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**Gastrectomy impact on the gut microbiome in patients with gastric cancer: A comprehensive review**

Maksimaityte V *et al*. Gastrectomy impact on the gut microbiome

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**Abstract**

Gastric cancer is one of the most common malignancies worldwide and gastrectomy remains the only potentially curative treatment option for this disease. However, the surgery leads to significant physiological and anatomical changes in the gastrointestinal (GI) tract including loss of the gastric barrier, an increase in oxygenation levels in the distal gut, and biliary diversion after gastrectomy. These changes in the GI tract influence the composition of the gut microbiome and thus, host health. Gastrectomy-induced dysbiosis is characterized by increased abundance of typical oral cavity bacteria, an increase in aero-tolerant bacteria (aerobes/facultative anaerobes), and increased abundance of bile acid-transforming bacteria. Furthermore, this dysbiosis is linked to intestinal inflammation, small intestinal bacterial overgrowth, various GI symptoms, and an increased risk of colorectal cancer.

**Key Words:** Gut microbiota; Dysbiosis; Gastric cancer; Gastrectomy; Microbiome; Comprehensive review

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**Core Tip:** In most cases of gastric cancer (GC) the only life-saving treatment is gastrectomy. Gastrectomy results in significant changes in gut microbiota: Higher abundance of oral cavity bacteria, aero-tolerant bacteria, and bile transforming bacteria, and these changes in the microbiome are related to host health. In this review we discuss current knowledge and the results of recent studies on the changes in gut microbiome after gastrectomy in patients with a history of GC.

**INTRODUCTION**

Gastric cancer (GC) is an important oncological problem responsible for over 1000000 new cases and more than 783000 deaths worldwide annually, making it the fifth most common cancer and the third leading cause of cancer death[1]. Surgery remains the only potentially curative treatment option for this disease[2]. However, gastrectomy has some adverse effects in long-term survivors, including persistent gastrointestinal (GI) symptoms[3-5] and an increased risk of metachronous cancers[6-8]. Gastrectomy leads to significant changes in the GI tract, including changes in pH, oxygenation levels, and biliary diversion. These alterations of the GI tract create a strong impetus on changes in the gut microbiome (Figure 1), which was suggested to be involved in postoperative outcomes[6]. Gastrectomy-induced dysbiosis is characterized by increased abundance of typical oral cavity bacteria, an increase in aero-tolerant bacteria (aerobes/facultative anaerobes), and increased abundance of bile acid-transforming bacteria.

The microbiome of the human gut is a complex and diverse population of bacteria, fungi, archaea, and viruses that inhabit the intestinal tract, mainly the large intestine[9,10]. The stable human gut bacterial species are divided into six main phyla: *Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, Verrucomicrobia,* and *Euryarchaeota*[11]. These microbes have tremendous potential to impact host physiology, both in health and disease[12]. They contribute metabolic functions, protect against pathogens, educate the immune system, and, through these basic functions, affect directly or indirectly most of our physiologic functions[12]. Recent advancements revealed the gut microbiome's role in a series of different diseases including Alzheimer’s disease[13,14], obesity[15], inflammatory bowel diseases (IBD)[16,17], cancer[18,19], functional GI disorders[20], and others. Furthermore, the role of the microbiome in postoperative weight loss and other outcomes are documented after sleeve gastrectomy and Roux-en-Y gastric bypass in bariatric patients[21-26]. Several recent studies investigated the gut microbiome after gastrectomy for GC[6,27-29]. This comprehensive review provides an overview of the current evidence on gut microbiome after gastrectomy for GC and its clinical implication.

**LITERATURE SEARCH**

A comprehensive literature search was conducted using the PubMed database up to 31st December, 2020. The search terms used were “gastrectomy AND microbiome”. No time restrictions for publications were used, but only manuscripts published in the English language were reviewed. All titles and abstracts were independently reviewed by two reviewers (V.M. and A.B.) to identify clinical studies investigating the impact of gastrectomy on the gut microbiome in GC patients. After relevant abstracts were identified the full-text articles were retrieved. To ensure a comprehensive literature search an additional manual search of the reference lists was performed.

**COMPREHENSIVE REVIEW**

Following a comprehensive review of the current literature, we identified 4 studies which investigated the gut microbiome after total or subtotal gastrectomy for GC, and these are summarized in Table 1. Three of these four studies were cross-sectional and investigated gut microbiome composition in GC patients at a median time of 3.75 years[27], 5 years[6], and 8.25 years[28] after gastrectomy and compared it with the corresponding controls. One small-scale study was longitudinal and investigated the gut microbiome composition before and approximately one week after gastrectomy[29].

Gut microbiome diversity and richness may be related to host health[30]. A reduction in the GI microbiome biodiversity was reported in obesity, inflammatory bowel disease, colorectal malignancy, and type 2 diabetes[21,30-33]. The impact of gastrectomy on bacterial richness and alpha diversity remains controversial because of conflicting results in current studies. Erawijantari *et al*[6] showed increased richness and diversity by increased Chao1 and Shannon indices in gastrectomized patients[6]. However, bacterial richness and alpha diversity may depend on the type of GI tract reconstruction. The study by Lin *et al*[28] showed increased richness and alpha diversity only after subtotal gastrectomy with Roux-en-Y reconstruction (RYGJ), but not in the case of Billroth II reconstruction (B2)[28]. Furthermore, similar richness and even decreased alpha diversity after subtotal gastrectomy with B2 reconstruction was reported by Horvath *et al*[27]. The impact of gastrectomy on bacterial richness and alpha diversity seems to be a long-term effect of the surgery since these changes were not observed by Liang *et al*[29] in the early perioperative period[29]. All the studies managed to identify and highlight specific features of the gut microbiome composition in the postsurgical period[27-29,34].

**GASTRIC BARRIER LOSS AFTER GASTRECTOMY AND ITS IMPACT ON GUT MICROBIOME COMPOSITION**

One of the typical changes in the GI tract after subtotal gastrectomy includes loss of the gastric barrier[27] due to reduced gastric acid secretion[27,35-37]. A pH of 4 is considered a threshold value for a powerful bactericidal effect[38] and it is significantly exceeded after subtotal gastrectomy, as the gastric pH increases from physiological levels to values above 6.0, irrespective of the type of reconstruction[39]. A very similar increase in gastric pH from approximately 2.0 to over 6.0 is described following proton pump inhibitor (PPI) intake[27]. In such conditions oral bacteria may survive during gastric passage and colonize the distal part of the GI tract, causing gut microbiome oralization, the phenomenon previously described in PPI users[40-43]. The comparable loss of gastric barrier function after subtotal gastrectomy and by PPI use may result in a similar impact on the gut microbiome.

Thus, it was not surprising, that a higher abundance of typical oral cavity bacteria-*Streptococcus, Veillonella, Prevotella, Oribacterium,* and *Mogibacterium*[44], were observed in the gut microbiome of gastrectomized patients[6,27,28]. Some of these bacteria are linked to host health and treatment efficacy. A recent study linked *Veillonella* with tumor response to Nivolumab in patients with progressive GC[45]. *Streptococcus* is a prevalent bacterial taxon in the oral cavity and the most commonly described bacterium in PPI-induced dysbiosis[27,41,43,46,47]. Previously, this bacterium was linked to intestinal inflammation and gut permeability in cirrhosis patients[40]. Similarly, *Streptococcus* was also associated with intestinal inflammation in gastrectomized patients[27]. Chronic intestinal inflammation may be involved in the pathogenesis of intermittent or permanent chronic diarrhea, which is present in up to 40% of long-term survivors after gastrectomy[3,48-50]. Previously post-gastrectomy diarrhea was attributed to vagotomy, endocrine hypofunction-related dyscoordination of the digestive tract, and abnormalities in the regulation of GI tract hormone secretion[50]. Although, as shown in IBD patients, chronic inflammation leads to damage of intestinal mucosa, dysregulation of intestinal ion transport, impaired and increased accessibility to the intestinal mucosa for pathogens[51]. Dysregulation of the expression and/or function of epithelial ion transporters and channels leads to electrolyte retention and water accumulation causing diarrhea[30]. Loss of epithelial barrier function contributes to diarrhea *via* a leak-flux mechanism, while mucosal penetration of enteric pathogens drives subsequent tissue damage[51]. Furthermore, patients suffering diarrhea after gastrectomy showed an increased abundance of *Mogibacterium* and decreased abundance of *Ruminococcus 1*[27]. *Mogibacterium* is increased in Crohn’s patients[52] and decreased *Ruminococcus 1* was associated with diarrhea in an experimental porcine model[53].

Other common GI symptoms in gastrectomized patients are abdominal discomfort and bloating[27,48-50]. Both of these symptoms were associated with a decrease in *Agathobacter*[27]*.* These butyrate producers live in symbiosis with *Bifidobacteria*, which provides acetate as a substrate for butyrate production[54]. Abdominal discomfort was also, associated with increased abundance of *Holdemanella*[27]*.* There is a lack of evidence on the impact of *Holdemanella* on host health, although, their taxonomic family *Erysipelotrichaceae* contains highly immunogenic species and is associated with pro-inflammatory conditions[27,55].

**INCREASED OXYGEN LEVEL IN THE GUT AFTER GASTRECTOMY AND ITS IMPACT ON THE GUT MICROBIOME**

The important anatomical and physiological changes in the GI tract after gastrectomy include increased oxygen in the distal part of the gut[56], which may provide an appropriate niche for aerobic and facultative anaerobic microbes. The studies on the gut microbiome after gastrectomy consistently showed an increased abundance of aero-tolerant microorganisms[27,28,34]. Erawijantari *et al*[6] demonstrated an increased abundance of aerobes (*Streptococcus, Enterococcus)* and facultative anaerobes (*Escherichia, Enterobacter,* and *Streptococcus)* in patients after gastrectomy*.* The study by Lin *et al*[28] showed a higher amount of aero-tolerant *Proteobacteria* phylum microorganisms including *Streptococcus, Escherichia*, and *Klebsiella*[28]. Similar, studies by Liang *et al*[29] and Horvath *et al*[27] demonstrated increased numbers of aerobes (*Streptococcus*) and facultative anaerobes (*Escherichia*) in patients after subtotal gastrectomy[27,29]. The increase in *Escherichia* was the most prominent difference between the microbiome of gastrectomy patients and controls documented in all studies[27-29,34]. *Escherichia* is a common protagonist in small intestinal bacterial overgrowth (SIBO)[57], which is a heterogeneous syndrome characterized by an increased number and/or abnormal type of bacteria in the small bowel[57]. SIBO occurs in the majority of patients after gastrectomy[58], and the clinical manifestation of this syndrome includes bloating, flatulence, abdominal discomfort, diarrhea, and abdominal pain[57], symptoms which are common in long-term survivors after gastrectomy[3,48-50].

Taken together, there is evidence associating GI symptoms after gastrectomy with specific changes in the gut microbiome composition, although further studies are warranted to confirm these findings and the exact mechanisms involved.

**The impact of BILIARY DIVERSION AFTER GASTRECTOMY ON THE GUT MICROBIOME**

GI tract reconstruction following gastrectomy may lead to biliary diversion. The altered bile acid flow potentially stimulates the growth of bile acid-transforming bacteria[34]. The study by Erawijantari *et al*[6] extensively analyzed the fecal metabolomic profile and showed increased abundance of the secondary bile acid - deoxycholic acid (DCA) in gastrectomized patients[6]. Deconjugation of human primary bile acids and their subsequent biotransformation to secondary bile acids is a well-recognized function carried out by the human gut microbiome with its implications for human health[59]. The 7α-dehydroxylation reaction has been described as the most quantitatively important process for the formation of secondary bile acids performed by the gut microbiome, specifically the bacteria that belong to the genus *Clostridium*[60]*.* The increased abundance of *Clostridium* following gastrectomy was confirmed in several studies[28,34]. Altered bile acid pool composition has been associated with several diseases including colorectal cancer[61,62], IBD, and metabolic syndrome[60].

DCA is a carcinogen in liver cancer and colorectal cancer[34,61,62]. Increased DCA in the intestine causes DNA damage through oxidative stress in intestinal epithelial cells and activates the epidermal growth factor receptor or Wnt pathways to promote colorectal cancer (CRC)[63]. These mechanisms may be responsible for the increased risk of metachronous CRC in GC patients[7,8]. Furthermore, the altered bile flow-induced gut microbiome changes were suggested as one of the potential mechanisms for the metabolic effect of gastrectomy[28]. Patients after subtotal gastrectomy with RYGJ or B2 reconstruction were shown to have a lower body mass index or waist circumference compared to age and sex-matched healthy controls in the study by Lin *et al*[28]. Also, subtotal gastrectomy had some more positive effects such as higher serum high-density lipoprotein, lower total cholesterol, and triglyceride levels[28]. Only patients who underwent RYGJ showed a lower prevalence of metabolic syndrome and type 2 diabetes[28]. The exact mechanisms linking subtotal gastrectomy with metabolic improvement remain unclear; however, some gut microbiome involving pathways were suggested[28]. They include: (1) The impact of the gut microbiome on the enteroendocrine function; (2) Altered bile acid flow, which is a driver for changes in microbiome composition; and (3) Decreased levels of circulating lipopolysaccharides and altered bacterial components promoting hepatic insulin sensitivity[28].

**LIMITATIONS OF THE CURRENT KNOWLEDGE AND PERSPECTIVES FOR FUTURE RESEARCH**

The knowledge provided by the current studies has some limitations. First, most of the studies were cross-sectional design[27,28,34], and the only longitudinal study by Liang *et al*[29] was limited by a very small sample size and short follow-up[29]. Thus, there is a lack of data showing microbiome composition changes pre- and post-gastrectomy. Second, some studies included controls who were on gastric acid suppression medications or did not record the history of antibiotic use. These medications have a strong effect on the gut microbiome, thus, the impact of gastrectomy may have been underestimated[64]. Third, the current studies included patients with different extents of gastrectomy (total *vs* subtotal) and different types of reconstructions (B2, RYGJ, Billroth I). The impact of gastrectomy on the gut microbiome may be specific for the type of surgery; thus, future studies should clarify the impact of types of reconstruction after gastrectomy. Together, the present knowledge provides evidence on the impact of gastrectomy on the gut microbiome. These changes are driven by an altered environment in the GI tract, including loss of the gastric barrier, an increase in oxygenation levels in the distal gut, and biliary diversion. Further well-designed and appropriate size longitudinal studies are necessary to confirm this concept. These studies should incorporate data on health-related quality of life, especially on GI symptoms, metabolomics, and markers on intestinal inflammation and permeability to provide robust evidence on the impact of gastrectomy-induced dysbiosis on host health.

Several ongoing studies are already investigating gut microbiome changes through the GC treatment pathway. The LEGACY-2 trial (NCT04015466) is a large-scale international study aiming to study biological factors, including microbiome impact on clinical outcomes. The NeoChance trial (NCT04196465) is investigating the microbiome as a predictive/prognostic biomarker in patients who receive neoadjuvant immune checkpoint inhibitor IMC-001 for resectable GC. The NutriGIT (NCT04476082) study is investigating the nutritional status of patients with various GI cancers, including GC, and one of the study outcomes is changes in the gut microbiome. Together, these studies will increase the knowledge on microbiome changes through GC treatment and will highlight the impact of these changes on treatment outcomes. However, current studies are not designed to specifically investigate gastrectomy-induced dysbiosis; thus, such studies are still necessary.

The recent studies linked gut microbiome composition with the effectiveness of anti-cancer therapy[45,65]. An exploratory analysis of genus from the DELIVER trial showed that *Odoribacter* and *Veillonella* were associated with tumor response to Nivolumab in patients with advanced GC[45]. As mentioned previously, the abundance of typical oral bacteria-*Veillonella* increases following subtotal gastrectomy, due to the oralization phenomenon[27]. However, there is currently a lack of evidence to reliably characterize the impact of gastrectomy-induced dysbiosis on the effectiveness of anti-cancer therapy. Assystemic therapy before and/or after surgery is the modern standard for GC, it would be of interest to investigate the association between gut microbiome and the efficacy of therapy in future studies.

**CONCLUSION**

Gastrectomy for GC impacts the composition of the gut microbiome. These changes are characterized by oralization, an increase in aero-tolerant bacteria (aerobes/facultative anaerobes), and increased abundance of bile acid-transforming bacteria. These changes are driven by an altered environment in the GI tract, including loss of the gastric barrier, an increase in oxygenation levels in the distal gut, and the biliary diversion after gastrectomy. Gastrectomy-induced dysbiosis is associated with host health. However, current evidence is limited; therefore, further longitudinal studies looking at different reconstructions of the GI tract are needed to confirm the concept and to investigate the mechanisms related to the impact of the gut microbiome on the health of GC patients.

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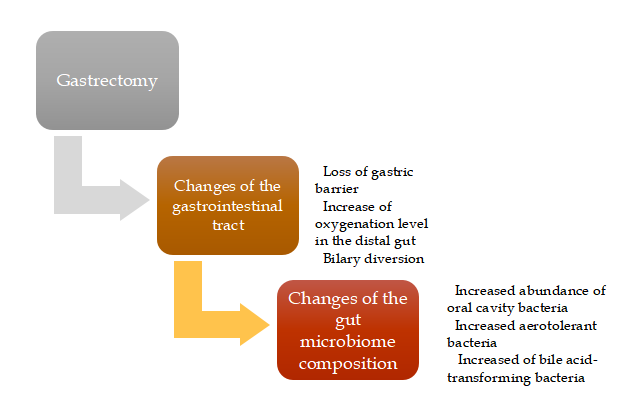
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**Figure Legends**



**Figure 1 Gastrectomy impact on the gastrointestinal tract environment and gut microbiome.**

**Table 1 Clinical studies investigating gut microbiome composition in patients after gastrectomy for gastric cancer**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Type of study** | **Participants (groups)** | **Exclusion criteria** | **Type of gastrectomy and method of reconstruction** | **Main findings of the study** | **Other metabolites investigated** |
| Erawijantari *et al*[6], 2020 | CSS | Gastrectomy group: Patients with a history of gastrectomy for GC (*n* = 50). Control group: Healthy controls without a history of gastrointestinal surgery (*n* = 56) | Recurrence of gastric cancer (gastrectomy group). History of gastrointestinal surgery (for controls) | Total (*n* = 12) gastrectomy and subtotal gastrectomy (*n* = 38). Types of reconstruction: Stomach-stomach (*n* = 1); Billroth I (*n* = 2); Jejunal interposition (*n* = 6); Pylorus-preserving gastrectomy (*n* = 8); Roux-en-Y (*n* = 29) | Higher species diversity and richness in gastrectomized patients. Higher abundance of aerobes, facultative anaerobes, and oral microbes in gastrectomized patients | Phosphate and amino acid transporters were more abundant in gastrectomized patients. Primary and conjugated forms of bile acid enriched in the control group and deoxycholic acid more abundant in gastrectomized patients |
| Liang *et al*[29], 2019 | LS | Gastrectomy group: Patients with a diagnosed GC one week before (*n* = 20) and ≥ 7 d after (*n* = 6) gastrectomy. Control group: Healthy controls (*n* = 22) | History of antibiotics, PPI or H2 receptor antagonist use 1 mo prior to inclusion. Endoscopic finding of peptic ulcer, tumor rupture, pyloric obstruction. Patients with a history of radiotherapy/chemotherapy and/or previous surgery | Distal gastrectomy (*n* = 6). Types of reconstruction: Billroth II (*n* = 1); Roux-en-Y (*n* = 5) | Increased abundance of *Bacteroidetes*, *Fusobacteria*, and *Verrucomicrobia* and decreased abundance of *Proteobacteria*, *Firmicutes*, and *Actinobacteria* after distal gastrectomy. The richness and diversity by Chao1; ACE; Shannon; and Simpson indices were similar before and after distal gastrectomy. LEfSe analysis attributed *Verrucomicrobiae* (genus *Akkermansia*) and genus *Escherichia/Shigella*, *Lactobacillus*, and *Dialister* to patients after gastrectomy, and the genus *Klebsiella* to patients before gastrectomy | Significantly decreased level of valeric acid after distal gastrectomy |
| Horvath *et al*[27], 2021 | CSS | Gastrectomy group: Patients with a history of distal gastrectomy with Billroth II reconstruction for early gastric cancer (*n* = 14). Control group: Patient’s in-house relatives without a history of gastric surgery (*n* = 8) | Chemotherapy or radiotherapy 12 mo before inclusion. Gastric stump cancer. Usage of antibiotics, pro-, pre-, or synbiotics, H2-blocker, or PPI 1 month before inclusion. History of any gastrointestinal tract resections other than SGB2. Recurrence of gastric cancer, and current nongastric malignancies | Distal gastrectomy (*n* = 14). Types of reconstruction: Billroth II (*n* = 14) | Alpha diversity assessed by Shannon index was significantly decreased in gastrectomy patients. Median bacterial richness quantified by Chao1 index was similar. Beta diversity analysis showed significant differences between the microbiome composition of patients and controls; ANCOM identified the genus *Escherichia-Shigella* to be more abundant in gastrectomized patients. LEfSe attributed 11 additional genera to the gastrectomy group and 17 genera to the control (approximately half of them already have been implicated in PPI-induced or PPI-associated dysbiosis in previous reports). Increased abundance of *Escherichia-Shigella*, *Enterococcus, Streptococcus*, and other typical oral cavity bacteria (*Veillonella, Oribacterium, and Mogibacterium*) in gastrectomized patients. | Fecal calprotectin marker was higher in gastrectomized patients. Fecal calprotectin was positively correlated with the abundance of *Streptococcus* and negatively correlated with the abundance of *Ruminococcaceae*, *Barnesiella*, *Ruminococcus* 2, *Ruminococcus* 1, and *Anaerostipes*. Abdominal discomfort was associated with a significantly higher abundance of *Holdemanella* and lower abundance of *Agathobacter;* Diarrhea was associated with a significantly higher abundance of *Mogibacterium* and significantly lower abundance of *Ruminococcus 1*; Bloating was associated with a significantly higher abundance of *Agathobacter* and *Streptococcus*. Patients who suffered from diarrhea also showed significantly higher serum levels of CRP and a trend to higher calprotectin level in stool compared with patients without diarrhea. |
| Lin *et al*[28], 2018 | CSS | Gastrectomy group: Patients with a history of distal gastrectomy for early GC (*n* = 111). Control group: Age and sex-matched subjects without a history of GI tract surgery (*n* = 344) | Age < 20 yr. Other underlying malignancies. Pre- and postoperative chemotherapy or chemoradiotherapy for GC. Other endocrine disorders such as DM, thyroid, pituitary, or adrenal disease. Moderate to severe cardiovascular, pulmonary, hepatic, or renal disease. Recurrent or uncured GC even after curative gastric surgery. The occurrence of complications after GC resection including anastomotic leakage, bleeding, intermittent intestinal adhesion, dumping syndrome, *etc*. Patients who received proton pump inhibitors, histamine-2 receptor antagonists, nonsteroidal anti-inflammatory drugs, antibiotics, or probiotics within one month of sample collection, | Distal gastrectomy (*n* = 111). Types of reconstruction: Billroth II (*n* = 37); Roux-en-Y (*n* = 74) | Significantly increased richness of gut microbiome after RYGJ by Chao1 index. Tendency of increased richness of gut microbiome after SGB2 by Chao1 index. Diversity assessed by Shannon index was similar in BII patients but higher in RYGJ patients. LEfSe attributed 24 known genera, which were differently abundant between SGB2 and controls, and 43 genera differently abundant between RYJG and controls. *Oscillospira, Prevotella, Coprococcus, Veillonella, Clostridium, Desulfovibrio, Anaerosinus, Slackia, Oxalobacter, Victivallis, Butyrivibrio, Sporobacter, and Campylobacter* were more abundant after subtotal gastrectomy irrespective of the type of reconstruction. Increased number of aero-tolerant *Streptococcus* and *Escherichia* in the RYGJ group and *Klebsiella* in the SGB2 group. Increased abundance of typical oral microbiota (such as *Streptococcus spp.* and *Veillonella spp.)* in the gut microbiome of gastrectomized patients | GC patients after subtotal gastrectomy with RYGJ had a lower occurrence of metabolic syndrome and type II diabetes |

CSS: Cross-sectional study; LS: Longitudinal study; GC: Gastric cancer; PPI: Proton pump inhibitors; SGB2: Subtotal gastrectomy with Billroth II reconstruction; CRP: C-reactive protein; RYGJ: Subtotal gastrectomy with Roux-en-Y reconstruction.