete health check-ups was 68% in 2013. By evaluating all aspects in the Health Checkup database and combining them with the claims database, the lack of laboratory and personal history data can be overcome. Furthermore, long-term follow-up of a single individual will allow us to perform longitudinal studies of casual relationships [24]. This study was approved by the Institutional Review Board of the Seoul National University Hospital and Yonsei University College of Medicine (Institutional Review Board No. E-1704-046-844). Informed consent was waived, because the study was based on routinely collected administrative data, and patient data were kept anonymous.

Study design

This population-based observational cohort study aimed to investigate the effect of statins on MR of gastric intraepithelial neoplasm after ER of EGC. The NHIS database from January 2002 to October 2016 was reviewed for outcome analysis and the database from January 2002 to December 2011 was used to identify the study cohort to secure a minimum follow-up duration of 5 years. ICD-10 was used to identify gastric cancer (C16.00–C16.99), gastric benign neoplasm (D13.1), diabetes (E10–14), and hyperlipidemia (E78.0–78.5) [25, 26]. We used procedural codes for ESD (ZQ933, ZX704), EMR (Q7652, QX701), and gastrectomy (Q0251–Q0259, Q2594, Q2598, QA536, Q2533–2537). Patients who previously underwent gastrectomy or ER and those who underwent ER for gastric adenoma were excluded. Overall, 12,589 patients had claimed payments for a first ER for EGC from January 2002 to December 2011. Among them, 132 were excluded due to inaccurate information ($n=37$) and claimed payments for both ER and gastrectomy from the same account ($n=95$). In addition, 889 patients were excluded for synchronous recurrence or incomplete resection, because ER or gastrectomy was claimed within 6 months from the first ER for EGC. In total, 11,568 patients were included in the final cohort (Fig. 1).

Statins exposure

The Statin groups included patients who had claimed payments for statins, respectively, after the first ER, and the control group included patients who had never claimed payments for statins after first ER. Korean drug codes were used to classify statins (atorvastatin, rosuvastatin, simvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, and pravastatin).

Defined daily dose (DDD) and average defined daily dose (ADDD)

To examine the dose–effect relationship between drug use and MR, we used DDD and ADDD. DDD is a unit for

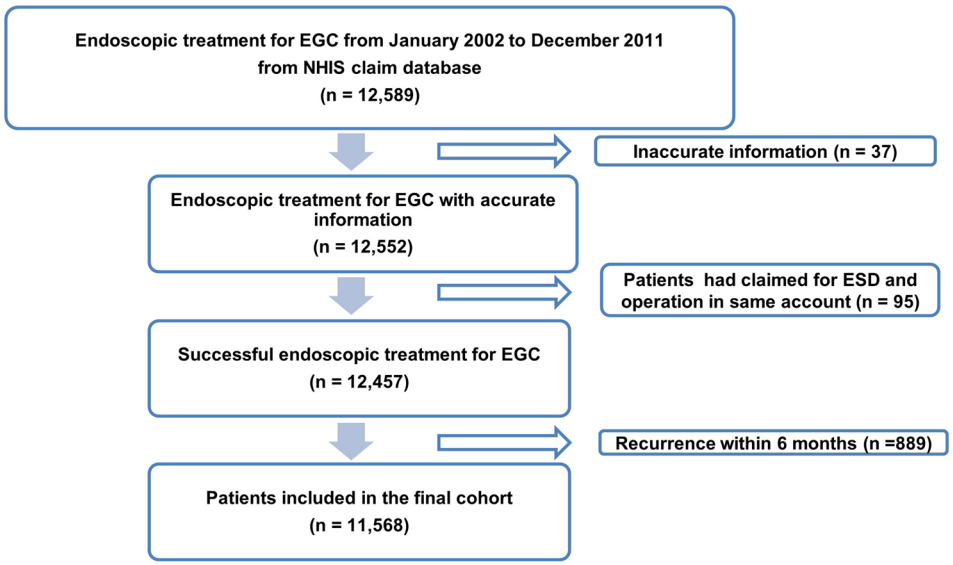

Fig. 1 Enrolment of patients. Overall, 12,589 patients had claimed payments for a first ER for EGC from January 2002 to December 2011. After exclusion, in total, 11,568 patients were included in the final cohort. *EGC* early gastric cancer, *NHIS* National Health Insurance Service, *ESD* endoscopic submucosal dissection

measuring a prescribed amount of drug. According to the World Health Organization, it is defined as "the assumed average maintenance dose per day of a drug consumed for its main indication in adults" [27]. For example, 1 DDD is equivalent to a single dose of 30 mg simvastatin or 20 mg atorvastatin. Cumulative DDD is the total number of drug pills times dose per tablet divided by DDD, and ADDD is cumulative DDD divided by follow-up time.

Covariates

The covariates that could plausibly confound associations between statin use and MR are as follows: age at diagnosis, sex, body mass index (BMI) at the time closest to and preceding diagnosis, smoking status, diabetes mellitus, and dyslipidemia, and dosage of statin. In the present study, the effect of *H. pylori* could not be analyzed, because the NHIS database only contains claims on drugs and laboratory prescriptions. Therefore, we were unable to study to results of *H. pylori* eradication.

Outcome measures

Outcome measurement was defined as the incidence of MR of gastric intraepithelial neoplasms. MR was defined as claims for ER or gastrectomy > 6 months after the first ER for EGC. We excluded patients who underwent ER or gastrectomy for gastric polyps, gastric subepithelial tumors, and peptic ulcer perforation, and only included those patients who had the disease code of gastric cancer or gastric adenoma registered at the time of the second claim.

Statistical analysis

Descriptive analyses were performed to delineate the characteristics of control and statin groups using the *t* test and Chi-square test. To compare the risk of MR with a matched population, we conducted propensity score matching (PSM) (control vs statin). A propensity score was calculated for each patient using a logistic regression model. The PSM model consisted of age, sex, BMI, diabetes, and follow-up duration; the nearest neighbor matching with the propensity score of each patient was used for 1:1 matching.

To adjust for death, which is a potential competing risk, we performed competing risk analysis using a semiparametric proportional hazard model for cumulative incidence of recurrence [28].

To avoid immortal time bias, we performed time-dependent cox regression analysis, which considered person-time before first statin prescription as unexposed [29]. Furthermore, sensitivity analysis conducted which assess statin exposure for the first 6 months as non-exposure to deal with the possibility that the effect of statin was overestimated.

In addition, Cox proportional hazard models with Efron's method were used to calculate the hazard ratio (HR) of MR. Adjusted HR and 95% confidence intervals (CI) in the multivariable Cox regression were calculated with adjustments for age, sex, BMI, and smoking. All statistical analyses were performed using the SAS version 9.2 software (SAS Institute, Inc., Cary, NC, USA) and the R Project for Statistical Computing (version 3.3.1; R Foundation for Statistical Computing, Vienna, Austria). A P value of < 0.05 was considered to be statistically significant.

Results

Clinical characteristics after PSM analysis

All included patients ($n = 11{,}568$) were divided into 2 groups based on drug use as control ($n = 2319$) and stain ($n = 2319$), after conducting propensity matching. Patients' baseline characteristics are presented in Table 1. The mean age was 63.0 years [standard deviation (SD), 9.9 years] and mean BMI was 24.1 kg/m^2 (SD, 2.9 kg/m^2). The mean follow-up duration was 8.8 years (SD, 3.1 years). Overall, patients were more likely to be non-smoking men. The MR rate was 7.3%, and it was lower in statin group than in the control group (12.5% vs 2.2%, respectively, $P < 0.01$).

Statin exposure and MR after ER of EGC

The log-rank test also confirmed the difference in cumulative MR between the two groups (12.5% vs. 2.2%, $P < 0.01$); after competing risk analyses according to the methods described above, we observed that statin group still showed a lower incidence rate of MR compared to that observed in the control group ($P < 0.01$). In the time-dependent cox regression analysis considering immortal time bias and additional analysis except for the initial 6 months statin exposure effect, statin group still showed a lower incidence rate of MR compared to that observed in the control group ($P < 0.01$) (Fig. 2).

Factors associated with MR

In PSM (control vs statin), age and BMI were associated with a high MR rate (HR 1.02; 95% CI 1.01–1.03; $P < 0.01$, HR 1.04; 95% CI 1.00–1.08; $P = 0.03$), and female sex and statin use were associated with a low MR rate (HR 0.73; 95% CI 0.57–0.95; $P = 0.021$, HR 0.17; 95% CI 0.13–0.24; $P < 0.01$) (Table 2).

Table 1 Baseline characteristics of patients after propensity score matching (1:1 matching)

	n	Total ($n = 4638$)	Control ($n = 2319$)	Statin ($n = 2319$)	*P*
Age, years	4638	63.0 ± 9.9	62.9 ± 10.4	63.0 ± 9.4	0.784
Sex	4638				0.172
Female		1569 (33.8%)	762 (32.9%)	807 (34.8%)	
Male		3069 (66.2%)	1557 (67.1%)	1512 (65.2%)	
BMI, Kg/m^2	4638	24.1 ± 2.9	24.1 ± 2.9	24.2 ± 2.9	0.563
Smoking	4563				0.073
Current		868 (19.0%)	404 (17.7%)	464 (20.3%)	
Former		806 (17.7%)	413 (18.1%)	393 (17.2%)	
Never		2889 (63.3%)	1465 (64.2%)	1424 (62.4%)	
DM	4638				0.698
No		4529 (97.6%)	2262 (97.5%)	2267 (97.8%)	
Yes		109 (2.4%)	57 (2.5%)	52 (2.2%)	
Hyperlipidemia	4638				< 0.01
No		2244 (96.9%)	2244 (96.8%)	0 (0.0%)	
Yes		2394 (51.6%)	75 (3.2%)	2319 (100%)	
Creatinine, mg/daysL	1587	1.0 ± 0.9	1.0 ± 0.7	1.1 ± 1.1	0.017
Follow-up, years	4638	8.8 ± 3.1	8.8 ± 3.2	8.8 ± 3.0	0.773
recur	4638				< 0.01
No		4298 (92.7%)	2030 (87.5%)	2268 (97.8%)	
Yes		340 (7.3%)	289 (12.5%)	51 (2.2%)	
Recurrence type	340				0.066
Adenoma		106 (31.2%)	84 (29.1%)	22 (43.1%)	
Cancer		234 (68.8%)	205 (70.9%)	29 (56.9%)	
Alive	4638				< 0.01
No		549 (11.8%)	344 (14.8%)	205 (8.8%)	
Yes		4089 (88.2%)	1975 (85.2%)	2114 (91.2%)	

BMI body mass index, *DM* diabetes mellitus

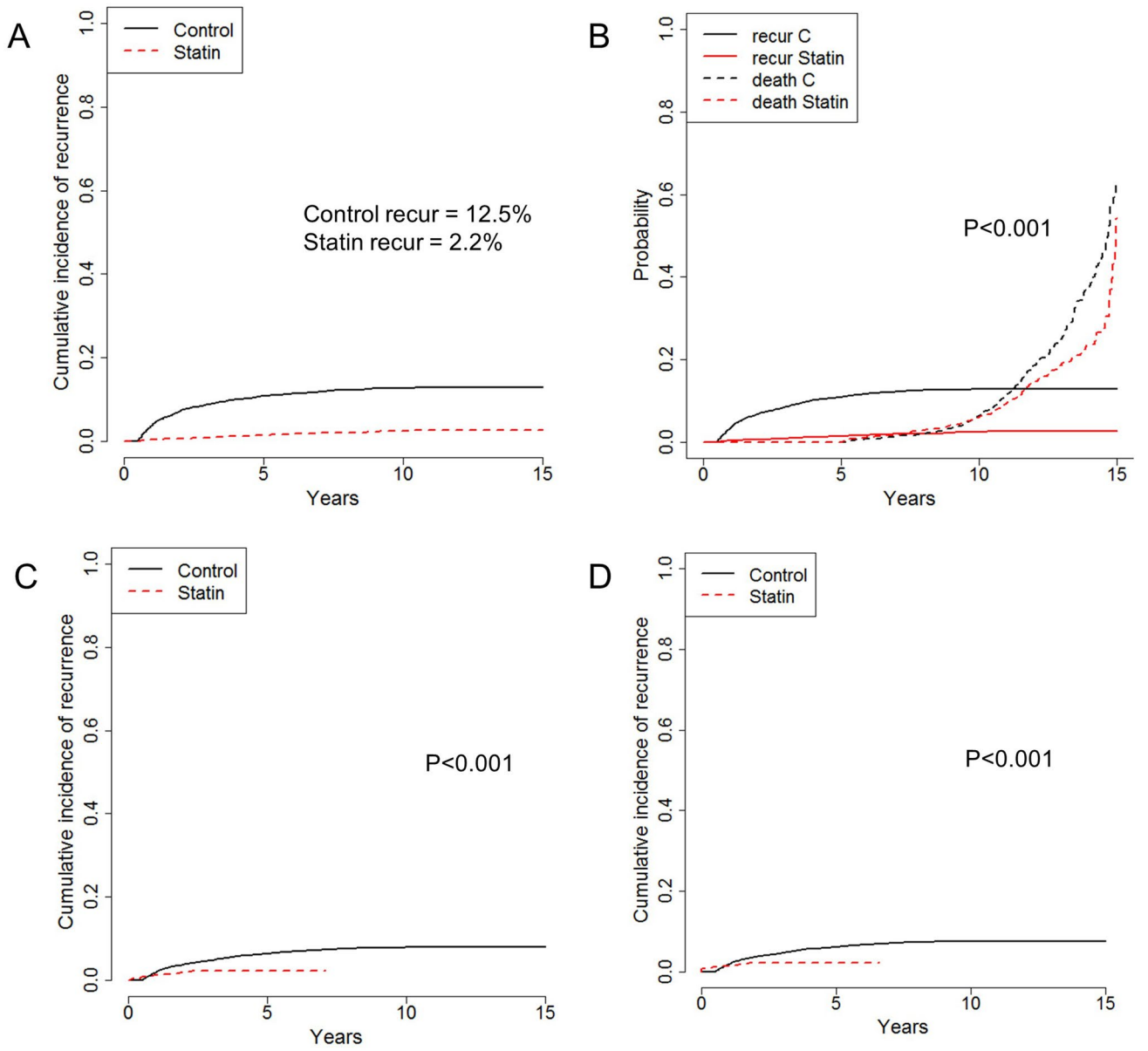

Fig. 2 Cumulative MR according to study group**.** The log-rank test (**a**), competing risk analysis (**b**), time-dependent cox regression analysis considering immortal time bias (**c**), and sensitivity analysis except for the initial 6 months statin exposure effect (**d**). In the all analysis, statin group showed a lower incidence rate of MR compared to that observed in the control group ($P < 0.01$)

Dose–response relationship

In the dose–response analysis using ADDD, a significant inverse dose–response relationship was observed between MR rate and statin use ($P < 0.01$) (Table 3).

Discussion

This population-based, nationwide, retrospective cohort study using the NHIS database demonstrated that statin was associated with a reduced incidence of MR in patients

Table 2 Relative risk of MR after endoscopic treatment for EGC

	Control vs statin					
	Unadjusted			Adjusted		
	HR	95% CI	*P*	HR	95% CI	*P*
Sex						
Male	1.00			1.00		
Female	0.81	0.64–1.02	0.072	0.73	0.57–0.95	0.021
Age	1.02	1.01–1.03	0.01	1.02	1.01–1.03	< 0.01
BMI	1.03	0.99–1.07	0.099	1.04	1.00–1.08	0.03
Smoking						
Current	1.00			1.00		
Former	0.92	0.63–1.32	0.639	0.84	0.58–1.21	0.351
Never	1.02	0.77–1.34	0.913	1.05	0.77–1.42	0.753
Statin use	0.17	0.13–0.23	< 0.01	0.17	0.13–0.24	< 0.01

BMI body mass index

[a]Covariates are sex, age, BMI, and smoking

Table 3 Average defined daily dose of statin and metformin and the risk for recurrence

	Matched cohort ($n = 4644$)	
	Statin HR (95% CI)	*P*
Statin		
Control	1.00	
$0 < ADDD \leq 0.05$	0.27 (0.20–0.38)	< 0.01
$0.05 < ADDD \leq 0.1$	0.05 (0.03–0.11)	< 0.01

ADDD average DDD = cumulative DDD/follow-up time, *cumulative DDD* total number of drug pills × dose per tablet/defined daily dose, *DDD* defined daily dose, *HR* hazard ratio

All HRs were adjusted for age, sex, BMI, and smoking

who underwent ER for EGC. Furthermore, significant inverse dose–response relationships were observed in statin-using groups.

Previously, several studies have demonstrated the protective effects of statins on gastric cancer.

Chiu et al. performed a population-based case–control study, which revealed that ever-use of any statins was associated with a significant decrease in the risk of gastric cancer (OR = 0.68, 95% CI = 0.49–0.95) [16]. In addition, meta-analysis of studies revealed that statins use and gastric cancer risk were dose-dependent in Asian and western populations [17]. Lee et al. [15] used an exact-matching case–control design and showed that statins use is inversely associated with gastric cancer risk (OR = 0.18; 95% CI = 0.14–0.24; $P < 0.0001$).

Experimental studies have demonstrated that the protective effects of statins in these studies are related to the principle of promoting apoptosis and inhibiting proliferation of gastric cancer cells [30, 31].

As stated above, most previous studies have focused on the risk of gastric cancer in patients using statins. To the best of our knowledge, ours is the only observational study that demonstrates the efficacy of statins on MR after ER for EGC. This study is a large cohort study involving more patients than previously reported, with a median follow-up period of 8.8 years (SD 3.1 years), which allowed meaningful recurrence analysis. Using the Prospective Prescription Record of NHIS, the recall bias was reduced compared to that with self-reported medication use and the measurement error with drug exposure was minimized compared to that with single- or multi-center studies.

In addition, propensity score matching was performed to minimize the difference between the groups, and to adjust for death, which is a potential competing risk, a competing risk analysis using a semiparametric proportional hazards model for cumulative incidence of the recurrence was performed [28]. In addition, we tried to avoid immortal time bias and the possibility that the effect of statin was overestimated, which may exaggerate associations[29]. Furthermore, we used time-varying nature of drug exposures (ADDD) for the sensitivity analyses of dose–response associations between statin and MR.

This study has some limitations. The risk factors for MR after endoscopic treatment for EGC are known as age, male sex, cigarette smoking, multiple initial EGCs, mucosal atrophy, intestinal metaplasia, and failure of *H. pylori* eradication [5, 6, 9–11]. Our data also demonstrated that age, male sex, and high BMI increase MR after the first ER for EGC. However, the effect of risk factors, such as *H. pylori* infection, and endoscopic findings, such as multiple initial EGCs, mucosal atrophy, and intestinal metaplasia, which

are not available in the NHIS claim database, could not be analyzed. As in the previous study [32], the results of *H. pylori* eradication were not indicated on the NHIS claims, which is a limitation. However, we found no statistically significant difference in the prescription rate of *H. pylori* eradication among groups in this study. Therefore, it can be assumed that the infection rate among the group is not significantly different.

In addition, coding errors are possible in this kind of huge nationwide database. However, there have been several sophisticated studies using the NHIS database with the same coding method as this study [25, 32] and the KCCR is highly accurate. In addition, endoscopic procedures and prescriptions for medicines are also paid after the screening of a health insurance review and an assessment service based on data requested by medical institutions, so that coding errors are expected to be low [8]. The diagnosis of MR was based on the insurance database that indicated ER or gastrectomy recurrence > 6 months after the first ER for EGC. The diagnosis and stage of recurrent disease was not clear. In addition, there might be some patients who did not receive additional treatment for MR due to several reasons (e.g., far advanced staged and poor general conditions); therefore, it is possible that the MR rate might be slightly underestimated. However, the rate of extragastric recurrence after ESD for EGC is very low and ER is a minimally invasive procedure, which allows for conscious sedation. Therefore, the effect of the patient's condition on the results is considered minimal. In addition, patients within the statin groups could have poorer health conditions that require more frequent clinic visits and may be more likely to undergo tests or procedures. It is, therefore, possible that these patients were diagnosed with an early disease stage and lower risk of recurrence, compared to patients with no other comorbidities who may have presented at a later stage with a greater risk of recurrence.

Since our study is based on a nationwide cohort that utilized a code database, it is difficult to distinguish between local recurrence and MR which is another limitation. However, we considered that local recurrence of 1–2% did not significantly affect our findings [1, 3, 4, 8]. Although we could not accurately determine the interval and frequency of follow-up endoscopy, in most hospitals, follow-up endoscopy and abdomen/pelvic computed tomography after ESD for EGC were performed 1–2 times a year for 5 years and an annual follow-up endoscopy was recommended after 5 years.

Although prior statins use before the first ER may have affected the results, the focus of our study was the statins effect had on MR after first ER; therefore, we only included the amount of statins after the first ER. To observe the effects of statins prior to the first ER, it is necessary to have an accurate starting point indicating when the medicine was initiated, but the NHIS claim database did not provide such information. Since the NHIS indicated the number of filled prescriptions, such data might not reflect the actual dose taken by the patients. We presumed that all medications were taken by the patients as prescribed, which could overestimate the actual ingested dosage. However, statins can only be obtained with a prescription in Korea, so the difference between the actual dose and the prescription dose will not be substantial, compared to over-the-counter drugs.

Finally, Koreans have a higher rate of gastric cancer than Westerners; thus, the applicability of our findings to the Western population is limited.

Despite these limitations, our results are remarkable, because we used statins in a large population using the NHIS claim database, to study the risk of metachronous gastric cancer after endoscopic treatment with EGC.

In conclusion, this study shows that statins may be independent chemopreventive agents, with dose–response effects in reducing MR of gastric intraepithelial neoplasm after ER of EGC. To confirm the antitumor effects of statins, it is necessary to investigate the efficacy, minimum effective dose, starting time, proper period of use, side effects, and response in cancer patients without hyperlipidemia by conducting a prospective randomized-controlled trial.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no association with or financial interest in any commercial company relevant to this study.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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