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Impact of metformin on gastric adenocarcinoma survival: A Belgian population based study

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ABSTRACT

Background: Preclinical studies have shown anticancer activities of metformin in gastric cancer and a recent epidemiological study showed a decrease in recurrence and mortality of gastric cancer in metformin users. This study aimed to assess the impact of metformin on gastric cancer survival in diabetic patients at a Belgian population level.

Methods: We conducted an observational, population-based study by linking data of the Belgian Cancer Registry with medical claims data coming from the health insurance companies for patients diagnosed with stage I to III gastric adenocarcinoma between 2006 and 2012. Information on gastric cancer-specific deaths was retrieved from mortality records collected by regional governments. Time-dependent Cox regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CI) for overall survival (OS) and cancer-specific mortality (CSS).

Results: In our population of 371 patients, a reduction in all-cause mortality was observed in metformin users (adjusted HR = 0.73, 95% CI: [0.52; 1.01], p = 0.06) but not for cancer specific mortality (adjusted HR = 0.86, 95% CI: [0.56; 1.33], p = 0.50). Pre-diagnosis exposure to metformin was associated with a significant improvement in OS (adjusted HR = 0.75, 95% CI: [0.57; 0.98], p = 0.04) that was not significant for CSS (adjusted HR = 0.89, 95% CI: [0.62; 1.28], p = 0.52). Moreover, no dose-response relationship between metformin use and either all-cause or cancer-specific mortality was observed.

Conclusion: In the first population based study of metformin use in gastric cancer adenocarcinoma patients with previous diabetes, our findings suggest that metformin use might improve overall mortality. However, no such association was found for cancer-specific survival. Additional studies in other populations are required.

1. Introduction

Gastric cancer is one of the most common cancers worldwide with more than 950 000 new cases diagnosed in 2012 [1]. Despite a recent decline in incidence in some European countries, gastric cancer remains one of the leading causes of cancer death globally, with approximatively 720 000 stomach cancer deaths in 2012 alone [1,2]. Similar to most European countries, in Belgium gastric cancer incidence is approximatively 5.4 per 100 000 men and 3.3 per 100 000 women and the five-year overall survival is approximatively 35% and 44% for men and women, respectively [3].

Diabetes and cancer have been studied intensely during the last decade and researchers focused on investigating the existence of a link between these two chronic conditions [4–6]. It has been shown that diabetes increases the risk of stomach, liver, pancreatic, colon, and rectum cancer [7,8]. Also, diabetes has been reported to be associated with premature death from several cancers [9].

Metformin is the most widely prescribed first-line treatment for type II diabetes and has a favourable safety profile, even in those without type II diabetes [10–13]. Experimental studies have shown that metformin can exert an anti-cancer effect on human cancer cells [14]. Evidence from observational and clinical studies, have shown

Abbreviations: BCR, Belgian cancer registry; IMA, intermutualistic agency; NNSS, national number for social security; ICD, international classification of disease; DDD, defined daily dose; OS, overall survival; CSS, cancer specific survival; HR, hazard ratio; CI, confidence interval; BMI, body mass index

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metformin to be inversely associated with cancer risk and progression however results from individual studies have not been consistent [12,14–20].

For gastric cancer in particular, experimental studies demonstrate that metformin can inhibit human gastric cancer cell proliferation and metastasis and can inhibit tumour growth and enhance the effect of rapamycin and cisplatin in mouse models [21–24].

Randomized clinical trials are the gold standard for assessing treatment efficacy and safety. However, in the field of pharmacoepidemiology, such studies suffer from limitations compared to observational studies such as selection bias and short follow up durations [25]. Therefore, well conducted observational studies are a good alternative to confirm preclinical hypotheses.

To date, only one single-institution study in South Korea has investigated metformin use and mortality from gastric cancer and results were encouraging: a 14% decrease in recurrence and a 13% decrease in mortality risk for diabetic gastric cancer patients for each 6 month of cumulative use of metformin after gastrectomy [26].

Despite promising preclinical evidence, data on metformin use and gastric cancer mortality remain scarce and such pharmacoepidemiological studies haven't been conducted at a population level yet. Therefore, the current study aimed to examine the impact of metformin use on overall and cancer specific survival in 371 diabetic patients with gastric adenocarcinoma, at the Belgian population level. Based on previous evidence, we hypothesized that metformin use might increase survival in diabetic patients with gastric cancer.

2. Material and methods

2.1. Data sources

The Belgian Cancer Registry (BCR) is a population-based registry covering more than 95% of the Belgian population from 2004 onwards [3]. In addition to detailed patient and tumour characteristics collected through standard cancer registrations, the BCR has authorization to collect medical claims data from the health insurance companies. These data are gathered on a national level by the Intermutualistic Agency (IMA) and can be linked to the BCR data using the national number for social security (NNSS). Available IMA information covers all reimbursed diagnostic and therapeutic procedures and pharmaceuticals for in- as well as out-patient dispenses for a period ranging from one year before until five years after diagnosis for each cancer patient.

Vital status is also retrieved based on NNSS from the Belgian Crossroads bank for Social Security (BCSS). Causes of death are extracted from death certificate data collected by the regional governments and probabilistically linked to the BCR data (> 98% successfully linked).

Informed written consent was not needed for this study, because the use of BCR data for scientific purposes is regulated by Belgian law since 2006 [27].

2.2. Study subjects

All patients diagnosed between the 1st January 2006 and the 31st December 2012 with stage I–III gastric adenocarcinoma and previous diabetes were selected from the BCR database (International Classification of Diseases (ICD), 10th revision: C16.1–C16.9). Cancers of the gastro-oesophageal junction were excluded as they were considered to be oesophageal cancers.

In addition, patients who died in the first 6 months after diagnosis were excluded as drug use during this time is unlikely to exert an effect on cancer death.

A patient was defined to be diabetic if he had a record of anti-diabetic medications (ATC code "A10") dispensed with a total sum of > 30 daily defined doses (DDD) in the year prior to diagnosis.

Additional exclusion criteria were: presence of a previous tumour (apart from non-melanoma skin cancer), not residing in Belgium at the time of diagnosis, an uncertain date of diagnosis, no national number for social security (NNSS), lost to follow up at the date of cancer incidence, or missing from the medical claims (IMA) database.

Cardiovascular and respiratory comorbidities in the year prior to diagnosis were also derived from claims data including in-and outpatient dispensed medication, according to a previously described methodology [28]. A patient was defined to have cardiovascular or respiratory disease if cardiovascular medications (ATC code "C01–C04", "C07–C09" and "B01" with exclusion of heparin) or respiratory medications (ATC code "R03") with a total sum of > 180 DDDs and > 80 DDDs respectively were dispensed in the year prior to diagnosis.

2.3. Outcome

The primary outcome was overall survival and follow-up was until July 1st, 2015. In the cancer-specific survival analysis, patients were followed until January 1st, 2014. Patients who died after this date were censored. Cancer specific deaths were defined as those with an underlying cause of death coded with ICD-10 C16.1–C16.9 for gastric cancer or C26 for malignant neoplasm of other and ill-defined digestive organs.

2.4. Covariates

Information available from the BCR included data on cancer diagnosis and other demographic and clinical information: age in categories (< 70years, ≥70years), sex, year of diagnosis (from 2006 to 2012 recoded into a binary variable: 2006–2008 and 2009–2012), and combined stage (stage I–III).

Metformin use, as well as cancer treatments in the 6 months after diagnosis were derived from prescription records provided by the IMA. Cancer treatment categories included primary surgery, peri-operative treatment (chemotherapy, radiotherapy or both), primary chemotherapy and/or radiotherapy, and no treatment.

2.5. Statistical analysis

Users and non-users of metformin were compared using Pearson chi square test or Fisher exact test where the former was invalid.

For post-diagnosis metformin use, time-dependent cox regression models were used to calculate adjusted and unadjusted hazards ratios (HR) with 95% confidence intervals (CI). Patients became metformin users only after they were dispensed a metformin prescription, therefore avoiding immortal-time bias [29]. Before this prescription, patients were considered as non-users.

Drug use was lagged by 6 months after diagnosis to remove prescriptions occurring immediately prior to death as they may reflect palliative care. Sensitivity analyses were performed to study the effect of varying the length of this lag.

Dose response effects were explored in two types of time-varying analyses. Firstly, we investigated increasing number of prescriptions. A patient was classified a non-user if prior to the first metformin prescription. Light use was classified as use from the first prescription until the 6th prescription after diagnosis. A patient was considered a heavy user if he had the 6 or more metformin prescriptions after diagnosis.

Secondly, we investigated increasing number of defined daily doses (DDDs). In DDD analyses, patients were classified as non-users if they had less than 1 DDD after the diagnosis. Then, assuming that one DDD corresponds to one day of metformin use, we classified light users as 1–182.5 DDDs, and heavy users as more than 182.5 DDDs.

In secondary analysis, we investigated the association between prediagnosis metformin use in the year prior to diagnosis without excluding those with less than 6 months of follow-up after diagnosis.

In a simplified post-diagnosis use, we compared metformin users to non-users in the first six months after the cancer diagnosis in

individuals living more than six months. This method controls for immortal time bias without the use of time varying covariates [30].

As metformin usage might be associated with possible benefits on cardiovascular outcomes [31,32], an additional analysis was conducted only for cardiovascular deaths including diabetes related deaths (ICD10 codes I00-I99, E14) and censoring other causes of deaths. Note that, in the cardiovascular specific analyses no adjustments for comorbidities were conducted as all cardiovascular deaths occurred in patients with cardiovascular but no respiratory disease.

In all analyses, censoring was conducted at 5 years after diagnosis. All models were adjusted for age at diagnosis, sex, incidence year, cancer stage, cancer treatments and cardiovascular and respiratory comorbidities.

All analyses were performed using the SAS Enterprise Guide statistical release 9.3 software. The statistical significance level was set at 0.05.

3. Results

3.1. Baseline characteristics

A total of 2552 participants with gastric cancer met the initial inclusion criteria (Fig. 1). Within these patients, 371 (15%) were identified as diabetics. The main analysis included 298 patients who had more than 6 months of follow-up. The median follow-up time was 48.6 months (95% CI, 36.1–58.3). During the follow up, 180 (60.4%) patients died. According to the death certificates, 114 (63.3%) deaths were due to cancer and 92 (51.1%) deaths were due to gastric cancer. Patient and tumour characteristics according to metformin use are summarized in Table 1.

The median age of patients was 75.0 years (Interquartile range (IQR): 66.0–80.0). Patients were more often diagnosed at stage I cancer (43.3%, n = 129), with poorly differentiated disease (46.3%, n = 138) and when specified, tumours localised in the pyloric antrum (29.9%, n = 89). Within diabetic patients with more than 6 months of follow up, 228 (76.5%) had a history of metformin use. The latter group was younger than the non-metformin users (median age (IQR): 74.0 (65.0–80.0) years for users versus 78.0 (69.0–82.0) years for non-users, p = 0.05).

There was no difference between metformin users and non-users in terms of sex, year of incidence, grade of differentiation, stage or comorbidities including cardiovascular and respiratory disease.

3.2. Post diagnosis use of metformin and survival

In unadjusted time dependent analysis, metformin use was associated with a significant increase in overall survival with a HR of 0.72 (95% CI: [0.52; 0.98], p = 0.04). After adjustment for age, sex, stage, year of diagnosis, cancer treatment and comorbidities, the reduction in hazards all-cause mortality remained (HR = 0.73, 95% CI: [0.52; 1.01], p = 0.06) (Table 2).

For metformin use and cancer specific survival, the association was not significant (HR = 0.80, 95% CI: [0.53; 1.21], p = 0.29), even after adjustment for potential confounders (adjusted HR = 0.86, 95% CI: [0.56; 1.33], p = 0.50) (Table 2).

There was no dose-response association observed between metformin use and mortality from all causes or from gastric cancer in analyses of increasing considering number of prescriptions or DDDs (for instance, adjusted HR for 1–6 prescriptions = 0.64, 95% CI: [0.44; 0.93], p = 0.02 and adjusted HR for more than 6 prescriptions = 0.92, 95% CI: [0.59; 1.43], p = 0.71) (Table 2).

3.3. Secondary and subgroup analysis

Tables 3 and 4 show results from sensitivity analyses for overall and cancer specific analysis, respectively. Using a time-varying definition for metformin use and no lag time, overall survival was associated with a significant increase in survival for metformin users (adjusted

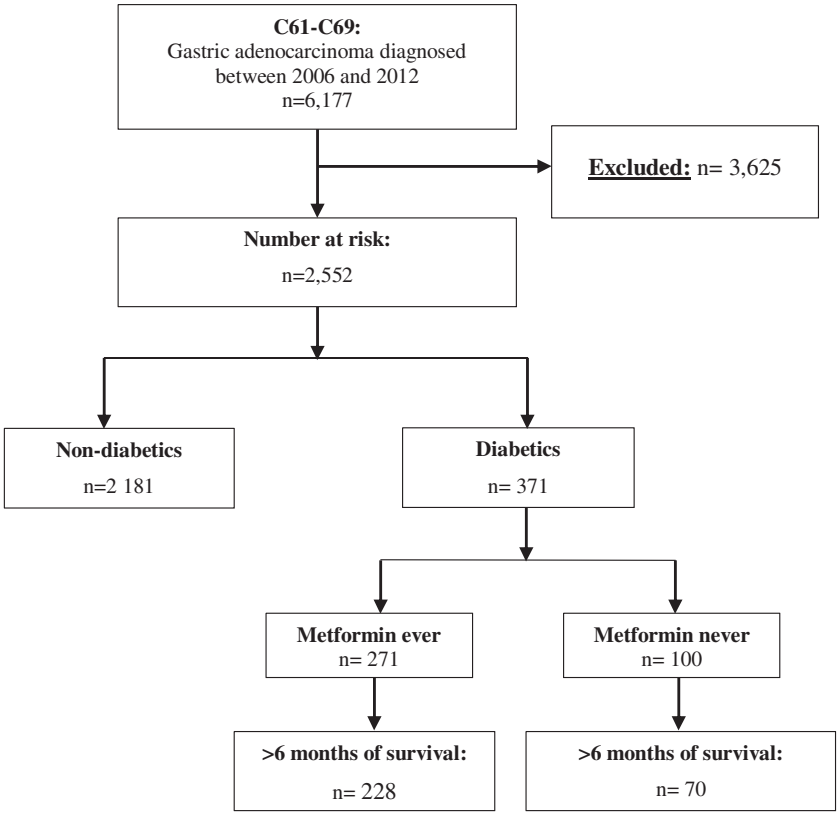

Fig. 1. Flowchart of Belgian patients with stage I–III gastric adenocarcinoma and diabetes.

Table 1
Baseline characteristics of patients with gastric adenocarcinoma and diabetes by metformin use in patients with more than 6 months' follow-up after diagnosis.

Characteristic	Total (N = 298)	Metformin Use		
		Ever (n = 228)	Never (n = 70)	p-value
Sex—n (%)				0.20
Male	169 (56.7)	134 (58.8)	35 (50.0)	
Age category—n (%)				0.14
≤69 years	98 (32.9)	80 (35.1)	18 (25.7)	
≥70 years	200 (67.1)	148 (64.9)	52 (74.3)	
Year of incidence—n (%)				0.14
< 2009	118 (39.6)	85 (37.3)	33 (47.1)	
≥2009	180 (60.4)	143 (62.7)	37 (52.9)	
Grade of differentiation—n (%)				0.73
Poorly	138 (46.3)	106 (46.5)	32 (45.7)	
Moderately	84 (28.2)	62 (27.2)	22 (31.4)	
Well	22 (7.4)	16 (7.0)	6 (8.6)	
Unknown/missing	54 (18.1)	44 (19.3)	10 (14.3)	
Combined stage—n (%)				0.07
I	129 (43.3)	99 (43.4)	30 (42.9)	
II	87 (29.2)	60 (26.3)	27 (38.6)	
III	82 (27.5)	69 (30.3)	13 (18.6)	
Vital Status—n (%)				0.11
Alive	140 (47.0)	113 (49.6)	27 (38.6)	
Dead	158 (53.0)	115 (50.4)	43 (61.4)	
Cardiovascular disease—n (%)				0.96
Yes	222 (74.5)	170 (74.6)	52 (74.3)	
Respiratory diseases—n (%)				> 0.99
Yes	16 (5.4)	12 (5.3)	4 (5.7)	
Cancer therapy within 6mths—n (%)				0.46
None	37 (12.4)	25 (11.0)	12 (17.1)	
Surgery alone	154 (51.7)	117 (50.9)	37 (52.9)	
Primary CT and/or RT	19 (6.4)	15 (6.6)	4 (5.7)	
Surgery and others treatment	88 (29.5)	71 (31.6)	17 (24.3)	

HR = 0.69, 95% CI: [0.53; 0.91], p = 0.01). Metformin use was also associated with an increase in overall survival when the lag time was set to 3 months (adjusted HR = 0.75, 95% CI: [0.55; 1.01], p = 0.06) or 1 year (adjusted HR = 0.67, 95% CI: [0.46; 1.00], p = 0.05). With a lag time of 2 years however, the estimate was similar but was no longer significant (adjusted HR = 0.70, 95% CI: [0.41; 1.18], p = 0.18) (Table 3). In cancer specific analysis, these associations were no longer significant (Table 4). Cardiovascular mortality risk appeared to be reduced in metformin users but results were non-significant (adjusted HR = 0.39, 95% CI: [0.14–1.10], p = 0.08).

In analysis of metformin use in the year before diagnosis, a significant protective association was observed for all-cause mortality (adjusted HR = 0.75, 95% CI: [0.57; 0.98]; p = 0.04) (Table 3). This significant survival advantage was not found for cancer specific mortality (adjusted HR = 0.89, 95% CI: [0.62; 1.28], p = 0.52) (Table 4).

In the simple analysis of post-diagnosis metformin use in the 6 months after diagnosis, no significant associations were found for all-cause mortality (adjusted HR = 0.76, 95% CI: [0.55; 1.06], p = 0.10) or cancer specific mortality (adjusted HR = 0.84, 95% CI: [0.55; 1.29]; p = 0.43) (Tables 3 and 4).

4. Discussion

In this population-based study, we sought to assess whether metformin use is associated with an improvement in survival in patients with diabetes and stage I–III gastric adenocarcinoma.

We observed a borderline 27% reduction in the overall mortality risk. However, no significant association was observed for cancer specific mortality. Caution is required in the interpretation of the findings for all-cause mortality as results were borderline significant and no dose-response association was observed for increasing metformin DDDs.

We aimed to avoid the potential biases which pharmacoepidemiological studies are prone to by using robust methods to investigate the association between metformin use and mortality. For example, metformin use was modelled as a time varying covariate in order to avoid immortal time bias in the definition of 'users', time lags were introduced for medication prescriptions to avoid bias due to end-of-life treatment, sensitivity analyses were carried out to investigate the impact of the choice of these time lags and all-cause mortality, cancer specific mortality and cardiovascular mortality were studied.

Reassuringly, the sensitivity analyses for different lag sizes on all-

Table 2
Association between metformin use and either all-cause mortality or cancer-specific mortality at 5 years in patients with diabetes and gastric adenocarcinoma diagnosed between 2006 and 2012 in Belgium.

Medication usage	5-yr event rate (%)		Person Years	Unadjusted			Adjusted[a]		
				HR	(95% CI)	p	HR	(95% CI)	p
All-cause mortality									
Post diagnosis metformin use as time varying covariate[b] (*n = 298*)									
Non-users	78/114	(68.4)	449	1			1		
Users	80/184	(43.5)	471	0.72	(0.52–0.98)	0.04	0.73	(0.52–1.01)	0.06
1 to 6 prescriptions	45/94	(47.9)	269	0.62	(0.43–0.90)	0.01	0.64	(0.44–0.93)	0.02
More than 6 prescriptions	35/90	(38.9)	202	0.92	(0.60–1.40)	0.68	0.92	(0.59–1.43)	0.71
1 to 182.5 DDDs	46/87	(52.9)	256	0.65	(0.45–0.94)	0.02	0.65	(0.47–0.92)	0.02
More than 182.5 DDDs	34/97	(35.1)	215	0.84	(0.55–1.30)	0.43	0.89	(0.57–1.40)	0.61
Cancer-specific mortality									
Post diagnosis metformin use as time varying covariate[b] (*n = 297*)									
Non-users	45/113	(39.8)	415	1			1		
Users	49/184	(26.6)	378	0.80	(0.53–1.21)	0.29	0.86	(0.56–1.33)	0.50
1 to 6 prescriptions	34/99	(34.3)	227	0.82	(0.52–1.28)	0.39	0.86	(0.54–1.36)	0.52
More than 6 prescriptions	15/85	(17.6)	151	0.76	(0.41–1.41)	0.38	0.87	(0.46–1.68)	0.69
1 to 182.5 DDDs	34/103	(33.0)	219	0.83	(0.53–1.30)	0.41	0.84	(0.53–1.34)	0.47
More than 182.5 DDDs	15/81	(18.5)	160	0.74	(0.40–1.37)	0.34	0.92	(0.48–1.78)	0.81

[a] Adjusted for age, sex, year of diagnosis, stage, cancer treatment, and comorbidities.
[b] Analyses include a lag of 6 months in individuals living more than 6 months.

Table 3
Sensitivity analysis on metformin use and all-cause mortality at 5 years in patients with diabetes and gastric adenocarcinoma diagnosed between 2006 and 2012 in Belgium.

All-cause mortality									
Medication usage	5-yr event rate (%)		Person Years	Unadjusted HR	(95% CI)	p	Adjusted[a] HR	(95% CI)	p
No lag[b] (*n = 371*)									
Non-users	118/154	(76.6)	365	1			1		
Users	112/217	(51.6)	570	0.69	(0.53–0.90)	0.006	0.69	(0.53–0.91)	0.01
3 months lag[c] (*n = 328*)									
Non-users	93/129	(72.1)	412	1			1		
Users	95/199	(47.7)	518	0.74	(0.55–0.99)	0.04	0.75	(0.55–1.01)	0.06
1 year lag[d] (*n = 250*)									
Non-users	56/92	(64.1)	498	1			1		
Users	54/158	(34.2)	386	0.66	(0.45–0.96)	0.03	0.67	(0.46–0.99)	0.05
2 years lag[e] (*n = 201*)									
Non-users	32/70	(45.7)	574	1			1		
Users	29/131	(22.1)	244	0.68	(0.41–1.13)	0.14	0.70	(0.41–1.18)	0.18
Metformin use before diagnosis[f] (*n = 371*)									
Non-users	87/122	(71.3)	282	1			1		
Users	143/249	(57.4)	653	0.72	(0.55–0.94)	0.01	0.75	(0.57–0.98)	0.04
Metformin use after diagnosis[g] (*n = 298*)									
Non-users	68/112	(60.7)	344	1			Ref		
Users	90/186	(48.4)	575	0.79	(0.58–1.08)	0.14	0.76	(0.55–1.06)	0.10

[a] Adjusted for age, sex, year of diagnosis, stage, cancer treatments, and comorbidities.
[b] No lag with no exclusion of deaths after diagnosis.
[c] Decreasing the lag to 3 months in time varying co-variate analysis in individuals with more than 3 months' follow-up.
[d] Increasing the lag to 1 year in time varying co-variate analysis in individuals with more than 1 years' follow-up.
[e] Increasing the lag to 2 year in time varying co-variate analysis in individuals with more than 2 years' follow-up.
[f] Previous users were individuals with at least one prescription in the year before diagnosis.
[g] Post diagnosis in the six months after diagnosis in individuals with more than 6 months' follow-up.

cause mortality as well as cancer-specific mortality showed similar protective effects (HR < 1) that once adjusted, did not reach a statistically significant level.

One might postulate that, at least in this diabetic population, metformin use was not found to significantly reduce cancer-specific mortality whilst suggesting a possible protective association for all-cause mortality could be explained by the fact that metformin is the first-line treatment for type II diabetes. Thus, metformin users could

Table 4
Sensitivity analysis on metformin use and gastric cancer specific mortality at 5 years in patients with diabetes and gastric adenocarcinoma diagnosed between 2006 and 2012 in Belgium.

Cancer-specific mortality									
Medication usage	5-yr event rate (%)		Person Years	Unadjusted HR	(95% CI)	p	Adjusted[a] HR	(95% CI)	p
No lag[b] (*n = 367*)									
Non-users	70/152	(46.1)	332	1			1		
Users	67/215	(31.2)	477	0.72	(0.51–1.01)	0.06	0.75	(0.53–1.07)	0.11
3 months lag[c] (*n = 326*)									
Non-users	56/128	(43.8)	378	1			1		
Users	58/198	(29.3)	426	0.80	(0.55–1.17)	0.25	0.86	(0.58–1.28)	0.46
1 year lag[d] (*n = 249*)									
Non-users	33/95	(34.7)	463	1			1		
Users	31/154	(20.1)	295	0.73	(0.44–1.20)	0.21	0.84	(0.50–1.42)	0.52
2 years lag[e] (*n = 169*)									
Non-users	15/69	(21.7)	474	1			1		
Users	15/100	(15.0)	173	0.83	(0.40–1.74)	0.63	0.99	(0.46–2.16)	0.99
Metformin use before diagnosis[f] (*n = 367*)									
Non-users	48/119	(40.3)	253	1			1		
Users	89/248	(35.9)	556	0.83	(0.58–1.17)	0.29	0.89	(0.62–1.28)	0.52
Metformin use after diagnosis[g] (*n = 297*)									
Non-users	41/111	(36.9)	308	1			1		
Users	53/186	(28.5)	485	0.81	(0.54–1.21)	0.30	0.84	(0.55–1.29)	0.43

[a] Adjusted for age, sex, year of diagnosis, stage, cancer treatments, and comorbidities.
[b] No lag with no exclusion of deaths after diagnosis.
[c] Decreasing the lag to 3 months in time varying co-variate analysis in individuals with more than 3 months' follow-up.
[d] Increasing the lag to 1 year in time varying co-variate analysis in individuals with more than 1 years' follow-up.
[e] Increasing the lag to 2 year in time varying co-variate analysis in individuals with more than 2 years' follow-up.
[f] Previous users were individuals with at least one prescription in the year before diagnosis.
[g] Post diagnosis in the six months after diagnosis in individuals with more than 6 months' follow-up.

have a better prognosis due to a lower morbidity from diabetes (confounding by indication) or possible benefits on cardiovascular outcomes [31,32]. This argument, while only a hypothesis, is strengthened by the results from the cardiovascular mortality analysis where a 60% reduction in cardiovascular mortality was observed for metformin users, albeit non-significant. However, this analysis could suffer from a lack of power due to low number of cardiovascular events. Similarly, the loss of statistical significance in the cause-specific analysis could also be explained by a lower number of events.

In our analysis, a lag of 6 month for metformin use was used and consistent results were found when varying this lag. The use of a lag for medication use is recommended in order to avoid reverse causation bias [33], however, as the lag time was increased, the number of events decreased, thus potentially leading to an underestimation of the hazard ratio and wider confidence intervals.

It is plausible that a number of limitations may have influenced our findings. We had no information on potential lifestyle confounders such as alcohol or tobacco use. Moreover, data about body mass index (BMI) or socioeconomic factors were unavailable. Therefore, residual confounding cannot be ruled out by unrecorded confounders. Also, our analyses were not adjusted for type of diabetes, diabetes duration, severity or glycemic control. Despite the use of a nation-wide gastric cancer cohort, the study was limited by a relatively small sample size. Therefore, subgroup analyses leading to further subdivision of the sample (e.g. by type of treatment) have not been conducted.

Lastly, patients included in the analysis were not all naïve to medication exposure before diagnosis and so differed from patients usually included in clinical trials. However, in the case of type II diabetes, it could be difficult to exclude patient with a history of metformin use as it is the first line treatment for this condition. Some clinical trials of metformin in cancer patients, have excluded diabetic patients in order to avoid previous exposure [34,35] however, in our study, the choice of focusing on a diabetic population allowed for a more homogenous cohort.

In addition, focusing on diabetic patients, also allowed to control partly for confounding by indication, as diabetes is associated with both metformin use and cancer outcome [36–38]. Confounding by indication is a frequent bias which occurs when the treatment is preferentially prescribed to a group of patient for a clinical reason and restriction is a method to reduce this bias [39].

Among the strengths of the study, we count the fact that this is the first study of metformin use and survival in gastric adenocarcinoma patients to be conducted at a population level. Only one clinical series study conducted in South Korea has assessed survival in relation to metformin use in gastric cancer patients after gastrectomy [26]. The authors showed that the cumulative use of metformin after gastrectomy in patients with type II diabetes was associated with an improved survival in stage I–III gastric cancer. They showed that for each cumulative 6 month of metformin use, there was a 13% reduction of cancer specific death and in all-cause deaths [26]. However, our study showed contradictory results, despite the similarity in the effect size in the cancer specific analysis. Also, there was no evidence of a dose-response relationship between metformin use and overall or cancer-specific mortality. The reason for these contradictory results may be due to population or tumours profiles differences and the fact that our analysis focused on post-diagnosis drug use and not on post-surgery exposure.

As describe, we used robust methods in this study in order to control for certain biases. We also used data from a nationwide cancer registry allowing for robust verification of cancer cases and deaths. Moreover, in Belgium, health insurance is mandatory; therefore, the information on dispensed drug use is comprehensive and avoids recall bias (without affecting the precision of our study).

So, in conclusion, despite of the fact that many biases were overcome by applying specific methods recommended in pharmacoepidemiological studies, it remains challenging to draw a conclusion about the effect of metformin use on survival of gastric cancer patients with diabetes.

Despite encouraging preclinical studies suggesting an anti-cancer effect for metformin in gastric cancer [21–24], only one previous study has been conducted. Therefore, our findings are important to contribute to the overall evidence base for metformin and gastric cancer progression, especially considering it is the only population-based study conducted. Larger (inter)nation-wide studies however are required to further elucidate the association between metformin use and mortality in gastric cancer patients.

5. Conclusion

In a nationwide study of gastric cancer patients with diabetes, our findings suggest that metformin use might reduce overall mortality, but not gastric cancer mortality. These findings, however need to be confirmed in other populations.

Authorship contributions

- **Conception and design of the study**: Chris R. Cardwell, Olivia Lacroix.
- **Acquisition of data**: Evelien Vaes, Harlinde De Schutter.
- **Analysis and/or interpretation of data**: Olivia Lacroix, Alexandra Couttenier, Evelien Vaes, Harlinde De Schutter, Annie Robert, Chris R. Cardwell.
- **Manuscript preparation**: Olivia Lacroix.
- **Revision of the manuscript**: Olivia Lacroix, Evelien Vaes, Harlinde De Schutter, Chris R. Cardwell, Annie Robert.
- **Final approval of the version to be published**: Olivia Lacroix, Evelien Vaes, Harlinde De Schutter, Chris R. Cardwell, Annie Robert, Alexandra Couttenier.

Conflict of interest

None.

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