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Association of vagus nerve severance and decreased risk of subsequent type 2 diabetes in peptic ulcer patients
An Asian population cohort study

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Abstract

Vagus nerve may play a role in serum glucose modulation. The complicated peptic ulcer patients (with perforation or/and bleeding) who received surgical procedures with or without vagotomy provided 2 patient populations for studying the impact of vagus nerve integrity. We assessed the risk of developing type 2 diabetes in peptic ulcer patients without and with complications by surgical treatment received in a retrospective population study using the National Health Insurance database in Taiwan.

A cohort of 163,385 patients with peptic ulcer and without *Helicobacter pylori* infection in 2000 to 2003 was established. A randomly selected cohort of 163,385 persons without peptic ulcer matched by age, sex, hypertension, hyperlipidemia, Charlson comorbidity index score, and index year was utilized for comparison. The risks of developing diabetes in both cohorts and in the complicated peptic ulcer patients who received truncal vagotomy or simple suture/hemostasis (SSH) were assessed at the end of 2011.

The overall diabetes incidence was higher in patients with peptic ulcer than those without peptic ulcer (15.87 vs 12.60 per 1000 person-years) by an adjusted hazard ratio (aHR) of 1.43 (95% confidence interval [CI] = 1.40–1.47) based on the multivariable Cox proportional hazards regression analysis (competing risk). Comparing ulcer patients with truncal vagotomy and SSH or those without surgical treatment, the aHR was the lowest in the vagotomy group (0.48, 95% CI = 0.41–0.56).

Peptic ulcer patients have an elevated risk of developing type 2 diabetes. Moreover, there were associations of vagus nerve severance and decreased risk of subsequent type 2 diabetes in complicated peptic ulcer patients.

Abbreviations: aHR = adjusted hazard ratio, CCI = Charlson comorbidity index, CI = confidence interval, GLP-1 = glucagon-like peptide-1, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, NHRI = National Health Research Institutes, SHR = subhazard ratio, SSH = simple suture/hemostasis, TVP = truncal vagotomy and pyloroplasty.

Keywords: ghrelin, peptic ulcer, type 2 diabetes, vagus nerve

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1. Introduction

Global incidence and prevalence of type 2 diabetes mellitus have been increasing.[1] Of more than 29.1 million people diagnosed with diabetes in the United States, type 2 diabetes is the most common form.[2] A recent study has estimated that globally there are 382 million diabetic patients with a prevalence of 8.3% in 2013, and type 2 diabetes comprised approximately 90% of the cases; the number of patients may increase to 592 million by 2035.[3] Patients with diabetes are at increased risks of developing complications, particularly cardiovascular diseases. Therefore, reducing the incidence of type 2 diabetes and optimal glucose control are important health priorities.

Diabetes development and management are associated with demographic features and clinical conditions. Diet control, exercise, weight loss, and medications are common approaches to manage the blood sugar level. Metabolic surgery has also attracted greater attention in diabetes control in recent years. Bariatric surgery was reported to reduce the risk of diabetes for obese patients or to improve glucose metabolism,[4,5] thus it accentuates the emerging surgical role for diabetes control. Moreover, vagotomy was reported to reduce the circulating ghrelin level, which modulates insulin secretion and glucose tolerance, implicating that vagus nerve may play a role in glucose homeostasis and type 2 diabetes control.[6,7]

Studies have shown that glucagon-like peptide-1 (GLP-1) secreted from the intestinal L cell after meals is associated with increased glucose-stimulated insulin release which decreases gastric tone and motility. As a result, the serum glucose level is modulated.[8] This mechanism is partly mediated by vagus nerve.[9] It has been reported that vagotomy is associated with suppression of GLP-1 secretion,[10,11] which indicates an impact of vagotomy on GLP-1 secretion.

The complications of exacerbated peptic ulcer include bleeding, perforation, and obstruction. There is a recent trend for surgical option for managing complicated peptic ulcer to shift from conventional vagotomy/drainage/gastrectomy to simple local suture or nonoperative endoscopic/angiographic hemostasis procedure.[12] With the notion that severance of hyperactive vagus nerve may have favorable action on serum glucose modulation and type 2 diabetes development, the present study was undertaken to assess the impact of vagotomy on the risk of developing diabetes in patients with peptic ulcer based on National Health Insurance database in Taiwan.

There were studies suggesting that *Helicobacter pylori* infection in peptic ulcer patients was associated with development of type 2 diabetes.[13–15] Thus, in order to refine the effect of vagus nerve severance, we excluded patients with *H. pylori* infection in the present study. Then, the population of peptic ulcer patients who received truncal vagotomy and pyloroplasty (TVP) was compared with those who received simple suture/hemostasis (SSH) on the risk of developing type 2 diabetes.

2. Methods and study design

2.1. Data source

The Taiwan Bureau of National Health Insurance is a universal single-payer insurance program started in 1995, with coverage of over 99% of population accomplished by 2000 (http://www.nhi. gov.tw). We obtained an inpatient data set, consisting of claims data from 1996 to 2011, from the National Health Research Institutes (NHRI), which has been in charge of managing the insurance data for research. The claims data provide the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) for identifying diseases and treatment procedures. For complying with the Personal Information Protection Act, all identifications of insured people were scrambled and replaced with surrogate numbers for research uses. This study was approved by the Research Ethics Committee at China Medical University and Hospital.

2.2. Study population

From the inpatient claims data, we identified patients hospitalized for peptic ulcer (ICD-9-CM 531–533) in 2000 to 2003 and defined the date 1 year after the hospitalization as the index date for ruling out cause and effect (Fig. 1). After excluding the patients with the history of diabetes (ICD-9-CM 250), cancer (ICD-9-CM 140–208), or *H. pylori* infection (ICD-9-CM 041.86), or received ulcer surgery before the baseline date, or with obesity diagnosis (body mass index >28 kg/m^2) (ICD-9-CM
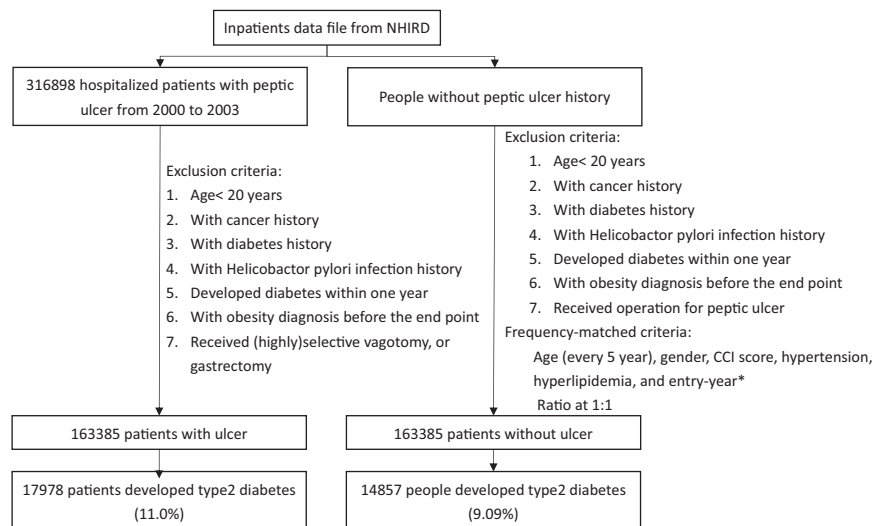

Figure 1. Flowchart for selecting study cohorts.

278.0) before the end point, or with diabetes within 1 year after index date, the remaining peptic ulcer patients were considered in the peptic ulcer cohort. In order to refine the effect of vagus nerve severance, the peptic ulcer patients who had received highly selective vagotomy (ICD-9-operation code 44.02), other selective vagotomy (ICD-9-operation code 44.03), or only gastrectomy (ICD-9-operation code 43.5–43.9) by the baseline date were also excluded from this study. Meanwhile, the peptic ulcer patients with complications (perforation or/and bleeding) but treated by TVP (ICD-9-operation code 44.01 and 44.2), control of hemorrhage and suture of ulcer of stomach or duodenum, that is, SSH (ICD-9-operation code 44.4), were included in this study.

For comparison, we randomly selected a cohort that was frequency matched by sex, age, baseline diagnosis date, hypertension, hyperlipidemia, and Charlson comorbidity index (CCI) score[16] of the ulcer patients in the same dataset from NHRI. Those with the history of ulcer, diabetes or cancer at baseline, and diabetes development within 1 year after the baseline date were excluded from this cohort. All study subjects were followed from the date of entering the study cohort until the date with diabetes diagnosed or censored because of death, or withdrew from the insurance program, or the end of 2011.

2.3. Statistical analysis

We used Kaplan–Meier method to measure the cumulative incidences of developing diabetes in peptic ulcer patients with and without surgery by the end of 2011, and the results were examined by a log-rank test. The age-, gender-, hypertension-, hyperlipidemia-, CCI score-, and follow-up duration–specific incidence rates of diabetes (per 1000 person-years) were then calculated for both cohorts. Interaction effect for diabetes between ulcer and ulcer-associated risk factor was estimated using the multivariable Cox proportional hazard model. The risk for diabetes in peptic ulcer patients was evaluated by treatment procedures using truncal vagotomy, control of hemorrhage and suture of ulcer of stomach or duodenum, and without surgery. We used the multivariable Cox proportional hazards regression analysis to obtain the adjusted hazard ratio (aHR) of diabetes with corresponding 95% confidence intervals (CIs). The Cox method was also used to assess aHR of diabetes by the peptic ulcer treatment. We used peptic ulcer patients without any surgery as the reference to estimate the diabetes hazards for patients with other 2 treatment procedures. Because the mortality in the peptic ulcer cohort was higher than that of the comparison cohort (17.3% vs 10.9%), we also considered competing risks and used Cox proportional hazards regression to assess the subhazard ratio (SHR) of diabetes based on Fine and Gray model. All analyses were performed using the SAS software version 9.3 (SAS Institute, Cary, NC), with a P value less than 0.05 in 2-sided test considered to be significant.

3. Results

The ulcer cohort consisted of 163,385 patients, and the comparison cohort also consisted of 163,385 persons in this study (Table 1). There were same proportions of age group, gender, CCI score level, hypertension, and hyperlipidemia between 2 cohorts. In ulcer cohort, there were more males than females (66.3% vs 33.7%); whereas there were 5.34% patients with CCI score ≥3, 20.1% with hypertension, and 4.96% with hyperlipidemia.

Table 1

Demographic status, comorbidity, and CCI score of study cohorts.

	Peptic ulcer (N = 163,385)		Comparison (N = 163,385)	
	N	%	N	%
Gender				
Women	55,047	33.7	55,047	33.7
Men	108,338	66.3	108,338	66.3
Age, y				
20–44	54,742	33.5	54,742	33.5
45–64	52,402	32.1	52,402	32.1
65+	56,241	34.4	56,241	34.4
Mean (SD)	54.8	(18.3)	54.8	(18.3)
CCI score				
0	115,333	70.6	115,333	70.6
1	28,964	17.7	28,964	17.7
2	10,362	6.34	10,362	6.34
3+	8726	5.34	8726	5.34
Hypertension	32,898	20.1	32,898	20.1
Hyperlipidemia	8104	4.96	8104	4.96

CCI score = Charlson comorbidity index score, SD = standard deviation.

As shown in Fig. 2 that peptic ulcer patients without any surgery in the 12-year follow-up experienced the highest cumulative incidence of type 2 diabetes, followed by patients received SSH, and then comparison cohort. Those patients who received TVP were with the lowest cumulative incidence among all patients in comparison.

The overall incidence of type 2 diabetes was 1.26-fold higher in peptic ulcer patients than in the comparison cohort (15.87 vs 12.60 per 1000 person-years). After considering the competing risk (death), the peptic ulcer patients had an SHR of 1.43 (95% CI = 1.40–1.47) for type 2 diabetes in comparison to the cohort without peptic ulcer. The observed diabetes incidence in this study was slightly higher in female than in male, was noticeable higher in hypertension and hyperlipidemia patients, increased with age and CCI score, and decreased with follow-up years in both cohorts. No matter under which condition, ulcer patients
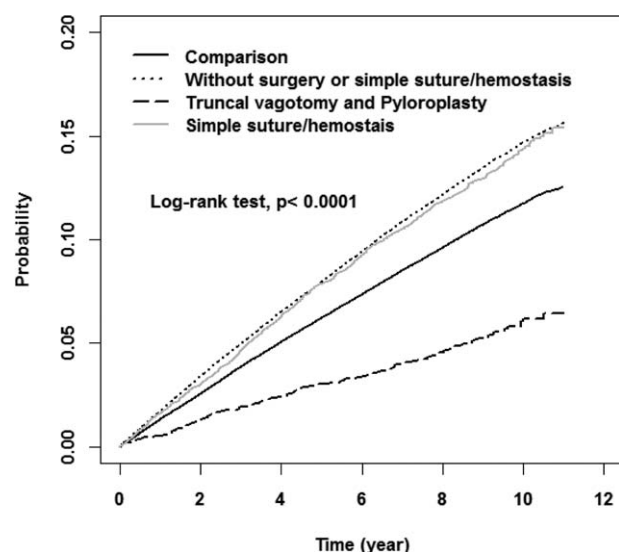
Figure 2. Kaplan–Meier analysis measured cumulative incidence of type 2 diabetes for comparison cohort and peptic ulcer cohort by treatment.

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Table 2

Incidence and Cox proportional hazards regression method estimated hazard ratio of type 2 diabetes mellitus by sex, age, hypertension, hyperlipidemia, CCI score, and follow-up.

	Peptic ulcer		Comparison			
	Case	IR	Case	IR	HR (95% CI)[*]	SHR (95% CI)[†]
Overall	17,978	15.87	14,857	12.60	1.26 (1.24–1.29)[‡]	1.43 (1.40–1.47)[‡]
Gender[§]						
Women	6482	16.65	5059	12.58	1.33 (1.28–1.38)[‡]	1.61 (1.55–1.67)[‡]
Men	11,496	15.47	9798	12.61	1.23 (1.20–1.26)[‡]	1.36 (1.33–1.40)[‡]
Age, y[§]						
20–45	4009	9.13	2795	6.18	1.49 (1.42–1.57)[‡]	1.36 (1.30–1.43)[‡]
45–64	7530	19.61	6569	16.36	1.20 (1.16–1.24)[‡]	1.22 (1.18–1.26)[‡]
65+	6439	20.80	5493	16.88	1.23 (1.19–1.27)[‡]	1.32 (1.27–1.37)[‡]
CCI score[§]						
0	12,381	14.18	10,383	11.64	1.22 (1.19–1.25)[‡]	1.39 (1.35–1.42)[‡]
1	3550	21.03	2800	15.00	1.39 (1.32–1.46)[‡]	1.54 (1.46–1.62)[‡]
2	1175	21.99	919	16.46	1.33 (1.22–1.45)[‡]	1.44 (1.32–1.58)[‡]
3+	872	23.50	755	16.88	1.37 (1.25–1.51)[‡]	1.43 (1.30–1.58)[‡]
Hypertension						
No	13,056	13.81	10,870	11.03	1.26 (1.23–1.29)[‡]	1.41 (1.37–1.45)[‡]
Yes	4922	26.31	3987	20.55	1.28 (1.23–1.34)[‡]	1.52 (1.45–1.58)[‡]
Hyperlipidemia[§]						
No	16,422	15.21	13,786	12.26	1.24 (1.22–1.27)[‡]	1.41 (1.38–1.45)[‡]
Yes	1556	29.45	1071	19.52	1.51 (1.39–1.63)[‡]	1.75 (1.62–1.90)[‡]
Follow-up years						
<1	2687	17.09	2103	13.24	1.29 (1.22–1.37)[‡]	1.48 (1.39–1.56)[‡]
1–3	4688	16.44	3826	12.36	1.36 (1.30–1.42)[‡]	1.58 (1.51–1.65)[‡]
4–5	4052	15.11	3296	10.10	1.49 (1.42–1.56)[‡]	1.83 (1.75–1.92)[‡]
>5	6551	15.03	5632	9.70	1.62 (1.56–1.68)[‡]	1.89 (1.82–1.95)[‡]

CCI score = Charlson comorbidity index score, CI = confidence interval, HR = hazard ratio, IR = incidence rate, SHR = subhazard ratio.

[*] Manually adjusted for age, gender, hypertension, hyperlipidemia, and CCI score in Cox proportional hazard regression.

[†] Manually adjusted for age, gender, hypertension, hyperlipidemia, and CCI score in Cox proportional hazard regression with competing risk (death).

[‡] $P < 0.001$.

[§] Interaction $P < 0.05$. Cox proportional assumption treat in model 1, $P = 0.03$.

had a significantly higher diabetes risk than comparisons (Table 2).

Table 3 presents the risks of type 2 diabetes in the comparison cohort and peptic ulcer patients by different medical treatments. Peptic ulcer patients without surgical treatment had the highest diabetes incidence (16.1 per 1000 person-years), with an adjusted HR of 1.28 (95% CI = 1.25–1.31) or SHR of 1.46 (95% CI = 1.43–1.49) relative to the comparison cohort. The incidence declined in patients with the drastic procedure to 6.02 per 1000 person-years for the subgroup receiving TVP with an adjusted HR of 0.56 (95% CI = 0.48–0.65) and SHR of 0.48 (95% CI = 0.41–0.56), compared to patients without any surgery.

There were similar results when we excluded patients with diabetes diagnosis within 6 months and 2 years after peptic ulcer (data not shown).

4. Discussion

In the current series, the complicated peptic ulcer patients (perforation or/and bleeding) who received surgical procedures with or without vagotomy provided 2 patient populations for studying the impact of maintaining the integrity of vagus nerve on subsequent development type 2 diabetes. After excluding peptic ulcer patients with *H. pylori* infection, our result showed that severance of vagus nerve (i.e., vagotomy) might play a role in the remission of subsequent type 2 diabetes.

Diabetes has been considered as an independent risk factor of peptic ulcer[17] and related mortality.[18] Results from the present study showed that patients with peptic ulcer were at 1.43-fold increased hazard for type 2 diabetes, comparing to the general population. In the current series, the risk of developing diabetes

Table 3

Multivariable Cox method measured hazard ratio of diabetes in comparison cohort and peptic ulcer patients by treatment methods.

Surgery	N	Case	IR	HR (95% CI)[*]		SHR (95% CI)[†]	
Comparison	163,385	14,857	12.60	1.00		1.00	
Peptic ulcer management							
Without surgery or SSH	150,344	16,758	16.14	1.28 (1.25–1.31)[‡]	1.00	1.46 (1.43–1.49)[‡]	1.00
TVP	3327	162	6.02	0.56 (0.48–0.65)[‡]	0.44 (0.38–1.51)[‡]	0.65 (0.56–0.76)[‡]	0.48 (0.41–0.56)[‡]
SSH	9714	1058	15.66	1.22 (1.14–1.29)[‡]	0.96 (0.90–1.02)	1.33 (1.25–1.42)[‡]	0.98 (0.92–1.04)

CI = confidence interval, HR = hazard ratio, IR = incidence rate, SHR = subhazard ratio, SSH = simple suture/hemostasis, TVP = truncal vagotomy and pyloroplasty.

[*] Adjusted for age, gender, hypertension, hyperlipidemia, and CCI score in Cox proportional hazard regression.

[†] Adjusted for age, gender, hypertension, hyperlipidemia, and CCI score in Cox proportional hazard regression with competing risk (death). CCI score, Charlson comorbidity index score.

[‡] $P < 0.001$.

among peptic ulcer patients varied by the treatment methods for the disease: a much greater protective effect for patients with TVP than for those with SSH (i.e., with integral vagus nerve). The hazard of diabetes was reduced by 56% for those who had a TVP (Table 3). No study has been conducted to investigate the mechanism of how surgery is reducing the diabetes risk in patients with peptic ulcer. From this study, we thought that this is likely to be associated with the ghrelin produced from the stomach submucosa, which is blocked following vagotomy for peptic ulcer.[7]

Ghrelin, a gut brain peptide with 28 amino acids, plays a critical role in the development of type 2 diabetes.[7] Ghrelin regulates appetite, glucose metabolism, adipogenic effects, and energy balance.[19,20] The plasma ghrelin level is elevated in patients with peptic ulcer,[21] including both acylated ghrelin and unacylated ghrelin.[7] Both vagal stimulation and fat ingestion may influence the release of ghrelin through vagus nerve.[22–25] Truncal vagotomy may block the synthesis of ghrelin and the neuroprotective function of ghrelin,[26–31] impairing the ghrelin's signals for starvation to the brain.[6] Reduction in circulating ghrelin level alters the diet-intake habit and decreases the risk of developing diabetes, and yet, not for those with SSH.

In addition, when truncal vagotomy affects the secretion of incretin hormone, such as GLP-1, a neuropeptide is secreted mainly from intestinal L cells after meals.[8] GLP-1 increases glucose-stimulated insulin and decreases gastric tone and motility, resulting in delayed carbohydrate absorption and contribute to a satiating effect.[32] GLP-1 may interact with ghrelin and leptin to inhibit feeding behavior and glucose metabolism, regulating the glucose homeostasis through vagal afferent neuron signaling.[33] Furthermore, the hepatic branch of vagus nerve plays a role in GLP-1 secretion,[34] severance of hepatic branch after truncal vagotomy blocks the afferent vagus signal from duodenum and consequently results in suppressed GLP-1-releasing capacity.[34,35] However, it has been reported that the GLP-1-releasing capacity persists no longer than 8 weeks after vagotomy,[36] indicating a short-term rather than a long-term impact of vagotomy on GLP-1 releasing capacity. The intermingled relation among ghrelin, GLP-1, and vagal tone is a complex one demanding further investigation.[37–39]

The vagus nerve is well recognized to associate with the pancreas' endocrine and exocrine function and regulated insulin secretion,[40] while the peptic ulcer could be considered as a physiological status of persistent vagal hyperactivity with systemic inflammation. It has been reported that stress and inflammatory process is a major cause of pancreatic cell death in type 2 diabetes,[41] whereas the oxidative stress and endoplasmic reticulum stress play significant roles in beta-cell insulin synthesis dysfunction and type 2 diabetes.[42,43] Therefore, alleviation of vagal hyperactivity in TVP patients might be related to the reduced inflammation process and endoplasmic reticulum stress in beta cell, which resulted in decreased type 2 diabetes incidences. However, further studies will be needed.

The effectiveness of truncal vagotomy for serum glucose modulation may be similar to the implantation and placement of a vagal blocking device to improve glycemic control in obese patients.[44] In an open-labeled human study for 28 obese patients, the intermittent biphasic pulse is laparoscopically implanted to block vagalneural impulse.[44] The results show meaningful weight loss as well as early and sustained Hemoglobin (Hb)A1c improvement in patients, indicating that there were close associations between vagus nerve block and serum glucose modulation.

Furthermore, the advances in management and eradication of *H. pylori* infection as well as the use of proton pump inhibitors for pharmacologic control of peptic ulcer have shifted the treatment from acid-reducing vagotomy to simple suture/hemostasis procedure in complicated peptic ulcer.[12] Yet, a recent study reported that vagotomy/drainage is superior to local oversaw in bleeding peptic ulcers that need emergency operation.[45] To the best of our knowledge, there were no similar studies focusing on a long-term effect of treatment in complicated peptic ulcer. In the present study, patients receiving acid-reducing vagotomy were associated with marked lower risk of developing type 2 diabetes when compared with those receiving SSH (Table 3). Our results showed that there might be a role for vagus nerve in the management of type 2 diabetes, as well as reappraisal for current surgical treatment in complicated peptic ulcer. However, further studies are warranted.

4.1. Limitation of the study

With reliable diagnosis and high follow-up rate, our study is strengthened with a large population with available data for longitudinal assessment and subgroup analysis of diabetes risk in patients with complicated peptic ulcer who underwent different treatment modalities. However, certain limitations are noted. First, variables including lifestyles with respect to drinking, smoking, diet, socioeconomic status, and genetic factors were not available for adjustment of the risk in developing type 2 diabetes. Second, there is lack of information for the use of aspirin, which is an important factor associated with both gastric ulcer and metabolism. Third, since all data used were anonymous, relevant clinical variables, such as pathology findings, imaging results, laboratory data, extent of glycemic control, and serum ghrelin/GLP-1 data after surgery, as well as body mass index and HbA1c were all not available. Fourth, biases inherent to retrospective studies should be noted. However, since the study cohorts were well matched by sex, age, and CCI scores, the biases are likely to be minimal. Furthermore, our data analysis has considered the competing risk to minimize bias related to death.

Another limitation in this study is that we have excluded the patients with body mass index >28 kg/m^2, patients received vagotomy with gastrectomy and patients received highly selective vagotomy. Therefore, the results in this study may not apply to those patients.

5. Conclusion

In this long-term cohort study for the management of peptic ulcer, the peptic ulcer patients were shown to have an elevated risk of developing type 2 diabetes. Furthermore, our study has revealed that there were associations between vagus nerve severance and decreased risk of subsequent type 2 diabetes in complicated peptic ulcer patients.

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