

Original Article



Analysis of the Occurrence of Diseases Following Gastrectomy for Early Gastric Cancer: a Nationwide Claims Study

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ABSTRACT

Purpose: Various changes in nutrition, metabolism, immunity, and psychological status occur through multiple mechanisms after gastrectomy. The purpose of this study was to predict disease status after gastrectomy by analyzing diseases pattern that occur or change after gastrectomy.

Materials and Methods: A retrospective cohort study was conducted using nationwide claims data. Patients with gastric cancer who underwent gastrectomy or endoscopic resection were included in the study. Eighteen target diseases were selected and categorized based on their underlying mechanism. The incidence of each target disease was compared by dividing the study sample into those who underwent gastrectomy (cases) and those who underwent endoscopic resection for early gastric cancer (controls). The cases were matched with controls using propensity score matching. Thereafter, Cox proportional hazard models were used to evaluate intergroup differences in disease incidence after gastrectomy.

Results: A total of 97,634 patients who underwent gastrectomy (84,830) or endoscopic resection (12,804) were included. The incidence of cholecystitis ($P<0.0001$), pancreatitis ($P=0.034$), acute kidney injury ($P=0.0083$), anemia ($P<0.0001$), and inguinal hernia ($P=0.0007$) were higher after gastrectomy, while incidence of dyslipidemia ($P<0.0001$), vascular diseases (ischemic heart disease, stroke, and atherosclerosis; $P<0.0001$, $P<0.0001$, and $P=0.0005$), and Parkinson's disease ($P=0.0093$) were lower after gastrectomy.

Conclusions: This study identifies diseases that may occur after gastrectomy in patients with gastric cancer.

Keywords: Gastrectomy; Stomach neoplasms; Big data; Incidence

INTRODUCTION

In 2014, the incidence of gastric cancer decreased to 35.8 per 100,000 people. However, an increase in its incidence has been observed since 2016, with the incidence of early gastric cancer (EGC) reaching approximately 76% in Korea [1]. The treatment of gastric cancer depends on the stage of the disease, and its fundamental treatment is gastrectomy.

Cancer Association. The sponsor of the study was not involved in the study design, analysis, and interpretation of data, writing of the report, or the decision to submit the study results for publication.

Author Contributions

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

The extent of gastrectomy is determined by the location, size, gross type, and stage of the tumor, and includes distal, proximal, total, and function-preserving gastrectomy [2]. Although there are some differences in results depending on the extent of resection, various changes in nutrition, metabolism, immunity, and psychological status of the patient occur through several mechanisms, such as changes in dietary habits, disorders in digestive function, changes in hormones, and changes in the anatomical structure after gastrectomy [3,4]. These changes are related to the occurrence, exacerbation, prevention, and improvement of various diseases. A recent study reported that the incidence of cardiovascular disease decreased after gastrectomy [5]. The study suggested that the risk of cardiovascular disease can be lowered due to positive effects, such as weight loss and decreased insulin resistance due to changes in nutritional intake after gastrectomy, and further showed the possibility of onco-metabolic surgery. Indeed, bariatric surgery can achieve these results and it is widely performed [6]. However, similar studies have reported that the incidence of osteoporosis, gall bladder stones, and pulmonary tuberculosis increases after gastrectomy [7-9].

Therefore, a well-planned study evaluating various diseases that may occur after gastrectomy is necessary to decrease cancer-unrelated deaths and improve the quality of life of survivors after gastrectomy. In this study, the occurrence, exacerbation, prevention, and improvement of 18 diseases that can occur after gastrectomy were analyzed using nationwide claims data.

MATERIALS AND METHODS

Study population

Data on disease incidence following gastrectomy were obtained from the National Health Insurance Services (NHIS) between 2002 and 2017. Inpatient and outpatient data of all populations was identified using the NHIS database owing to the single-payer healthcare insurance system in Korea. Cohorts were identified by the International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) codes and pharmaceutical codes, along with procedure or operation codes. The gastrectomy group (case) included individuals diagnosed with the ICD-10 code C16 who had undergone procedural codes of gastrectomy, including subtotal or total gastrectomy, regardless of procedural codes of endoscopic resection (ER). The exclusion criteria included the following: other malignancies (ICD-10 codes C00–97, except C16), patients who received any systemic or radiation treatment, or recurrent gastric cancer. Recurrent stomach cancer was defined as patients who underwent total gastrectomy at least one year after subtotal gastrectomy or received additional systemic or radiation therapy at least one year after gastrectomy. The majority of the patients included were diagnosed with EGC. Lastly, patients suffering from a target disease or exposed to well-known risk factors for the target disease were excluded to reduce external effect bias. The control group included patients undergoing ER for gastric cancer to compensate for

Table 1. Definition and codes of each disease

Disease	Variables	Definition	ICD-10 codes	Procedure or operation (procedural codes)	Medication (pharmaceutical codes)
Gastrectomy (Case)	Inclusion	Diagnosis and procedure	C16	Gastrectomy	
	Exclusion	Diagnosis or medication	C00-97, except C16		Platinum, fluorouracil, Tecan, taxel, Herceptin, nivolumab, ramucirumab
EMR/ESD (Control)	Inclusion	Diagnosis and procedure	C16	EMR/ESD	
	Exclusion	Diagnosis or procedure or medication	C00-97, except C16	Gastrectomy	Platinum, fluorouracil, Tecan, taxel, Herceptin, nivolumab, ramucirumab

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Post-gastrectomy Disease Occurrence

Table 1. (Continued) Definition and codes of each disease

Disease	Variables	Definition	ICD-10 codes	Procedure or operation (procedural codes)	Medication (pharmaceutical codes)
Digestive disease					
Cholecystitis	Inclusion	Diagnosis and procedure	K80-83	Cholecystectomy, cholecystostomy	
	Additional matching				
	Date of disease occurrence	Procedure day			
Pancreatitis	Inclusion	Diagnosis and medication	K85, K86	Pancreatectomy, pancreatic surgery, pancreas transplantation	Pancreatin, Biodiastase, Simethicone, mesilate, ulinastatin
	Additional matching	Diagnosis or procedure	E08-11, E13		
	Date of disease occurrence	Administration of first medication			
	Washout period	1 month (post-operative complication)			
Metabolic disease					
Osteoporosis	Inclusion	Diagnosis and medication	M80-82		SERM, Bisphosphonate, STEAR, Calcitonin, Vitamin D
	Additional matching	Diagnosis or medication	E05, E21, N95, Z79		
	Date of disease occurrence	Administration of first medication			
	Washout period	3 months (metabolic change after gastrectomy)			
Type 2 diabetes mellitus	Inclusion	Diagnosis	E11		
	Additional matching	Diagnosis	I10, I15, I20-25, I63, E78		
	Date of disease occurrence	Diagnosis day			
	Washout period	3 months (metabolic change after gastrectomy)			
Acute kidney injury	Inclusion	Diagnosis and procedure (duration less than 3 months)	N17	Hemodialysis, peritoneal dialysis	
	Additional matching	Diagnosis	E08-11, E13, I10, I15		
	Date of disease occurrence	Administration of first dialysis			
	Washout period	3 months (metabolic change after gastrectomy)			
Dyslipidemia	Inclusion	Diagnosis and medication	E78		Acipimox, statin, cholestyramine, evolocumab, ezetimibe, fenofibrate, omega-3-acid, irbesartan
	Additional matching				
	Date of disease occurrence	Administration of first medication			
	Washout period	3 months (metabolic change after gastrectomy)			
Anemia (iron deficiency)	Inclusion	Diagnosis and medication	D50		Iron, ferric hydroxide, ferrous sulfate
	Additional matching				
	Date of disease occurrence	Administration of first medication			
	Washout period	3 months (metabolic change after gastrectomy)			
Anemia (vitamin B12 deficiency)	Inclusion	Diagnosis and medication	D51		Cobamide, cyanocobalamin
	Additional matching				
	Date of disease occurrence	Administration of first medication			
	Washout period	3 months (metabolic change after gastrectomy)			

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Post-gastrectomy Disease Occurrence

Table 1. (Continued) Definition and codes of each disease

Disease	Variables	Definition	ICD-10 codes	Procedure or operation (procedural codes)	Medication (pharmaceutical codes)
Vascular disease					
Ischemic heart disease	Inclusion	Diagnosis	I20-25		
	Additional matching	Diagnosis	I10, I15, E08-11, E13, E78		
	Date of disease occurrence	Diagnosis day			
	Washout period	3 months (metabolic change after gastrectomy)			
Stroke	Inclusion	Diagnosis	I63		
	Additional matching	Diagnosis	I10, I15, E08-11, E13, E78		
	Date of disease occurrence	Diagnosis day			
	Washout period	3 months (metabolic change after gastrectomy)			
Atherosclerosis	Inclusion	Diagnosis	I70		
	Additional matching	Diagnosis	I10, I15, E08-11, E13, E78		
	Date of disease occurrence	Diagnosis day			
	Washout period	3 months (metabolic change after gastrectomy)			
Infectious disease					
Infectious gastroenteritis	Inclusion	Diagnosis	A04, A05, A08, A09, K52		
	Additional matching	Diagnosis or procedure or medication	B20, Z94	Transplantation (liver, kidney, pancreas, heart, lung, small intestine, bone marrow)	Immunoglobulin, immunosuppressant, steroid
	Date of disease occurrence	Diagnosis day			
	Washout period	3 months (immunologic change after gastrectomy)			
Tuberculosis	Inclusion	Diagnosis	A15, A17-19		
	Additional matching	Diagnosis or procedure or medication	B20, E08-11, E13, N18, Z94	Transplantation (liver, kidney, pancreas, heart, lung, small intestine, bone marrow)	Immunoglobulin, immunosuppressant, steroid
	Date of disease occurrence	Diagnosis day			
	Washout period	3 months (immunologic change after gastrectomy)			
Syphilis	Inclusion	Diagnosis	A51-53		
	Additional matching	Diagnosis or procedure or medication	B20, Z94	Transplantation (liver, kidney, pancreas, heart, lung, small intestine, bone marrow)	Immunoglobulin, immunosuppressant, steroid
	Date of disease occurrence	Diagnosis day			
	Washout period	3 months (immunologic change after gastrectomy)			
Pneumonia	Inclusion	Diagnosis	J13-18, J20-22		
	Additional matching	Diagnosis or procedure or medication	B20, Z94	Transplantation (liver, kidney, pancreas, heart, lung, small intestine, bone marrow)	Immunoglobulin, immunosuppressant, steroid
	Date of disease occurrence	Diagnosis day			
	Washout period	3 months (immunologic change after gastrectomy)			

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Table 1. (Continued) Definition and codes of each disease

Disease	Variables	Definition	ICD-10 codes	Procedure or operation (procedural codes)	Medication (pharmaceutical codes)
Other diseases					
Inguinal hernia	Inclusion	Diagnosis and procedure	K40	Herniorrhaphy	
	Additional matching				
	Date of disease occurrence	Procedure day			
	Washout period	3 months (metabolic change after gastrectomy)			
Parkinson's disease	Inclusion	Diagnosis	G20		
	Additional matching	Diagnosis	I10, I15, I63, I70, E08-11, E13, E78		
	Date of disease occurrence	Diagnosis day			
	Washout period	3 months (metabolic change after gastrectomy)			
Dementia	Inclusion	Diagnosis	F01-03, G30		
	Additional matching	Diagnosis	I10, I15, I63, I70, E08-11, E13, E78		
	Date of disease occurrence	Diagnosis day			
	Washout period	3 months (metabolic change after gastrectomy)			

ICD-10 = International Classification of Disease, Tenth Revision; EMR = endoscopic mucosal resection; ESD = endoscopic submucosal dissection.

the effects of gastric cancer itself. The ER group (control) was similar to the gastrectomy group; however, only patients who underwent ER were included, while those who underwent additional gastrectomy were excluded (**Table 1**). The study was reviewed by the Institutional Review Board of the Gachon University Gil Medical Center and ethics approval was waived in compliance with governmental laws and regulations (protocol GFIRB2019-167), as well as informed consent since we only accessed de-identified data.

Matching and washout period

The following data were matched between the cohorts using the propensity score: year of treatment, sex, age, Charlson comorbidity index (CCI), residential area, and type of health coverage divided into two categories, health insurance and medical aid beneficiary, based on income level. Additionally, the well-known risk factors for each target disease were matched. Regarding the time required for changes in nutrition, metabolism, immunity, or psychological status following gastrectomy, a washout period was established for each disease, and events that occurred after that period were defined as disease occurrence. The washout periods were set to one month or three months based on the postoperative short-term complication period and rapid weight-loss period (**Table 1**) [10].

Target diseases

Each disease was categorized into one of five groups: digestive, metabolic, vascular, infectious, or other diseases. Digestive diseases included cholecystitis and pancreatitis; metabolic diseases included osteoporosis, type 2 diabetes mellitus (T2DM), acute kidney injury (AKI), dyslipidemia, iron deficiency anemia (IDA), and vitamin B12 deficiency anemia (VBDA); vascular diseases included ischemic heart disease (IHD), stroke, and atherosclerosis; and infectious diseases included infectious gastroenteritis, tuberculosis, syphilis, and pneumonia. Other target diseases included inguinal hernia, Parkinson's disease, and dementia (**Supplementary Fig. 1**). We selected diseases that are easy to define, collect, and not likely to have a significant bias in the HIRA database among various diseases

known to change after gastrectomy or that may have a change in incidence. To evaluate the appropriateness of the model, diseases that are known to increase after gastrectomy, such as cholecystitis, were included.

Statistical analyses

After propensity score matching was performed, cumulative incidence using the Cox proportional hazard model was used to compensate for the difference between groups and to compare the incidence of diseases after gastric cancer surgery. The multivariate Cox model used variables showing significant differences that persisted even after propensity score matching for covariates. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) software. Drs. JHJ and HSS had full access to all study data and were responsible for data integrity and accuracy of data analysis.

RESULTS

A total of 97,634 patients who underwent gastrectomy (84,830) or ER (12,804) were included (**Supplementary Fig. 2**). **Supplementary Tables 1-18** show the baseline characteristics and Cox regression analysis for each disease. **Fig. 1** shows the forest plots of the adjusted hazard ratios (HRs) obtained from Cox regression analyses of each target disease.

Digestive diseases

In the multivariate Cox regression analysis, gastrectomy was an independent risk factor for cholecystitis (HR, 1.696; 95% confidence interval [CI], 1.291–2.228; P=0.0001) with a higher

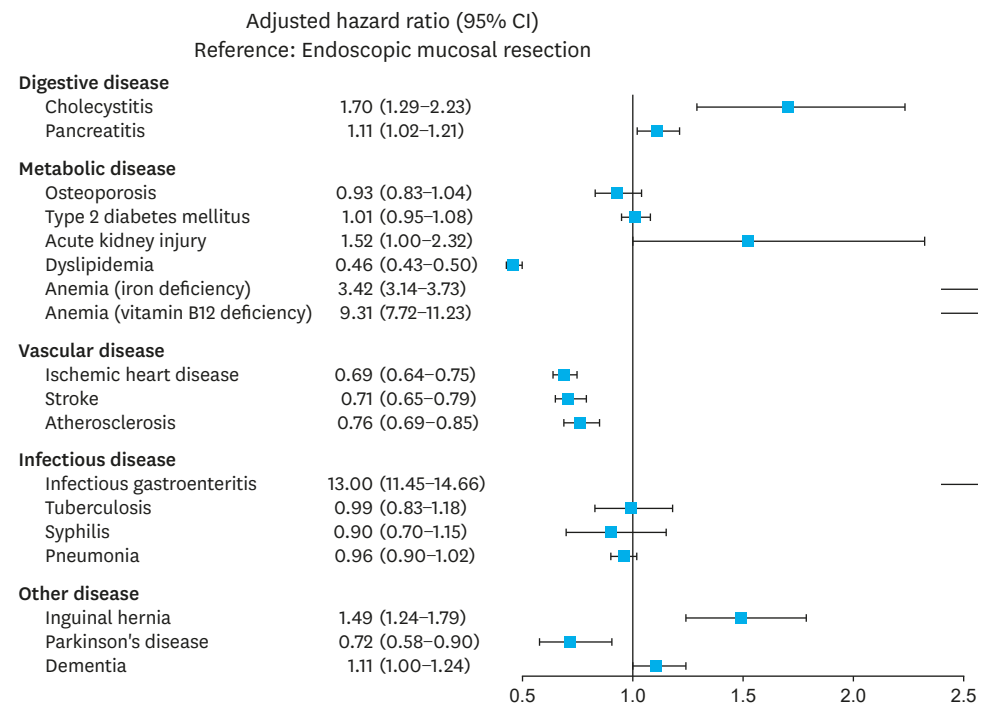


Fig. 1. Forest plot of the adjusted hazard ratio of each target disease. 95% CI = 95% confidence interval.

Post-gastrectomy Disease Occurrence

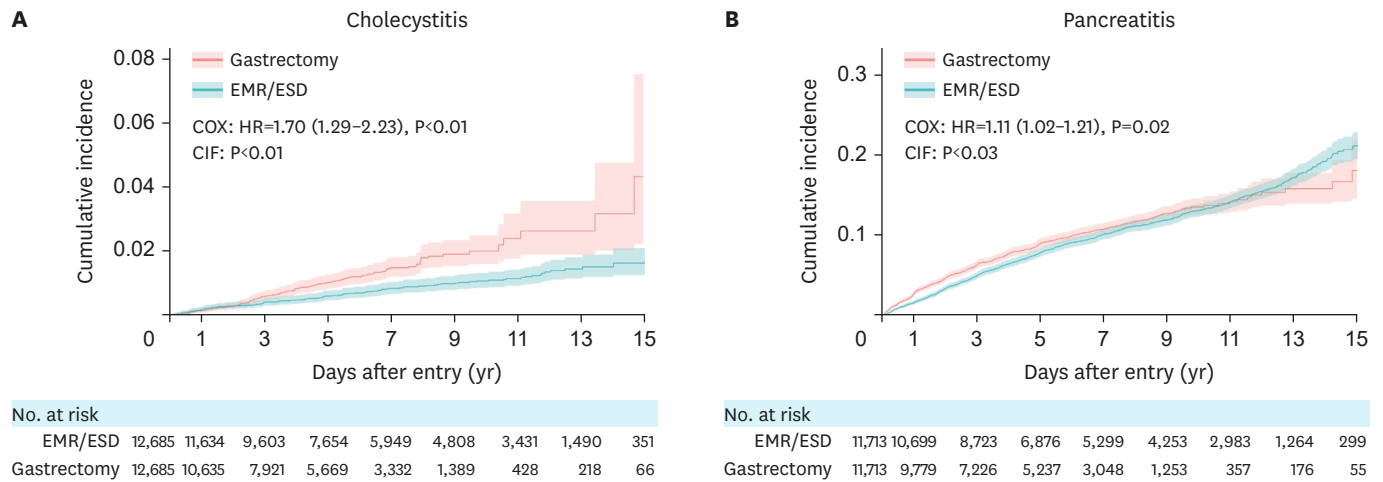


Fig. 2. Cumulative incidence function based on the treatment modality in the category of digestive diseases. (A) Cholecystectomy and (B) Pancreatitis. EMR = endoscopic mucosal resection; ESD = endoscopic submucosal dissection; CIF = cumulative incidence function.

CCI compared to the other diseases. As a result of the cumulative incidence function (CIF), the occurrence of cholecystitis was significantly higher following gastrectomy than that after ER ($P<0.0001$; **Fig. 2A**). Gastrectomy was an independent risk factor for pancreatitis, along with a higher CCI and medical aid beneficiary compared to the other diseases (HR, 1.109; 95% CI, 1.015–1.213; $P=0.0228$), suggesting that the occurrence of pancreatitis was significantly higher following gastrectomy ($P=0.034$; **Fig. 2B**; **Supplementary Tables 1 and 2**).

Metabolic diseases

Gastrectomy was not an independent risk or protective factor for osteoporosis or T2DM in the multivariate analysis. The risk factors for osteoporosis included female sex, older age, and higher CCI, whereas male sex, older age, higher CCI, and being a medical aid beneficiary were risk factors for T2DM. No significant difference was observed between gastrectomy and ER in CIF for osteoporosis and T2DM ($P=0.8026$, $P=0.3117$, respectively; **Fig. 3A and B**). Along with older age and higher CCI, gastrectomy was an independent risk factor (HR, 1.524; 95% CI, 1.004–2.315; $P=0.0481$) for AKI with dialysis, which was more frequently observed after gastrectomy ($P=0.0083$; **Fig. 3C**). In contrast, gastrectomy was an independent protective factor for dyslipidemia (HR, 0.461; 95% CI, 0.426–0.499; $P<0.0001$), along with male sex, younger age, and lower CCI, and occurred more frequently following ER than that after gastrectomy ($P<0.0001$; **Fig. 3D**). Gastrectomy was an independent risk factor for anemia, along with higher CCI and both IDA and VBDA (HR, 3.418; 95% CI, 3.135–3.726; $P<0.0001$; and HR, 9.313; 95% CI, 7.722–11.232; $P<0.0001$, respectively). A higher occurrence of both IDA and VBDA was observed following gastrectomy in terms of CIF ($P<0.0001$ and $P<0.0001$, respectively; **Fig. 3E and F**; **Supplementary Tables 3–8**).

Vascular diseases

All three types of vascular diseases showed similar results, while gastrectomy was an independent protective factor for IHD, stroke, and atherosclerosis (HR, 0.692; 95% CI, 0.641–0.746; $P<0.0001$; HR, 0.713; 95% CI, 0.647–0.785; $P<0.0001$; and HR, 0.763; 95% CI, 0.688–0.847; $P<0.0001$, respectively), along with female sex, younger age, lower CCI, and health insurance. All vascular diseases occurred more frequently following ER in CIF ($P<0.0001$, $P<0.0001$, $P=0.0005$, respectively; **Fig. 4A, B, and C**; **Supplementary Tables 9–11**).

Post-gastrectomy Disease Occurrence

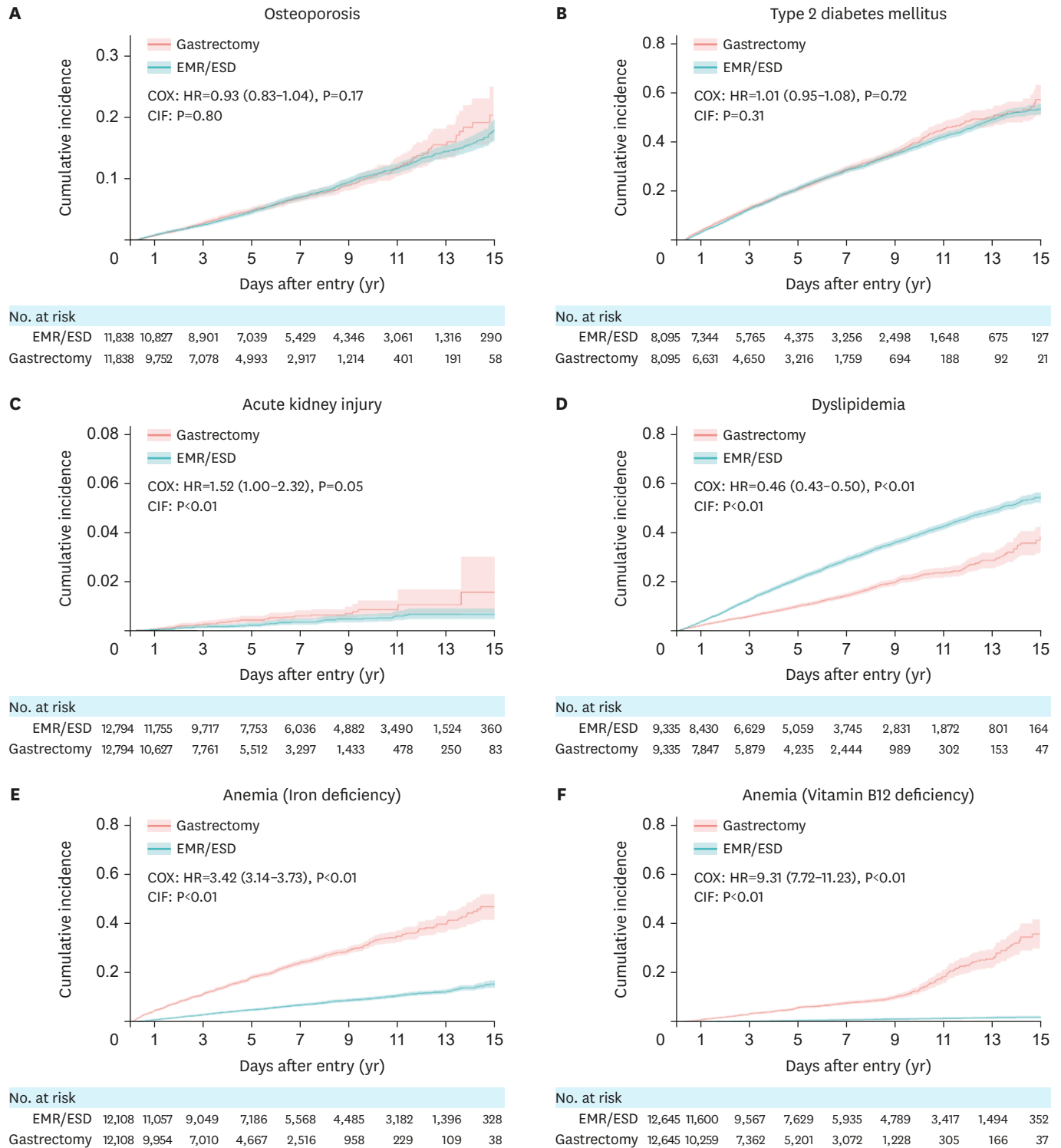


Fig. 3. Cumulative incidence function based on the treatment modality in the category of metabolic diseases. (A) Osteoporosis, (B) Type 2 diabetes mellitus, (C) Acute kidney injury, (D) Dyslipidemia, (E) Iron deficiency anemia, and (F) Vitamin B12 deficiency anemia. EMR = endoscopic mucosal resection; ESD = endoscopic submucosal dissection; CIF = cumulative incidence function; HR = hazard ratio.

Post-gastrectomy Disease Occurrence

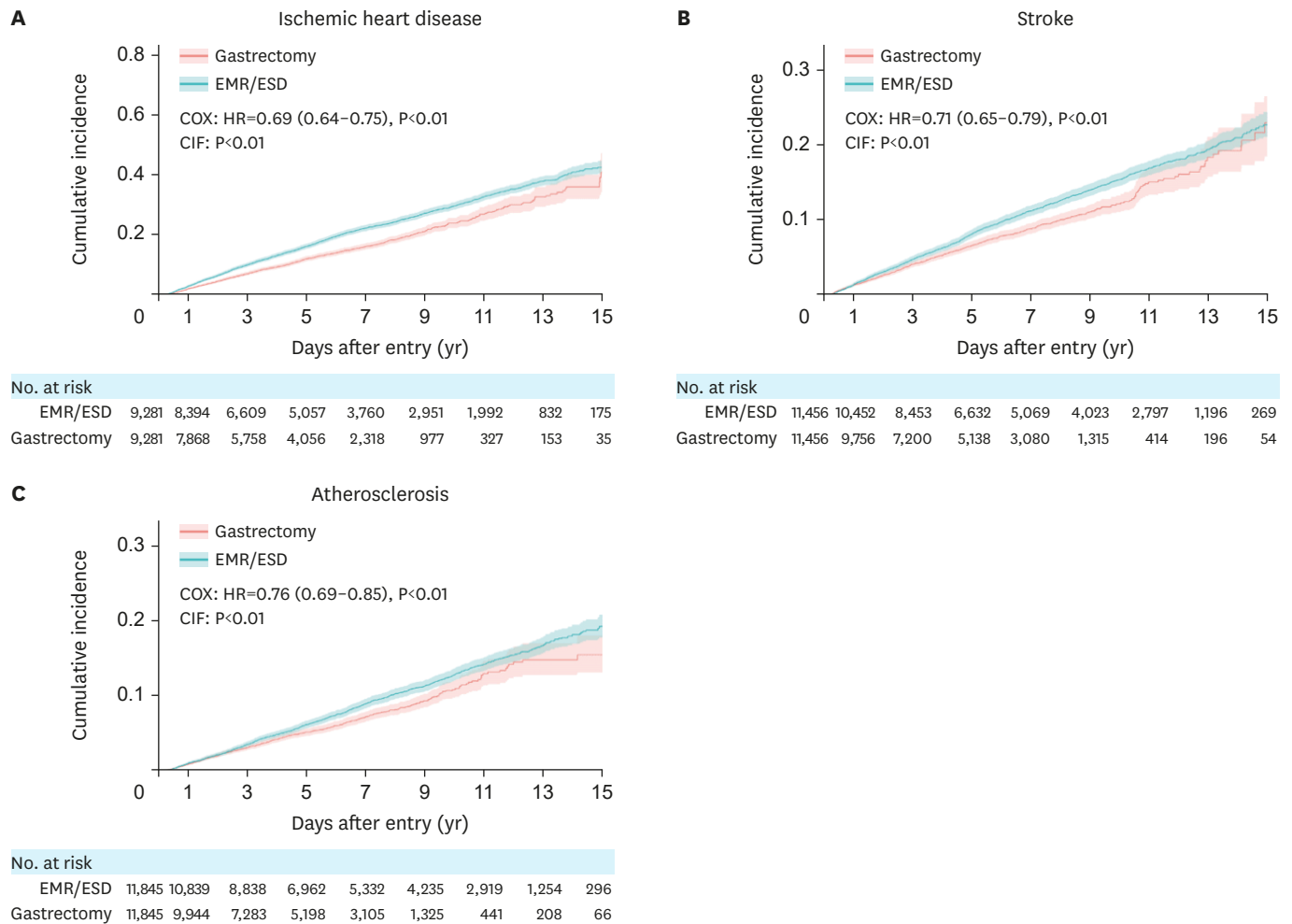


Fig. 4. Cumulative incidence function based on the treatment modality in the category of vascular disease. (A) Ischemic heart disease, (B) Stroke, and (C) Atherosclerosis. EMR = endoscopic mucosal resection; ESD = endoscopic submucosal dissection; CIF = cumulative incidence function; HR = hazard ratio.

Infectious diseases

Gastrectomy was an independent risk factor for infectious gastroenteritis (HR, 12.965; 95% CI, 11.446–14.685; P<0.0001). Infectious gastroenteritis was more frequently observed following gastrectomy in patients with CIF (P<0.0001; **Fig. 5A**). In contrast, gastrectomy was not a risk or protective factor for other infectious diseases, such as tuberculosis, syphilis, or pneumonia (P=0.9306, P=0.3859, and P=0.2027, respectively). There was no significant difference between gastrectomy and ER in CIF of these infectious diseases (P=0.8036, P=0.1992, and P=0.1062, respectively; **Fig. 5B, C, and D; Supplementary Tables 12-15**).

Other diseases

Gastrectomy was an independent risk factor for inguinal hernia (HR, 1.486; 95% CI, 1.237–1.785; P<0.0001), along with male sex and older age. Inguinal hernia occurred more frequently following gastrectomy than that after ER in CIF (P=0.0007; **Fig. 6A**). In contrast, gastrectomy was an independent protective factor for Parkinson's disease (HR, 0.718; 95% CI, 0.575–0.897; P=0.0035), along with older age and higher CCI. The occurrence of Parkinson's disease was high following ER in CIF (P=0.0093; **Fig. 6B**). However, gastrectomy was not an independent risk or protective factor for dementia (P=0.0583). However, female

Post-gastrectomy Disease Occurrence

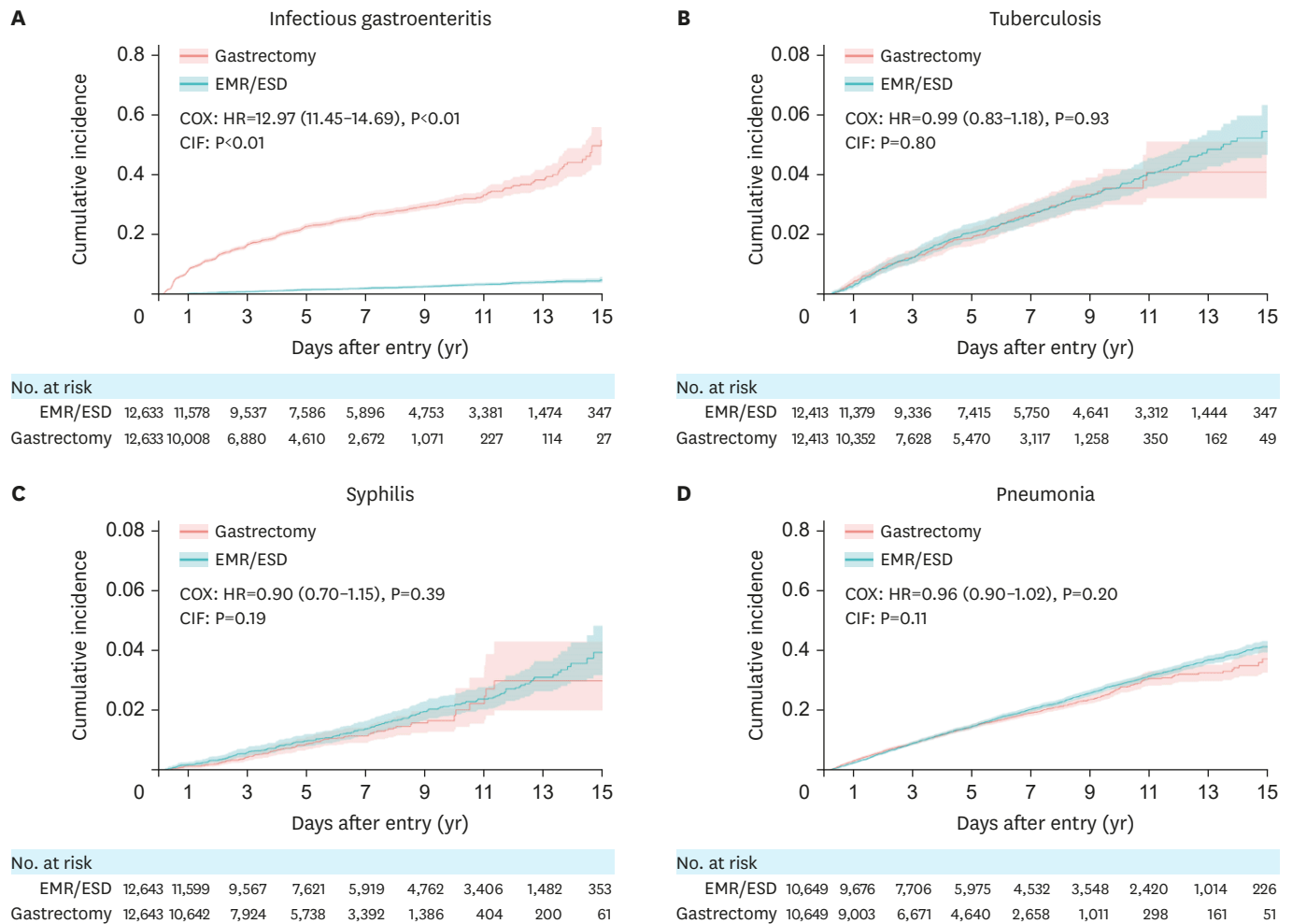


Fig. 5. Cumulative incidence function based on the treatment modality in the category of infectious diseases. (A) Infectious gastroenteritis, (B) Tuberculosis, (C) Syphilis, and (D) Pneumonia. EMR = endoscopic mucosal resection; ESD = endoscopic submucosal dissection; HR = hazard ratio; CIF = cumulative incidence function.

sex, older age, and higher CCI alone were independent risk factors for dementia. In addition, there was no significant difference between gastrectomy and ER in the CIF of dementia (P=0.1127; **Fig. 6C**; **Supplementary Tables 16-18**).

DISCUSSION

We investigated the incidence of various diseases following gastrectomy in order to determine the anatomical, metabolic, nutritional, immunological, and psychological changes in gastric cancer survivors. In summary, the incidence of cholecystitis, pancreatitis, AKI, anemia, infectious gastroenteritis, and inguinal hernia increases, while the incidence of dyslipidemia, vascular diseases, and Parkinson's disease decreases following gastrectomy. Cancer patients are generally more attentive to health management after diagnosis of cancer, and various changes, such as improvements in lifestyle and diet control, are typically implemented [11,12]. In addition, changes may occur due to the pathophysiology of cancer itself, which may act as a bias in the analyses performed in this study [13,14]. Therefore, to reduce this bias, patients diagnosed with gastric cancer who underwent ER alone, instead

Post-gastrectomy Disease Occurrence

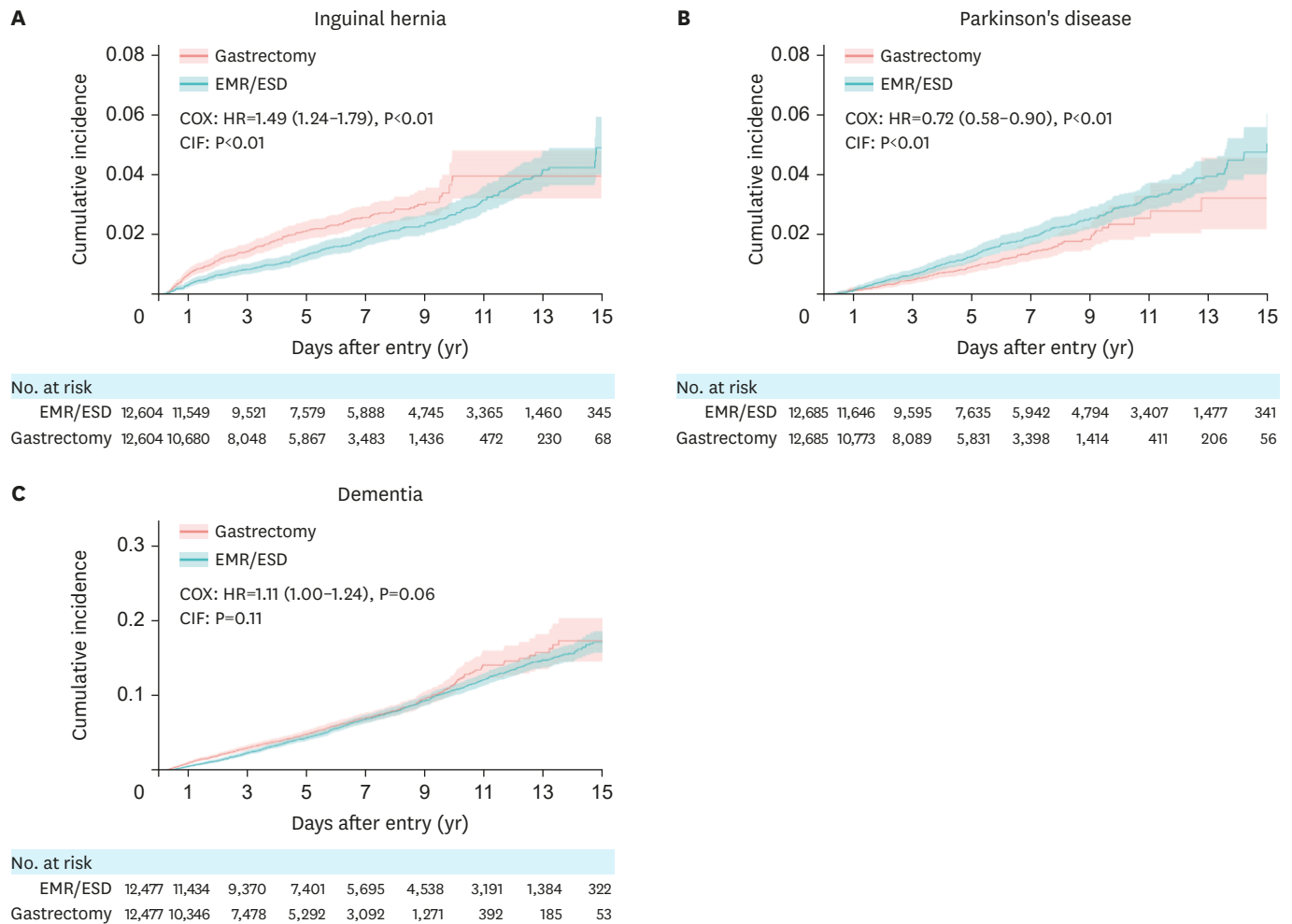


Fig. 6. Cumulative incidence function based on the treatment modality in the category of other diseases. (A) Inguinal hernia, (B) Parkinson's disease, and (C) Dementia. EMR = endoscopic mucosal resection; ESD = endoscopic submucosal dissection; HR = hazard ratio; CIF = cumulative incidence function.

of gastrectomy, were included in the control group. In addition, to eliminate the effects of chemotherapy and advanced gastric cancer, all patients who had been administered chemotherapeutic agents were excluded from the study. Although patients who received chemotherapy were excluded, patients who refused chemotherapy or who could not receive chemotherapy due to poor general conditions may have been included. In addition, there were patients who had only performed ER without gastrectomy in the ER group due to poor clinical status. However, we suspect that the number was very small, and it was more important to eliminate the effects of chemotherapy than to select patients that meet the definition of EGC. Therefore, the inclusion of a small number of patients with advanced gastric cancer is not expected to significantly affect the results of this study.

In addition to the effect of cancer, patients diagnosed with the target disease before gastrectomy or patients with well-known risk factors related to the target disease were excluded to reduce the external effect bias. In patients with well-known risk factors related to the target disease, the effect of the risk factors would be more significant than the impact of gastrectomy. Despite the possibility that well-known risk factors were not identified, it would not be many cases, and they were expected to exist to a similar degree in both groups. Hence,

we suspect that undetected risk factors were not a significant bias in this study, which was performed with a sufficient number of cases. Therefore, it can be said that the results of this study depict the effects of gastrectomy on gastric cancer survivors.

In gastric cancer, the extent of gastrectomy is determined based on tumor location [2,15]. As a standard therapy, subtotal or total gastrectomy is performed, and 60%–100% of the stomach is removed during this process [16,17]. In the case of subtotal gastrectomy, the antrum and body are removed, and in this process, parietal, mucus, chief, G-, D-, and endocrine cells are removed [18,19]. As a result, acid secretion is reduced along with gastric secretory products, such as pepsin, prostaglandin, histamine, gastrin, somatostatin, intrinsic factor, and ghrelin [20–22]. IDA is a common post-gastrectomy syndrome resulting from decreased iron absorption due to impaired acid secretion following gastrectomy [23,24]. In this study, the HR of gastrectomy for IDA was 3.418. In addition, decreased intrinsic factors cause impairment of vitamin B12 absorption, which, in turn, causes VBDA [25]. In this study, the HR of gastrectomy for VBDA was 9.313. These two types of anemia (IDA and VBDA) are the most common post-gastrectomy syndromes, suggesting that the cohort for this study was properly selected [26]. In addition, this study is the first large-scale study conducted to identify the effect of gastrectomy on IDA or VBDA, compared to the effects of ER on these two conditions.

Post-gastrectomy metabolic disturbance is one of the most common causes of osteoporosis [8,27]. However, in this study, there was no significant difference in the incidence of osteoporosis between the gastrectomy and ER groups. This could be attributed to a lack of interest in osteoporosis among patients with cancer. In Korea, bone mineral densitometry is covered by national insurance for men over 70 years of age and women over 65 years of age. However, similar to patients, physicians are often less interested in osteoporosis, a relatively mild disease and, therefore, do not perform appropriate evaluations such as bone mineral densitometry. Breast cancer and post-menopausal status are closely related to osteoporosis, and most studies on osteoporosis in cancer patients are focused on these patients [28]. However, gastrectomy is also a significant risk factor for the occurrence of osteoporosis; therefore, the use of appropriate examinations by physicians for the early diagnosis of osteoporosis is essential for treating gastric cancer. Similarly, metabolic disturbances can cause body shape changes, such as abdominal wall loosening. Advancing age and lower body mass index are thought to be risk factors for inguinal hernia [29]; indeed, abdominal wall loosening, which is caused by aging, elevated intra-abdominal pressure, and decreased muscle strength, may be the reason for the occurrence of these risk factors [30]. In this study, gastrectomy showed an HR of 1.486 for inguinal hernia. We assumed that this was a result of body shape changes following gastrectomy. Therefore, proper follow-up and evaluation of inguinal hernia after gastrectomy are necessary. It is noteworthy that this is the first study to report the relationship between gastrectomy and inguinal hernia.

Although peri-gastric anatomy changes following gastrectomy for gastric cancer depend on the extent of gastrectomy and reconstruction methods, in the case of distal gastrectomy, the pylorus is removed, and the remnant stomach is anastomosed to the duodenum or jejunum. Indeed, in a previous study, the storage function of the remnant stomach decreased and the function of the antrum disappeared [21]. Also, after distal gastrectomy, there are various reconstruction methods, such as Billroth-I, Billroth-II, or Roux-en-Y reconstruction, and various changes such as bypassing the duodenum or changing the peristaltic direction, appear in addition to weight loss according to the reconstruction methods. Although there is

debate about the advantages and disadvantages of each anastomosis method, the anatomical changes are manifested by dumping syndrome, gastric stasis, and malabsorption [23]. These anatomical changes have been reported to be effective in metabolic surgery, specifically bariatric surgery, and are widely used as treatment for various metabolic diseases, such as T2DM and dyslipidemia [6]. The theory of metabolic surgery has been verified in various studies related to bariatric surgery, and research on onco-metabolic surgery is also underway [31,32]. In this study, the HRs of IHD, stroke, and atherosclerosis were 0.692, 0.713, and 0.763, respectively, after gastrectomy. In addition, the HR of dyslipidemia, which is a significant risk factor for IHD, stroke, and atherosclerosis, was 0.461 after gastrectomy. These results suggest that metabolic disturbances following gastrectomy reduce the incidence of dyslipidemia and further reduce the overall incidence of vascular disease. Several studies have reported that gastrectomy reduces the incidence of IHD [5]. In contrast, regarding T2DM, the main target of onco-metabolic surgery, no significant difference was observed between the gastrectomy and ER groups in this study. In a previous study, metabolic surgery was performed for patients with severe T2DM requiring insulin administration or with HbA1c >6.0 [6]. However, the definition of T2DM in this study did not account for the severity of T2DM, since it was intended for cases with ICD-10 diagnostic codes. Therefore, cases of mild T2DM were included, in which medication was not administered and diet control alone was followed. In addition, while previous metabolic surgery-related studies have focused on the treatment of T2DM, this study focused on the incidence of T2DM [32]. This is thought to have caused differences in our results compared with previous studies. In the case of renal diseases, chronic kidney disease and AKI were classified based on whether the duration of dialysis was greater, equal to, or less than three months [33]. The incidence of AKI following gastrectomy increased, with an HR of 1.524. Although the cause and timing of AKI are not clear in this study, dehydration may play a causal role, as it is common after gastrectomy [34]. In particular, intestinal obstruction may result in severe dehydration, which is a common complication after gastrectomy [35].

Previous studies have reported that malnutrition after gastrectomy causes immune disturbances [36,37]. Therefore, the incidence of infectious diseases was analyzed to determine whether malnutrition following gastrectomy could indeed cause an immune disturbance in the real world. As a result, infectious gastroenteritis rapidly increased after gastrectomy. However, no significant difference between the groups was observed for other infectious diseases, such as tuberculosis, syphilis, and pneumonia. These results suggest that immunologic changes may occur due to malnutrition following gastrectomy; however, in our study, they were not severe and could be managed relatively well with appropriate supportive care. In addition, infectious gastroenteritis was thought to be caused by increased exposure to infectious sources, such as food poisoning, owing to decreased acid secretion, rather than immune disturbance after gastrectomy [22]. Although diseases, such as hepatitis A virus infection, acquired immunodeficiency syndrome, and herpes infection, could not be analyzed due to their extremely low incidence, this study is the first to analyze immunologic changes in patients with gastric cancer after gastrectomy.

Lymph node (LN) dissection is important in gastric cancer [2]. During supra-pancreatic LN dissection, pancreatic compression is performed, which can manifest as postoperative pancreatitis or pancreatic fistula [38]. Most studies on postoperative pancreatitis have focused on short-term outcomes, and there is a lack of evidence on the long-term outcomes of pancreatitis and pancreatic fistula [39]. Occasionally, there is a case in which serum amylase increases without symptoms, and medication is administered during the follow-

up process after gastrectomy. In this study, the incidence of pancreatitis was higher in the gastrectomy group, with an HR of 1.109. Since the definition of the occurrence of pancreatitis involved simply a diagnosis with a medication code, asymptomatic pancreatitis was also included. Thus, a follow-up study to analyze the long-term outcomes of asymptomatic pancreatitis is needed to validate our findings and for clinical significance.

LN station #1 dissection is necessary for standard radical gastrectomy, and truncal vagotomy must be performed during this process [15]. Truncal vagotomy is not performed during pylorus-preserving gastrectomy; however, the latter is a rare procedure [40]. When vagotomy is performed, cholestasis occurs owing to a decrease in the motility of the gall bladder, and, subsequently, the incidence of gallstones and cholecystitis increases [7]. In this study, the incidence of cholecystitis increased with an HR of 1.696 following gastrectomy. This result is consistent with the PEGASUS-D trial results and suggests that proper follow-up and evaluation of cholecystitis after gastrectomy are necessary [41]. Parkinson's disease is one of the diseases associated with vagotomy [42]. The "dual hit" hypothesis is that a neurotropic pathogen enters the brain via the nasal or gastric route through the vagal nerve. Thus, truncal vagotomy may lower the incidence of PD [43]. In this study, gastrectomy reduced Parkinson's disease, with an HR of 0.718; also, this is the first study to analyze the association between vagotomy performed during gastrectomy for gastric cancer and Parkinson's disease. Dementia is either vascular or caused by Lewy bodies or atrophy of the brain [44]. We analyzed whether the incidence of dementia was affected following gastrectomy. However, no significant difference was observed between the groups, with a trend of a slightly increased incidence of dementia after gastrectomy. This may be due to various reasons, such as malnutrition or heterogeneity of dementia itself, and warrants further study.

This study has several limitations. First, we evaluated a large dataset collected from a single nation. However, along with Japan, Korea has the highest incidence of gastric cancer worldwide with many survivors, owing to its very high survival rate [45]. Therefore, Korea is considered the most appropriate area for conducting this study. Also, we were unable to explain the causal relationship and mechanism between gastrectomy and the respective diseases. Additionally, detailed individual data and cancer stages were not included. This is a common limitation observed while evaluating large datasets, such as the HIRA database, and appropriate interpretation is required using existing knowledge. Additionally, an adequate analysis was not possible for some diseases, as they had a very low incidence rate. These diseases require additional basic research and animal studies. Also, there is insufficient evidence for the washout period. However, based on the fact that the postoperative short-term surgical outcome had been set at one month in the general study and the body mass index rapidly decreased and started to recover within six months after gastrectomy, the washout period was set to one month and three months, respectively [10].

In this study, 18 diseases that can occur after gastrectomy for gastric cancer were investigated. For some diseases, previously known information could be verified, and the value of HR could be confirmed, while for other diseases, a possible new association with gastrectomy was identified. To investigate the mechanism of these diseases, specific studies on each disease are needed. The results of this study reveal the specific diseases that physicians should focus on while treating patients after gastrectomy. In addition, our study results can serve to provide the basis for the appropriate implementation and insurance coverage for the examination of these diseases.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Baseline characteristics and COX regression analysis for cholecystitis

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Supplementary Table 2

Baseline characteristics and COX regression analysis for pancreatitis

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Supplementary Table 3

Baseline characteristics and COX regression analysis for osteoporosis

[Click here to view](#)

Supplementary Table 4

Baseline characteristics and COX regression analysis for type 2 DM

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Supplementary Table 5

Baseline characteristics and COX regression analysis for acute kidney injury

[Click here to view](#)

Supplementary Table 6

Baseline characteristics and COX regression analysis for dyslipidemia

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Supplementary Table 7

Baseline characteristics and COX regression analysis for anemia (iron deficiency)

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Supplementary Table 8

Baseline characteristics and COX regression analysis for anemia (vitamin B12 deficiency)

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Supplementary Table 9

Baseline characteristics and COX regression analysis for ischemic heart disease

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Supplementary Table 10

Baseline characteristics and COX regression analysis for stroke

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Supplementary Table 11

Baseline characteristics and COX regression analysis for atherosclerosis

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Supplementary Table 12

Baseline characteristics and COX regression analysis for infectious gastroenteritis

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Supplementary Table 13

Baseline characteristics and COX regression analysis for tuberculosis

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Supplementary Table 14

Baseline characteristics and COX regression analysis for syphilis

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Supplementary Table 15

Baseline characteristics and COX regression analysis for pneumonia

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Supplementary Table 16

Baseline characteristics and COX regression analysis for inguinal hernia

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Supplementary Table 17

Baseline characteristics and COX regression analysis for Parkinson's disease

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Supplementary Table 18

Baseline characteristics and COX regression analysis for dementia

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Supplementary Fig. 1

Five categories and eighteen diseases.

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Supplementary Fig. 2

Flowsheet of the cohort.

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