DIABETES MELLITUS INCREASES RISK OF GASTRIC CANCER AFTER *HELICOBACTER PYLORI* ERADICATION: A TERRITORY-WIDE STUDY WITH PROPENSITY SCORE ANALYSIS

Ka Shing Cheung, MBBS, MPH;[1] Esther W Chan, PhD;[2] Lijia Chen, B. Med, MPH;[1] Wai Kay Seto, MD;[1] Ian CK Wong, PhD;[2,3] Wai K Leung, MD[1]

[1]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

[2]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong

[3]UCL School of Pharmacy, University College London, London, United Kingdom

Correspondence to:

Wai K. Leung, Department of Medicine, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong

Email: waikleung@hku.hk

Fax: +852 2816 2863

Phone: + 852 2255 3348

Guarantor of the article: Prof. Wai K Leung

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of manuscript; and approval of the final version of the manuscript. Dr. Esther W Chan, and Ms. Lijia Chen were involved with acquisition of data; critical revision of the manuscript for important intellectual content; and approval of the final version of the manuscript. Professors Ian CK Wong and Wai K Leung were involved with the study concept and design; analysis and interpretation of data; drafting of manuscript; critical revision of the manuscript for important intellectual content; study supervision; and approval of the final version of the manuscript.

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ABSTRACT

Background: Whether diabetes mellitus (DM) increases gastric cancer (GC) risk remains controversial due to inadequate adjustment for important risk factors, including *Helicobacter pylori* (HP) status, concomitant medication usage and cancer site. We aimed to investigate whether type II diabetes mellitus (DM) increased GC risk in patients after HP treatment.

Research design and methods: This was a territory-wide cohort study of patients aged ≥45 years who had received clarithromycin-based triple therapy for HP between 2003 and 2012 in Hong Kong. Data were retrieved from the public electronic health database. Observation started from HP therapy to GC diagnosis, death or end of study (December 2015). Exclusion criteria included type I DM, GC diagnosed within first year of HP therapy, prior GC or gastrectomy, and retreatment for HP. The adjusted hazard ratio (aHR) of GC with type II DM was calculated by Cox model with propensity score regression adjustment for 20 covariates (age, sex, comorbidities and medications).

Results: During a median follow-up of 7.1 years (IQR:4.8–9.3), 153 (0.33%) of 46,460 patients developed GC at a median age of 72.4 years. Type II DM was associated with an increased GC risk (aHR:1.73; 95% CI:1.08–2.79). Stratified analysis showed increase in risk for cardia cancer only (aHR:3.40, 95% CI:1.45–7.97) and those with suboptimal DM control (time-weighted average HbA1c ≥6.0% [42mmol/mol]; aHR:1.68, 95% CI:1.07–2.63).

Conclusions: Type II DM was associated with an increased GC risk among HP-eradicated patients, in particular cardia GC and those with suboptimal DM control.

INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer and third leading cause of cancer-related death worldwide.[1] *Helicobacter pylori (H. pylori)* infection is the most important risk factor for GC (at least three-fold increase in risk),[2, 3] by triggering Correa's cascade of multi-stage gastric carcinogenesis.[4] Despite *H. pylori* eradication, GC risk can only be reduced by 38% among asymptomatic individuals in a recent meta-analysis.[5]

In addition to *H. pylori*, diabetes mellitus (DM) has been linked to GC development. Various biological mechanisms have been proposed including stimulation of cell proliferation via hyperinsulinemia and increased insulin-growth factor (IGF) production,[6] promotion of angiogenesis by increasing vascular endothelial growth factor (VEGF) level,[7] DNA damage by direct effect of hyperglycemia[8] and indirect effect from increased production of reactive oxygen species.[9] As yet, data on this association have been conflicting. While a meta-analysis of 17 observational studies showed that diabetes mellitus (DM) increased GC risk by 19%,[10] this association was refuted by another meta-analysis of 15 cohort studies (pooled relative risk:1.10; 95% CI:0.94–1.29).[11]

Failure to stratify for *H. pylori* infection in patients with DM may be an important reason for this disparity. In addition, GC risk was higher among *H. pylori*-infected subjects with higher hemoglobin A1c (HbA1c) levels in a Japanese population-based cohort study. When compared to individuals with HbA1c levels of 5.0–5.9% [31–41mmol/mol], those with HbA1c levels of ≥ 6.0% [42mmol/mol] had more than two-fold increase in GC risk.[12] Furthermore, all existing studies failed to adjust for

concomitant medication usage which may modulate GC risk including aspirin,[13] non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, statins,[14] metformin,[15] and proton pump inhibitors (PPIs).[16, 17] Failure to adjust for potential chemopreventive agents could bias a positive association between DM and GC to null as a higher proportion of patients with DM may require aspirin, statins and metformin. Lastly, GC from cardia and non-cardia regions have different tumor characteristics and risk factors, but so far only two studies reported GC risk according to cancer sites.[18, 19]

With more than 12-14% of adult population having DM worldwide,[20] the potential burden of GC attributable to DM could be substantial. Herein, we conducted a territory-wide cohort study to investigate the association between type II DM and GC among *H. pylori*-infected patients who had received eradication therapy in Hong Kong, after adjusting for major confounding factors.

METHODS

Study design and data source

This was a retrospective cohort study based on the territory-wide electronic healthcare database of Hong Kong, the Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority. The Hospital Authority is the only statutory public healthcare provider in Hong Kong that serves the 7.3 million local population. It covers 87-94% of secondary and tertiary healthcare services. Patient clinical data recorded in CDARS include demographics, diagnoses, drug prescription and dispensing records, investigation results, hospitalization details, outpatient and emergency department visits, and death. Medications are prescribed and dispensed by hospital pharmacy on the same day at a cost of US$2 per item for 16 weeks, and therefore prescription records usually match with dispensing records. A number of high-quality clinical studies have been conducted by utilising this database.[13, 16, 21-23] The International Classification of Diseases, Ninth Revision (ICD-9) was used for diagnosis coding in CDARS, with previous studies demonstrating a high degree of accuracy (positive and negative predictive values of more than 90%).

Patients were de-identified in CDARS by unique reference keys. Ethics approval was obtained from the Institutional Review Board of the University of Hong Kong and the West Cluster of the Hong Kong Hospital Authority (reference no: UW 16-545).

Study Subjects

We identified all *H. pylori*-infected adults (aged ≥45 years), who had received a course of clarithromycin-based triple therapy for *H. pylori* between 1 January 2003 and 31 December 2012. Prescription of clarithromycin-based triple therapy for *H.*

pylori infection was defined by co-prescription of one of the PPIs with clarithromycin and either amoxicillin or metronidazole with the correct doses, same prescription start date and a treatment duration of 7-14 days. Clarithromycin-based triple therapy was the first-line treatment for *H. pylori* due to relatively low clarithromycin resistance rate (8%)[24] and high eradication rate (> 90%) in Hong Kong during the study period.[25] *H. pylori* infection was diagnosed by one of the two available tests in local public hospitals, which are endoscopy-based tests (rapid urease test or histology) and urea breath test.

Exclusion criteria were: (1) type I DM; (2) GC diagnosed within first year of *H. pylori* eradication therapy (as these could be missed cancer); (3) prior GC; (4) prior gastrectomy; (5) retreatment for *H. pylori* (defined as need of a repeat course of clarithromycin-based triple therapy, or subsequent prescriptions of either a second-line therapy [either PPI-levofloxacin-amoxycillin or bismuth-based quadruple therapy], or a third-line therapy [rifabutin-based therapy]). The patient selection process is depicted in **eFigure 1.**

Study Outcome

The outcome of interest was gastric adenocarcinoma after receiving *H. pylori* eradication therapy. We observed patients from the first day of *H. pylori* eradication therapy (i.e. index date) till GC diagnosis, death or end of study (31 December 2015). GC diagnosis date referred to the earliest date of hospitalization for workup (e.g. upper endoscopy or imaging) and/or treatment (surgery, chemotherapy, radiotherapy or endoscopic treatment). **eTable 1** shows ICD-9 codes of gastric adenocarcinoma.

Exposure of interest and covariates

The exposure of interest was type II DM (ICD-9 codes of 250 and 250.x) (simplified as DM in subsequent sections) at and/or after *H. pylori* eradication therapy. Overall glycemic control during observation period was represented by time-weighted average HbA1c, which was the average HbA1c weighted by time interval between successive measurements, to avoid bias from irregular time intervals.

Covariates of interest included age of receiving *H. pylori* eradication therapy, sex, smoking, alcohol use, past history of gastric and duodenal ulcers, other comorbidities (atrial fibrillation, ischemic heart disease, congestive heart failure, chronic renal failure, cirrhosis, stroke, hypertension and obesity) as well as usage of other medications (aspirin, non-steroidal anti-inflammatory drugs [NSAIDs], cyclooxygenase-2 [COX-2] inhibitors, statins, PPIs and H2 receptor antagonists (H2RAs). Smoking status was identified directly by ICD-9 code of V15.82 or indirectly by presence of chronic obstructive pulmonary disease (COPD). Alcohol use was suggested by presence of alcohol-related diseases (gastrointestinal, hepatic, psychiatric and neurological diseases). **eTable 1** shows ICD-9 codes of covariates. We defined drug exposure as more than 180-day use after receiving *H. pylori* eradication therapy during the observation period.

Data validation

Due to anonymous nature of patient's information in CDARS, we could only validate the diagnosis of patients from the electronic medical records of our own center (Queen Mary Hospital). Among 14 (9.2%) patients with codes "gastric cancer", all

were histologically confirmed adenocarcinoma without *H. pylori* infection and two arose from cardia.

Statistical analyses

All statistical analyses were performed using R version 3.2.3 (R Foundation for Statistical Computing) statistical software. Continuous variables were expressed as median and interquartile range (IQR). PS analysis was performed to control for confounding so that any observed difference in GC risk would likely arise from the diagnosis of DM alone. PS was estimated by multivariable logistic regression on aforementioned 20 covariates (age, sex, comorbidities and medications). PS analysis is preferred to traditional outcome regression models in the circumstances of relatively few outcomes but many variables (i.e. event per variables less than 10) as in this study.[26]

PS regression adjustment was used as the primary PS methodology, in which DM and PS (derived from the aforementioned 20 covariates) were included in the Cox proportional hazards model to calculate the adjusted hazard ratio (HR) of GC with DM. PS adjusted absolute risk difference between patients with and without DM was calculated as follows: (adjusted HR – 1) x (crude incidence rate of GC in patients without DM).

Subgroup analysis

Metformin was associated with a lower GC risk in a meta-analysis.[15] Subgroup analysis was performed according to metformin use, glycemic control (i.e. time-weighted average HbA1c level) and cancer site (cardia and non-cardia). A cut-off

value of 6.0% (42mmol/mol) for HbA1c was used because a higher level has been

shown to increase GC risk in *H. pylori*-infected subjects.[12]

<u>Sensitivity analyses</u>

Sensitivity analyses were conducted by Cox regression model using PS matching

(patients with DM were matched to those without DM in a 1:2 ratio without

replacement using a greedy distance-based matching algorithm with the logit of the

PS within 0.1 standard deviation) and inverse probability of treatment weighting

(IPTW).[27] The balance of covariates between the two groups was assessed by absolute

standardized difference (ASD), which was the absolute difference in means or

proportions divided by pooled standard deviation. An ASD of < 0.20 signifies good

balance for a particular covariate. We also used the competing risk regression model

with PS regression adjustment to calculate the adjusted subdistribution hazard ratio

(SHR)[28] to eliminate bias from competing risk of death due to higher risk of

cardiovascular diseases among patients with DM. To further characterize the effect of

metformin on GC risk, we used multivariable Cox regression model with inclusion of

DM, the 20 aforementioned covariates as well as metformin to calculate the adjusted

HR.

Sensitivity analyses were also performed by retaining gastric cancer cases diagnosed

within one year after receiving *H. pylori* eradication therapy and all patients who

needed retreatment for *H. pylori*, as well as excluding patients with other malignant

neoplasms (**eTable 1**), with adjustment for duration of DM and complications of DM

(retinopathy, nephropathy and peripheral neuropathy).

In this study, the comparison group, unless otherwise specified, refers to patients without DM (main, subgroup and sensitivity analyses). **eTable 2** summarizes the statistical methods used in this study. For all analyses, a two-sided p-value of <0.05 was used to define statistical significance.

RESULTS

Patient characteristics

Table 1 shows baseline characteristics of the whole cohort (n=46,460). There were

22,093 (47.6%) males and 6,900 (14.9%) had DM. The median age of receiving

clarithromycin-based triple therapy was 58.7 years (IQR:52.0–69.2). Compared with

patients without DM, a higher proportion of patients with DM had cardiovascular risk

factors and diseases (hypertension, dyslipidemia, obesity, ischemic heart disease,

congestive heart failure, stroke) as well as use of aspirin and statins.

During a median follow-up of 7.1 years (IQR:4.8–9.8) with 337,313 person-years,

153 (0.33%) patients were diagnosed with GC (incidence rate:4.5 per 10,000 person-

years). The median age of GC diagnosis was 72.4 years (IQR:63.8– 82.6), and the

median age of receiving *H. pylori* eradication therapy was 67.9 years (IQR:57.4–77.5).

There were 31 (20.3%) cardia cancers and 88 (57.5%) non-cardia cancers, while the

remaining 34 (22.2%) cases did not have site specified.

Association between diabetes mellitus and gastric cancer

Among the 6,900 patients with DM, 36 (0.5%) were diagnosed with GC (incidence

rate: 7.3 per 10,000 person-years). Of the 39,560 patients without DM, 117 (0.3%)

were diagnosed with GC (incidence rate: 4.1 per 10,000 person-years). Compared

with non-DM, DM was associated with an increased GC risk on both univariate

analysis (HR:1.81, 95% CI:1.25–2.64) and PS regression adjustment (adjusted

HR:1.67, 95% CI:1.08–2.58) (**Table 2**). The PS adjusted absolute risk difference was

2.96 (95% CI:0.32–7.27) more GC cases per 10,000 person-years among patients with

DM than those without DM.

Sensitivity analyses by Cox model using PS matching, IPTW, and competing risk model using PS regression adjustment yield consistent results (e**Table 3**). In the PS-matched cohort, all covariates were balanced between patients with and without DM (ASD <0.20) (**eTable 4**). For the multivariable Cox regression model including metformin, the adjusted HR of GC with DM compared with non-DM was 2.41 (95% CI: 1.38–4.23). Subgroup analysis showed the adjusted HR of GC with DM but without metformin use as compared with non-DM was 2.34 (95% CI: 1.33–4.13), while the adjusted HR of GC with DM and metformin use was 1.31 (95% CI: 0.77–2.23) as compared with non-DM.

Table 3 shows the sensitivity analysis by including gastric cancer cases diagnosed within first year of *H. pylori* therapy, patients who required retreatment for *H. pylori* and after excluding all other malignant neoplasms. The adjusted HR of GC with DM compared with non-DM was 2.12 (95% CI: 1.54–2.93). DM was associated with an increased risk of GC in those who received single course of *H. pylori* treatment (adjusted HR: 1.98, 95 % CI: 1.37–2.85) and those who required retreatment (adjusted HR: 2.54, 95% CI: 1.27–5.07).

Table 2 shows the consequences of not adjusting for certain covariates on the effect size (i.e. HR) of GC with DM and its variance. Notably, the association between DM and GC was no longer statistically significant if statins were not adjusted for (HR: 1.43, 95% CI:0.93–2.19). The HR was further reduced to 1.32 (95% CI: 0.86–2.02) if both statins and aspirin were not considered; and to 1.30 (95% CI:0.85 – 1.99) if all drugs were not considered. There was however no significant change in HR if aspirin,

NSAIDs/COX-2 inhibitors or PPIs alone were not adjusted for. On the other hand, HR increased to 1.92 (95% CI: 1.28–2.90) without adjusting for comorbidities.

Subgroup analysis

Among 6,900 patients with DM, 6,379 (92.4%) had a time-weighted average HbA1c level ≥6.0% (42 mmol/mol) and 5,083 (73.7%) used metformin. **Table 4** shows subgroup analysis according to time-weighted average HbA1c level, cancer site and metformin use. Suboptimal DM control (time-weighted average HbA1c level ≥6.0% [42 mmol/mol]) was associated with an increased GC risk (HR:1.68, 95% CI:1.07–2.63) compared with non-DM. This increased risk was not statistically significant in those with HbA1c <6.0% (42 mmol/mol) (HR:1.99, 95% CI:0.71–5.54). The association between DM and gastric cancer was also only significant for cardia cancer (HR: 3.4, 95% CI:1.45–7.97; DM *versus* non-DM) but not for non-cardia cancer (HR:1.53, 95% CI:0.84–2.78; DM *versus* non-DM). In addition, the increased GC risk was only observed among non-metformin users (HR:2.59, 95% CI:1.42–4.74; DM *versus* non-DM) but not metformin users (HR:1.28, 95% CI:0.74–2.20; DM *versus* non-DM).

DISCUSSION

In this territory-wide cohort study of more than 46,000 patients who had received *H. pylori* therapy, we showed that DM was associated with a 67% increase in GC risk. Subgroup analysis further showed that the increase in GC risk appears to associate with cardia cancer, patients with suboptimal glycemic control as well as those not using metformin. Moreover, we demonstrated potential source of biasing the association between DM and GC towards null if the usage of certain medications were not properly adjusted for, and inflation of cancer risk if comorbidities were not considered.

Despite a reported 19% increase in GC risk attributed to DM in a meta-analysis by Yoon et al,[10] nine of the 17 included observational studies did not find an association.[29-37] A subsequent meta-analysis of 22 observational studies by Miao et al[11] concluded that DM did not increase GC risk. Inadequate adjustment for various risk factors, in particular *H. pylori* status, likely contributed to this conflicting result. Another reason for this discrepancy could be due to the significantly different inclusion criteria of these two meta-analyses (study design and ethnicity). The meta-analysis by Yoon et al included 11 cohort studies, 5 case-control studies and 1 nested case control study. Six studies were conducted in Asia, 5 in Europe, 5 in North America, and 1 in Israel. Two of the studies adjusted for *H. pylori* status. On the other hand, the meta-analysis by Miao et al included cohort studies only. Seven studies were conducted in Asia, 9 in Europe, and 6 in the USA. None of the studies adjusted for *H. pylori* status. Specifically, only 7 of the cohort studies were included in both meta-analyses.

One major limitation of previous studies is the failure to stratify for the *H. pylori* status of the patients, with only two studies analysing GC risk according to *H. pylori* status.[12, 32] Inclusion of *H. pylori*-negative subjects with low GC risk may bias causal association towards null, as illustrated by Ikeda et al in which GC risk was only increased among patients with both *H. pylori*-infection and HbA1c ≥6.0% (42 mmol/mol).[12] In this study, we included a large cohort of *H. pylori*-infected patients who had received eradication therapy. Precancerous changes may have already developed before *H. pylori* eradication, rendering individuals remain at higher risk of GC even after receiving eradication therapy.[3] Sensitivity analysis including patients who required retreatment for *H. pylori* (i.e. failure of initial therapy) also demonstrated an increase in GC risk among patients with DM in our study. More importantly, those DM patients who required retreatment had an even higher risk of GC than those who received a single course of eradication therapy only (**Table 3**).

Besides demonstrating the association between DM and GC, we have further illustrated the importance of adjustment for concomitant medications and comorbidities. So far, no studies took into account the effect of concomitant medications despite ample evidence including our previous studies showing modulation of GC risk by drugs including aspirin,[13] NSAIDs, COX-2 inhibitors, statins[14], metformin[38] and PPIs[16]. In particular, patients with DM are more likely to receive statins and aspirin for the associated metabolic risk factors and diseases. Both statins and aspirin have been proposed to have chemopreventive effects against gastric cancer. Statins may arrest cell-cycle progression, induce apoptosis and inhibit angiogenesis, while aspirin inhibits cancer development via its action on different pathways such as COX-2, phosphatidylinositol 3-kinase, nuclear factor-κB, Wnt-ß-

catenin, extracellular signal-regulated kinase and activated protein1. In our study, failure to adjust for statins alone led to statistically insignificant result, with HR further attenuated in by omitting aspirin (1.32) and other drugs (1.30) (**Table 2**). This illustrates that aspirin and statins may negate the potential carcinogenic effect of DM on gastric cancer. Moreover, subgroup analysis also shows that GC risk increased only for patients with DM who did not use metformin. This observation complements our previous finding that metformin reduced GC risk in patients with DM who had received *H. pylori* eradication therapy.[39]

On the other hand, HR would be spuriously augmented from 1.67 to 1.92 if comorbidities were not adjusted for. Prior studies rarely considered a wide array of comorbidities as comprehensive as in our study. In particular, only few studies specifically investigated GC as the only primary outcome,[12, 32] while the remainders studied risks of cancers in multiple organs (e.g. liver, pancreas, prostate, endometrium). Our subgroup analysis on HbA1c level showed that a higher GC risk was only observed among DM patients with time-weighted average HbA1c $\geq 6.0\%$ (42mmol/mol), implying that a very strict glycemic control could help to prevent GC development.

So far, only two studies reported GC risk in DM patients according to tumor location.[18, 19] Lin et al[18] found that there was a significant association between self-reported DM and cardia cancer risk (HR 1.89, 95% CI: 1.43–2.50), while Kim et al[18] refuted this association (HR 0.64, 95% CI: 0.14–2.94). Our subgroup analysis according to cancer subsite was more consistent with that reported by Lin et al. While the pathogenesis and the etiological agents of cardia and non-cardia cancer are

believed to be different, our findings could provide new insights into how DM

increases GC risk with more prominent effect on cardia cancer development. In

general, patients with type II DM are overweight or even obese, which would increase

the risk of gastroesophageal reflux disease (GERD) and hence cardia cancer.

Eradication of *H. pylori* could restore gastric acid production by improvement of

corpus inflammation, and there is a potential risk of worsening of GERD.[40] In contrast,

non-cardia cancer are usually characterized by *H. pylori*-associated atrophic gastritis

and hypochlorhydria, which is protective against cardia cancer development.

Although it is tempting to speculate that the risk of cardia cancer could be increased

by eradication of *H. pylori* in these susceptible patients with DM, further studies are

needed to characterize the interaction between DM, *H. pylori* eradication and cardia

cancer development.

The merits of our study include large sample size (>46,000) and long follow-up

(median 7.1 years) that allows for more precise estimation of the effect size and

subgroup analysis. In addition, biases such as selection and recall biases common to

traditional observational studies were avoided in this territory-wide cohort study using

electronic health records. Inclusion of *H. pylori*-infected patients who had received

eradication therapy eliminated the important confounding effect of *H. pylori* infection

status. Sensitivity analyses by different PS methodologies and competing risk analysis

further verify the robustness of our study results.

Several limitations of our study deserves attention. First, residual and unmeasured

confounding is still possible in observational study despite PS methodology. Second,

data on some risk factors of GC like family history and diet could not be ascertained

from the electronic database. Third, using ICD codes alone may underestimate true prevalence of DM, smoking, alcohol use and obesity. However, it is unlikely that a significant proportion of patients with DM were missed as the proportion of DM in our cohort was 14.9% as compared with 10% prevalence in the general population in Hong Kong. Obesity, a risk factor for cardia GC, is more common in patients with DM, but data on body mass index (BMI) were not available. Nevertheless, Lin et al[19] reported an increased risk of cardia GC among patients with DM despite adjustment for BMI. Fourth, the actual post-treatment *H. pylori* status data was unavailable in the electronic database. However, the retreatment rate of 14% in our study was similar to what was previously reported,[24] and the inclusion of retreatment groups in the sensitivity analysis yielded consistent results. Fifth, as the majority of study subjects were ethnic Chines, studies on other ethnic groups are needed to confirm the generalizability of our findings to other populations. Lastly, the inclusion/exclusion criteria and coding accuracy could only be validated on a small subset of patients who were followed up in our center. However, it is unlikely that the coding practice will deviate significantly across different hospitals under the same management system of the Hospital Authority.

CONCLUSIONS

Type II DM was associated with an increased GC risk (particularly cardia cancer) in *H. pylori*-infected patients who had received eradication therapy, in particular those with suboptimal glycemic control and those who did not use metformin. Targeted screening of high-risk *H. pylori*-infected patients with DM after eradication therapy shall be considered.

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Table 1. Baseline characteristics of study cohort

	All (n=46,460)	Patients with DM (n=6,900)	Patients without DM (n=39,560)
Age at triple therapy (years)*	58.7 (52.0–69.2)	66.1 (57.5– 74.7)	57.6 (51.4–67.6)
Male sex (n, %)	22093 (47.6%)	3590 (52.0%)	18503 (46.8%)
Duration of follow-up (years)*	7.1 (4.8–9.8)	7.0 (4.6–9.7)	7.1 (4.8–9.8)
Smoking (n, %)	1550 (3.3%)	380 (5.5%)	1170 (3.0%)
Alcohol (n, %)	462 (1.0%)	107 (1.6%)	355 (0.9%)
History of GU (n, %)	1272 (2.7%)	278 (4.0%)	994 (2.5%)
History of DU (n, %)	1413 (3.0%)	289 (4.1%)	1124 (2.8%)
Hypertension (n, %)	12094 (26.0%)	4383 (63.5%)	7711 (19.5%)
Dyslipidemia (n, %)	4648 (10.0%)	1908 (27.7%)	2740 (6.9%)
Obesity (n, %)	471(1.0%)	310 (4.5%)	161 (0.4%)
IHD (n, %)	3660(7.9%)	1837 (26.6%)	3477 (8.8%)
AF (n, %)	2317 (5.0%)	645 (9.3%)	1672 (4.2%)
CHF (n, %)	2442 (5.3%)	992 (14.4%)	1450(3.7%)
Stroke (n, %)	3719 (8.0%)	1317 (19.1%)	2402 (6.1%)
CRF (n, %)	1368 (2.9%)	757 (11.0%)	611 (1.5%)
Cirrhosis (n, %)	942 (2.0%)	262 (3.8%)	680 (1.7%)
Aspirin (n, %)	8885 (19.1%)	2939 (42.6%)	5946 (15.0%)
NSAIDs/COX-2 inhibitors (n, %)	4671 (10.1%)	710 (10.3%)	3961 (10.0%)
Statins (n, %)	11943 (25.7%)	4181 (60.6%)	7762 (19.6%)
PPIs (n, %)	3664 (7.9%)	930 (13.5%)	2734 (6.9%)
H2RAs (n, %)	22754 (49.0%)	4144 (60.1%)	18610 (47.0%)

* Continuous variables were expressed as median (years) with interquartile range

Categorical variables were expressed as number (%)

Drug use was defined as use for more than 180 days, and expressed as number (%)

Smoking status was identified either directly by ICD-9 code of V15.82 or indirectly by presence of chronic obstructive pulmonary disease (COPD); alcohol use was suggested by presence of alcohol-related diseases (gastrointestinal, hepatic, psychiatric and neurological diseases)

Abbreviations: DM, diabetes mellitus; GU, gastric ulcer; DU, duodenal ulcer; IHD, ischemic heart disease; AF, atrial fibrillation; CHF, congestive heart failure; CRF, chronic renal failure; NSAIDs, non-steroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2; PPIs, proton pump inhibitors; H2RAs, histamine-2 receptor antagonists

Table 2. Association between diabetes mellitus and gastric cancer

	No. of patients without DM and GC	No. of patients with DM and GC	HR	95% CI	p-value
Univariate analysis					
DM	39,560 (GC = 117)	6,900 (GC=36)	1.81	1.25 – 2.64	0.002
PS regression adjustment					
All variables adjusted for*	39,560 (GC = 117)	6,900 (GC=36)	1.67	1.08 – 2.58	0.021
All variables adjusted for, except aspirin	39,560 (GC = 117)	6,900 (GC=36)	1.65	1.07 – 2.55	0.024
All variables adjusted for, except NSAIDs/COX-2 inhibitors	39,560 (GC = 117)	6,900 (GC=36)	1.67	1.08 – 2.58	0.020
All variables adjusted for, except statins	39,560 (GC = 117)	6,900 (GC=36)	1.43	0.93 – 2.19	0.101
All variables adjusted for, except PPIs	39,560 (GC = 117)	6,900 (GC=36)	1.67	1.08 – 2.58	0.020
All variables adjusted for, except statins and aspirin	39,560 (GC = 117)	6,900 (GC=36)	1.32	0.86 – 2.02	0.203
All variables adjusted for, except for all drugs	39,560 (GC = 117)	6,900 (GC=36)	1.30	0.85 – 1.99	0.234
All variables adjusted for, except comorbidities	39,560 (GC = 117)	6,900 (GC=36)	1.92	1.28 – 2.90	0.002

* Variables include age of receiving *Helicobacter pylori* eradication therapy, sex, smoking, alcohol use, past history of gastric and duodenal ulcers, other comorbidities (atrial fibrillation, ischemic heart

disease, congestive heart failure, chronic renal failure, cirrhosis, stroke, hypertension and obesity) as well as usage of other medications (aspirin, NSAIDs, COX-2 inhibitors, statins, PPIs and H2RAs)

Abbreviations: DM, diabetes mellitus; GC, gastric cancer; HR, hazard ratio; 95% CI, 95% confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2; PPIs, proton pump inhibitors; H2RAs, H2 receptor antagonists

Table 3. Association between diabetes mellitus and gastric cancer (sensitivity analysis including gastric cancer cases diagnosed within first year and patients requiring retreatment but excluding all other malignancy)

	No. of	No. of	aHR*	95% CI	p-value

	patients without DM and GC	patients with DM and GC			
Whole cohort# (n=48,211, GC=320)	40,598 (GC=250)	7,613 (GC=70)	2.12	1.54 – 2.93	< 0.001
HP treatment status#					
Single treatment group (n=41,932, GC=265)	35,764 (GC=210)	6,168 (GC=55)	1.98	1.37 – 2.85	< 0.001
Retreatment group (n=6,279, GC=55)	4,834 (GC=40)	1,445 (GC=15)	2.54	1.27 – 5.07	0.008

Retreatment groups and patients with gastric cancer diagnosed within the 1st year of receiving HP eradication therapy were included while those with other cancers excluded

*Adjustment for age of receiving HP eradication therapy, sex, smoking, alcohol use, past history of gastric and duodenal ulcers, other comorbidities (atrial fibrillation, ischemic heart disease, congestive heart failure, chronic renal failure, cirrhosis, stroke, hypertension and obesity), usage of other medications (aspirin, NSAIDs, COX-2 inhibitors, statins, PPIs and H2RAs), duration of DM and DM complications

Abbreviations: DM, diabetes mellitus; GC, gastric cancer; aHR, adjusted HR; 95% CI, 95% confidence interval; HP: *Helicobacter pylori*; NSAIDs, non-steroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2; PPIs, proton pump inhibitors

Table 4. Subgroup analysis on the association between diabetes mellitus and gastric cancer (PS regression adjustment)

No. of patients	No. of patients	aHR	95% CI	p-value

	without DM and GC	with DM and GC			
Metformin use					
Yes	39,560 (GC=117)	5,083 (GC=19)	1.28	0.74 – 2.20	0.378
No	39,560 (GC=117)	1,817 (GC=17)	2.59	1.42 – 4.74	0.002
Time-weighted average HbA1c level					
HbA1c ≥ 6.0% (42 mmol/mol)	39,560 (GC=117)	6,379 (GC=32)	1.68	1.07 – 2.63	0.025
HbA1c < 6.0% (42 mmol/mol)	39,560 (GC = 117)	521 (GC=4)	1.99	0.71 – 5.54	0.188
Cancer site*					
Cardia	39,462 (GC=19)	6,876 (GC=12)	3.40	1.45 – 7.97	0.005
Non-cardia	39,513 (GC=70)	6,882 (GC=18)	1.53	0.84 – 2.78	0.161
Non-cardia + unspecified site	39,541 (GC=98)	6,888 (GC=24)	1.33	0.80 – 2.23	0.271

* total cancer cases = 153 (non-cardia: 88, cardia: 31, unspecified: 34). Variables adjusted for include age of receiving *Helicobacter pylori* eradication therapy, sex, smoking, alcohol use, past history of gastric and duodenal ulcers, other comorbidities (atrial fibrillation, ischemic heart disease, congestive heart failure, chronic renal failure, cirrhosis, stroke, hypertension and obesity) as well as usage of other medications (aspirin, NSAIDs, COX-2 inhibitors, statins, PPIs and H2RAs)

Abbreviations: DM, diabetes mellitus; GC, gastric cancer; aHR, adjusted hazard ratio; 95% CI, 95% confidence interval; HbA1c, hemoglobin A1c