Small Intestinal Bacterial Overgrowth after total and subtotal gastrectomy; high incidence - not connected to gastrointestinal symptoms

Sindrom bakterijske razrasti v tankem črevesu po totalni ali subtotalni gastrektomiji; visoka incidenca, ki ni povezana z gastrointestinalnimi simptomi

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***Ključne besede**: prekomerna razrast bakterij (SIBO), karcinom želodca, totalna gastrektomija, subtotalna gastrektomija, simptomi, zapleti*

ABSTRACT

Background. Surgical resections of the gastrointestinal tract due to gastric carcinoma are connected to a higher risk of developing Small intestinal bacterial overgrowth (SIBO), which is a condition with an excessive number of bacteria in the small intestine, prompting a wide variety of symptoms and short and long-term complications. SIBO increases the incidence of nutritional deficiencies after gastrectomy and increases the overall incidence of complications.

IZVLEČEK

Izhodišče. Kirurške resekcije prebavil zaradi karcinoma želodca so povezane z večjim tveganjem za razvoj bakterijske razrasti tankega črevesa (SIBO), ki je stanje s prekomernim številom bakterij v tankem črevesu, kar povzroča različne simptome ter kratkoročne in dolgoročne zaplete. SIBO poveča pogostost prehranskih pomanjkljivosti po gastrektomiji in poveča splošno pogostost zapletov.

Namen študije. Namen te študije je bil oceniti natančno incidenco SIBO po totalni in subtotalni ga-

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Aims. This study aimed to evaluate the exact incidence of SIBO after total and subtotal gastrectomy due to gastric carcinoma and to compare symptoms, (neo)adjuvant chemo/radiotherapy treatment and eating patterns in patients with and without SIBO.

Methods. In an observatory randomised analytical cross-sectional study, patients after total and subtotal gastrectomy underwent a hydrogen (H_2) breathing test (BT) with glucose substrate (25 g/200 mL of water). Demographic, anthropometric data, symptoms, (neo)adjuvant chemo/radiotherapy treatment and eating patterns were analysed with a questionnaire.

Results. Of the 37 patients included, 7 had subtotal gastrectomy and 30 had total gastrectomy. H_2 BT was positive in 2/7 (29%) and 9/30 (30%) of patients after subtotal and total gastrectomy respectively. There was no statistically significant difference in demographic data, symptoms, eating patterns and treatment with chemo/radiotherapy.

Conclusions. The incidence of SIBO in patients who underwent subtotal and total gastrectomy is worryingly high, being 29 and 30 % respectively. SIBO occurs more frequently in patients with gastric cancer due to altered physiological defence mechanisms, cancer-related cachexia and nutritional disorders. SIBO further exacerbates and impairs the mechanisms triggered by surgery, chemotherapy and radiotherapy, with consequent micronutrient deficiencies and clinical signs. The incidence of SIBO is currently underestimated, which could be connected to developing systemic complications, malabsorption, and its consequences. The results of our study confirm that there is an urgent need to systematically address SIBO in patients undergoing total and subtotal gastrectomy already at high risk of post-surgical nutritional deficiency which would significantly improve treatment outcomes and prevent the development of short and long-term complications.

strektomiji zaradi karcinoma želodca ter primerjati simptome, (neo)adjuvantno zdravljenje s kemoterapijo/radioterapijo in vzorce prehranjevanja pri bolnikih s SIBO in brez nje.

Metode. V opazovalni randomizirani analitični presečni študiji so pri bolnikih po totalni in subtotalni gastrektomiji opravili test dihanja z vodikom (H_2) z glukoznim substratom (25 g/200 ml vode). Z vprašalnikom so analizirali demografske in antropometrične podatke, simptome, (neo)adjuvantno zdravljenje s kemoterapijo/radioterapijo in prehranjevalne navade.

Rezultati. Od 37 vključenih bolnikov jih je imelo 7 subtotalno gastrektomijo, 30 pa totalno gastrektomijo. H_2BT je bil pozitiven pri 2/7 (29 %) in 9/30 (30 %) bolnikov po subtotalni oziroma totalni gastrektomiji. V demografskih podatkih, simptomih, načinu prehranjevanja in zdravljenju s kemoterapijo/radioterapijo ni bilo statistično pomembnih razlik.

Zaključki. Pojavnost SIBO pri bolnikih, pri katerih je bila opravljena subtotalna in totalna gastrektomija, je zaskrbljujoče visoka in znaša 29 oziroma 30 %. SIBO se pogosteje pojavlja pri bolnikih z rakom želodca zaradi spremenjenih fizioloških obrambnih mehanizmov, z rakom povezane kaheksije in prehranskih motenj. SIBO dodatno poslabša in poslabša mehanizme, ki jih sprožijo operacija ter kemoterapija in radioterapija, zaradi česar se pogosteje in zgodnejše pojavijo znaki pomanjkanja mikrohranil in klinični znaki. Pojavnost SIBO je trenutno podcenjena, kar je povezano z razvojem sistemskih zapletov, malabsorpcije in njenih posledic. Rezultati naše študije potrjujejo, da je nujna sistematična obravnava SIBO pri bolnikih po totalni in subtotalni gastrektomiji, pri katerih že obstaja veliko tveganje za pooperativno presnovne pomanjkljivosti in zaplete; na takšen način bi lahko bistveno izboljšali rezultate zdravljenja ter preprečili razvoj kratkoročnih in dolgoročnih zapletov.

INTRODUCTION

Gastric cancer is the third leading cause of cancer death and fifth most prevalent worldwide, with a higher incidence in Asia, Central and South America and Eastern Europe, and a lower incidence in North America and Africa (1–3). All parts of the organ from the gastroesophageal junction to the pylorus may be affected and it has already been reported that some cancers are associated with infection by specific bacteria (3, 4). H. pylori is identified as an infectious agent related to carcinogenesis by inducing DNA mutation and causing chronic inflammation which may progress from atrophic gastritis to intestinal metaplasia, dysplasia, and gastric adenocarcinoma (3, 5). In recent decades, the incidence of gastric cancer has been declining due to the treatment of Helicobacter pylori infection and due to earlier detection and new treatment options (6).

Gastrectomy with or without lymphadenectomy and reconstruction of the gastrointestinal tract represents the mainstay of treatment for gastric carcinoma (3). The ongoing process in oncological gastric surgery has led to increased patient survival rates and improved quality of life, however after surgery, the five-year survival rate remains around 45%, with perioperative chemotherapy improving that rate only around 10% (3, 7). Improved cure rates for gastric cancer have increased focus on disease-related complications, development of health-related complications due to different treatment modalities and quality of life (HR-QL) in survivorship (2, 8, 9). Even so, nowadays efficient curative treatment for gastric carcinoma is still lacking (3, 5, 10, 11).

Despite considerable advances in gastric cancer surgeries the underestimated incidence of malabsorption, small intestinal bacterial overgrowth, and the consequences due to the surgery itself significantly reduce the quality of patient care, affect the incidence of postoperative and metabolic complications, irrespective of the type of surgical resection (10). Malnutrition may trigger weight loss, muscle mass reduction, and essential nutrient deficiencies, it increases the risk of tumour recurrence thus detrimentally impacting patients' quality of life and prognosis (10). In addition, gut and pancreatic insufficiency represent modifiable targets in the interdisciplinary approach to recovery of HR-QL (10).

Micronutrient deficiencies are also prevalent after gastric surgery, as functional and anatomical modification because surgical resection and reconstruction impact their absorption (10). Surprisingly, these deficiencies appear to be similarly prevalent in patients who have undergone surgery, with iron, vitamins A, B1, B12, D and E deficiencies commonly observed in up to 78,3% of patients (10). Recognizing and treating the distinct consequences associated with each type of deficiency underscores the importance of implementing preventive measures, early detection, and prompt management (10).

It remains to be elucidated whether changes in the gastric and gut microbiome have a role in gastric carcinogenesis or are a consequence of the surgery and tumour evolution (3). It was suggested that colonizing the stomach with commensal bacteria from other parts of the gastrointestinal region could promote gastric carcinogenesis associated with H. pylori (11). In animal models' gastric colonization with altered intestinal microbiota was correlated with pathology, immune responses, and mRNA expression for proinflammatory and cancer-related genes (11). Different composition of gastrointestinal microbiota is probably connected to different responses to H. pylori infection as well as to different pathological reactions and immunology status (11). The gut microbiome affects many types of cancer as well as gastric carcinoma cacinogenesis and the response and prognosis of gastric cancer treatment (3). The importance of the gut microbiome for the interactions between cancer and immunity is gaining attention, along with possible new treatment options targeting changed microbiota composition (7, 11).

The predominant phyla in normal gut microbiota are Bacteroidetes (19,7%), Firmicutes (40%), Actinobacteria (20%) and Proteobacteria (2,15%) (12–14). Small intestinal bacterial overgrowth (SIBO) is a type of dysbiosis and a clinical condition, which is characterised as an excess number of colon-dominant bacteria in the small intestine, responsible for digestive symptoms such as bloating, abdominal pain, nausea, and diarrhoea (15–18). The suggested pathophysiologic mechanisms of SIBO in abdominal surgery include changes in anatomical features, such as adhesions after surgery, influx of substances in the intestine and changed gastric acidity (2, 19, 20).

Our study aimed to evaluate the exact incidence of SIBO after resections of the upper gastrointestinal tract due to gastric carcinoma and evaluate the presence of symptoms, comorbidities, and eating patterns in patients with and without SIBO. The goal of this study is to present the importance of diagnosing and treating SIBO after gastrectomy to prevent short- and long-term complications and improve the prognosis and quality of life.

METHODS

Study design

Observatory randomised analytical cross-sectional study was performed at University Medical Centre (UMC) Ljubljana between January 2021 and June 2022. Of the 37 patients included in the study, all had had a glucose hydrogen (H_2) breathing test (BT) and filled out the Questionnaire.

This study was approved by the Slovenian Republican Committee for Medical Ethics (national ethics committee) under the number 0120-515/2020/3, by Medical Faculty Ljubljana and UMC Ljubljana. All procedures performed in the study involving human participants were by the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Participants

Patients included were adults (> 18 years old), who had surgical resection of gastric carcinoma, being subtotal or total gastrectomy between January 2017 and June 2022, with or without gastrointestinal symptoms that signed the free consent form. We excluded patients who were incapable of preparing, executing or finishing the study, were using antibiotics, prokinetics and/or laxatives in the past two weeks and had basal concentration of H_2 at the start of the H_2BT in two different measures, 20 minutes apart, > 10 parts per million (ppm).

Glucose Hydrogen Breathing Test

Participants were instructed to ingest a low-fermentation diet 24 hours before the exam and to avoid smoking and physical activity on the day of the exam. Participants fasted overnight (12 h) and during the H_2 BT. At the start of the test, a basal sample of expired air was collected using an H_2BT device (Lactofan 2 Fischer®, Leipzig, Germany). The results were expressed as ppm. If the first measure (basal concentration) of H_2 was < 10 ppm, the participants ingested 25 g of glucose diluted in 200 mL of water. Every 20 min, in total of 120 min, 6 expired air samples were collected. An elevation of more than 12 ppm according to the basal value, within 120 min was deemed to be a positive result, indicating SIBO.

Questionnaire

Demographic and anthropometric data (age, gender, weight, educational level, socioeconomic status, time after surgery), symptoms and comorbidities (adjusted The Gastrointestinal Symptoms Rating Scale Questionnaire and adjusted SIBO Questionnaire), eating patterns (frequency of meals, snacks, breakfast, refined sugars, vegetable, fruit, fast food, and starch), treatment with (neo) adjuvant chemo/radiotherapy and quality of life (36-Item Short Form Survey (SF-36) Questionnaire) were analysed with the Questionnaire.

Table 1. Characteristics of patients according to positive or negative postoperative breath tests

Variable	Positive breath test (n = 11)	Negative breath test (n = 26)	p
Age (years)	59,2 ± 11,3	64,2 ± 11,3	0,272
Women (n, (%))	5 (45,5 %)	8 (30,8 %)	0,465
BMI (kg/m^2)	24,0 ± 4,3	23,4 ± 3,4	0,654
Education level	3,91 ± 1,38	4,15 ± 1,35	0,523
SE status	5,91 ± 1,97	6,08 ± 1,92	0,851
Time after S (months)	15,8 ± 14,9	28,8 ± 20,7	0,056
No complications (%)	90,9	76,9	0,649

The variables are expressed as mean ± SD (standard deviation); n (%) represents the number and percentage of variables. Statistical analysis was done using Mann-Whitney U and Fisher exact tests; p < 0,05
BMI – body mass index, S – surgery, SE – socioeconomic status

Surgical procedures

Surgical procedures were open or laparoscopic standard subtotal or total curative gastrectomy with lymphadenectomy performed by experienced surgeons with mainly Roux-en-Y reconstruction of the digestive tract.

STATISTICAL ANALYSIS

For statical analysis, categorical variables were expressed as number of participants and percentage (%) and numerical variables were expressed as mean value ± standard deviation. Categorical variables were analysed using the Chi-square test and Fischer exact test, depending on sample size. Numerical variables were analysed with a nonparametric test in case of non-sufficient sample size and with a parametric Student's t-test in the case of sufficient sample size. The Spearman correlation was used for small observed group statistical analysis. A 95% confidence interval was calculated and a p-value < 0,05 was considered statistically significant.

RESULTS

Characteristics of the population.

Out of 37 patients, 7 underwent subtotal gastrectomy and 30 underwent total gastrectomy, 24/37 (65,9%) were male and 13/37 (35,1%) were female. Mean age was 62,676 ± 11,36 years (range 33–81 years), mean body weight was 72,927 ± 12,42 kg (range 52–100 kg), mean BMI was 23,589 ± 3,62 kg/m^2 (range 15,8–34,6 kg/m^2), mean level of education was 2 (range 1–6), mean time after surgery was 24,956 ± 19,88 months (range 1,00–96,00).

Incidence of SIBO and Factors Associated with SIBO

Glucose H_2 BT was positive in 2/7 (29%) and negative in 5/7 (71%) patients after subtotal gastrectomy. Glucose H_2 BT was positive in 9/30 (30%) and negative in 21/30 (70%) patients after total gastrectomy. Characteristics of patients according to positive or negative postoperative BT are presented in Table 1. Symptoms according to positive and negative BT are presented in Table 2.

Table 2. Symptoms according to positive and negative postoperative breath tests after total and subtotal gastrectomy

Variable	Positive breath test (n = 11)	Negative breath test (n = 26)	p
Chronic pain	2,27 ± 1,85	2,27 ± 2,38	0,795
Diarrhoea	1,82 ± 1,33	2,42 ± 2,04	0,435
Frequent defecation	2,18 ± 0,60	1,98 ± 0,65	0,320
Obstipation	2,00 ± 2,72	1,54 ± 1,17	0,853
Floating stools	1,45 ± 0,52	1,77 ± 0,43	0,065
Abdominal cramps	2,23 ± 1,51	2,27 ± 2,38	0,580
Flatulence and bloating	6,18 ± 3,40	4,42 ± 2,67	0,107
Nausea	2,00 ± 1,79	1,85 ± 1,74	0,447
Vomiting	1,00 ± 0,00	1,77 ± 1,68	0,087
Belching	4,00 ± 3,35	2,65 ± 2,23	0,413
Loss of appetite	1,91 ± 2,39	2,31 ± 2,59	0,773
Bloating	4,27 ± 3,26	3,46 ± 2,55	0,465
Fever	1,00 ± 0,00	1,00 ± 0,00	NA
Joint pain	1,82 ± 1,83	2,69 ± 2,19	0,162
Fatigue	3,05 ± 3,10	3,54 ± 2,97	0,605
Skin lesions	1,64 ± 1,80	1,57 ± 1,45	0,942
Confusion and memory loss	1,73 ± 1,35	2,04 ± 2,01	0,789
Nausea with belching	2,00 ± 1,73	2,50 ± 2,10	0,399
Flatulence	2,5 ± 1,6	2,3 ± 1,0	0,524
Belching after meals	1,91 ± 1,51	2,04 ± 1,48	0,786
Pain and bloating	1,18 ± 1,54	1,40 ± 1,34	0,490
Obstipation	0,46 ± 1,21	0,46 ± 0,95	0,627
Diarrhoea and obstipation exchanging	0,36 ± 0,92	0,31 ± 0,68	0,817
Diarrhoea and obstipation	0,27 ± 0,65	0,31 ± 0,55	0,657

The variables are expressed as mean ± SD (standard deviation). Statistical analysis was done using Student's t-test

Neo (adjuvant) chemotherapy/radiotherapy

17/37 (45,9%) patients had neoadjuvant chemotherapy, 4/37 (10,8%) had neoadjuvant radiotherapy, 16/37 (43,2%) had adjuvant chemotherapy and 4/37 (10,8%) had adjuvant radiotherapy.

DISCUSSION

The main treatment for gastric cancer remains surgery that consists of gastric removal with/without lymphadenectomy and reconstruction of the gastrointestinal tract (3). Nowadays effective treatment is still lacking, with curative intent of gastric resections being nearly 50% with neoadjuvant therapy contributing to an improved survival rate up to 10% (3, 21). Although gastrectomy aims to achieve radical resection of the primary tumour and the lymph nodes, it has been indicated that surgery, especially Roux-en-Y anastomosis affects gastrointestinal microbiota in diversity and community composition (15, 20, 22–24). Patients with gastrectomy are at higher risk of developing type II diabetes and metabolic syndrome, as well as developing metachronous cancer, including colorectal cancer (3). Additionally, the importance of the altered gut microbiota composition for the interactions between cancer and immunity is gaining attention, along with a further introduction of immunotherapies into clinical practice (3). Finally, despite significant progress in the field of gastric surgery, postoperative malnutrition with weight loss, muscle mass reduction, and essential nutrient deficiencies is detrimentally impacting patients' quality of life and prognosis (10). Therefore, new strategies to find effective treatment for gastric carcinoma are necessary.

It is known that some cancers are associated with infection by specific bacteria, for example, Helicobacter pylori, which has been found to contribute to the development of MALT lymphoma and gastric cancer by causing chronic inflammation (3). Gastric microbiome compromises a population of its own and it has been reported that H. pylori-infected in comparison to non-infected individuals exhibited significant differences between gastric bacterial communities (3, 21). In non-infected or with proton pump inhibitors treated patients, luminal microbiota consists of Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria (3). Mucosal microbiota mainly consists of acid-resistant species, such as Veillonella, Lactobacillus, and Clostridium (3), while in H. pylori-infected patients Streptococcus, Neisseria, Staphylococcus, and Roche were also identified (3, 25). It was suggested that colonizing the stomach with commensal bacteria from other parts of the gastrointestinal region could promote gastric carcinogenesis associated with H. Pylori (3). Microbiota in gastric carcinogenesis are changed in a way there is an increase in the functional characteristics of nitrosing, an aspect compatible with the microbial community with increasing genotoxic potential (3). This later implies the response and prognosis of gastric cancer treatment (3).

The historical and empirical safety limit of gut shortening procedures has been mainly based on maintaining absorptive physiological functioning of the gastrointestinal tract based on the lack of threatening clinical malabsorption features (26). However, gut shortening is related to impaired resorptive function due to withdrawal and/or exclusion of the part of the digestive tract where micronutrient resorption and altered absorption surfaces occur under physiological conditions (26, 27). Gastric resection and reconstruction lead to prominent changes in oxygen availability, intestinal pH, gastric acid secretion, food transit time, intestinal motility, and hormonal activity, affecting the microbiome and faecal metabolism (3). These significant changes in the intestinal environment could lead to the growth of certain species. Gut microbiota in patients after gastrectomy consists of different microbiome composition and metabolite profiles compared to the control group (3).

The altered gut microbiome affects many types of cancer and can also affect gastric carcinoma carcinogenesis and the response and prognosis of gastric cancer treatment (3). Surgery for gastric carcinoma influences the postoperative composition of the gut microbiome, in particular, distal gastrectomy is related to the great abundance of Escherichia/Shigella, Veillonella, and Clostridium XVIII and Bacteroidetes in lower quantities (28). Faecal microbiota alterations may be connected to different responses to H. Pylori infection, especially alterations in the Bacteroidetes, Firmicutes and Proteobacteria phyla may be implicated in the progression of gastric lesions associated with H. pylori infection (29).

The altered gut microbiota could be applied in gastric carcinogenesis through immunomodulation, and it may as well affect the effectiveness of chemotherapy in patients with gastric carcinoma (3). Qui et al showed a correlation between intestinal dysbiosis in gastric cancer patients to peripheral cellular immunity with CD3+T cells being linked to the relative abundance of Lactobacillus and Streptococcus, while CD3+ T cells, CD4+ T cells, and NK cells are linked to Lachnospiraceae (30). These findings may suggest that Lachnospira and Lactobacillus may play vital roles in the alterations to the intestinal microbiota in gastric cancer patients and could be important targets for restoring the homeostasis of the intestinal bacterial community (30). Excessive amounts of the metabolic products of these bacteria characteristic of SIBO are associated with the extent of clinical signs in patients before and after gastrectomy, with an important impact of increased butyrate production.

The high prevalence of SIBO in patients who underwent gastrectomy has been reported, ranging from 15–83%, even reaching up to 96,2% in symptomatic patients after subtotal and total gastrectomy (31). Dysregulated intestinal microbiota in SIBO could be related to carcinogenesis by promoting inflammation which in the preoperative period contributes to the burden of disease with impaired peripheral cellular immunity (3). Inflammatory mediators due to the altered microbiome could facilitate cell proliferation, mutagenesis, angiogenesis, and oncogene activation related to gastric cancer but also other types of cancer such as metachronous liver, pancreatic, colon, oesophageal and pulmonary cancers (32). The candidate mechanism to promote carcinogenesis is cell proliferation via the activation of NF-κB and the inhibition of cellular apoptosis. Another important aspect is the relationship between gastric resection into the impairment of the oral microbiota and a consequent abundance of P. gingivalis and Aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans), associated with a decreased relative abundance of Fusobacterium and its genus Leptotrichiae, which are connected to the increased risk of pancreatic cancer via cytokine signalization and receptor degradation (33).

In this present study we have found that in the cohort of symptomatic and asymptotic patients, SIBO is present in 29% of patients after subtotal gastrectomy and in 30% of patients after total gastrectomy, which is similar to the data found in the literature. We are aware that our study could have underestimated the incidence of SIBO after such surgery procedures as we have used lower amounts of glucose (25g) to avoid developing dumping symptoms in our patients, with most of the other studies having used higher amounts of glucose, ranging from 50–75 g. We conclude that the incidence of SIBO after total and subtotal gastrectomy is worryingly high and therefore necessary to address its diagnostics in such patients.

Surgical resection of the gastrointestinal tract changes its normal anatomy and leads to certain anatomical and physiological changes, which in turn may predispose to SIBO (20, 26, 34). Development of the blind loop after gastric reconstruction is such an anatomical change, although the literature on blind loop predisposing to SIBO is contradictory (26, 35). Another reason connected to developing SIBO after surgery is the delayed action of bile acids on the gastrointestinal tract due to the reconstruction and with it loss of their antimicrobial function (20). Other potentially important anatomic or physiologic mechanisms are also strictures, adhesions, reduced small bowel motility, gastroparesis, neuropathy, impaired transit time, impaired gastric acid secretion and impairment of immunological mechanisms (9, 20, 24, 26, 35). After all, systemic treatment such as the use of (neo)adjuvant chemo-radiotherapy which could harm the mucosa barrier either through direct effects or by causing diminished intestinal blood circulation could predispose to SIBO (36). Due to the bidirectional connection of the portal vein between the intestinal microbiome and the liver, intestinal dysbiosis can also affect the progression of liver disease to liver cirrhosis and its complications via the impairment of the so-called gut liver axis (37–39).

New therapies for gastric cancer have been developed recently, targeting gut microbiota, which has already been approved by FDA (3). It is proposed that the microbiome may have a role in cancer treatment with multiple mechanisms responsible for antineoplastic effects by which the bacteria could exert anticancer effects. In general, bacteria exhibit anticancer activity through four major mechanisms including improving the host immunity; decreasing the required tumour metabolic and proliferation factors; biofilm formation and colonizing into the tumour; using as a target delivery vehicle and releasing relevant substances (40). Immunotherapy for gastric cancer based on immune checkpoint inhibitors (nivolumab, pembrolizumab) can be introduced in patients with high levels of microsatellite instability and/or mismatch repair gen and high tumour mutational burden, HER2 positive combined with trastuzumab (3). The introduction of immunotherapy to standard protocols of chemotherapy treatment for gastric carcinoma has an additional impact on the altered microbiota in the gastrointestinal tract, including both the altered microbiota in the gastric remnant after subtotal gastrectomy and the altered microbiota in the jejunum and ileum, as well as the oral microbiota (3). The literature also reveals that pre- and postoperative probiotics contribute to gut microbiota homeostasis with reduction of inflammation, maintenance of the intestinal barrier and improved immunity (3, 41).

Changes after gastric cancer surgery also have implications for postoperative nutrition. In the modern era, the prospects of cure and prolonged survivorship have improved in patients with gastric cancer, that are treated with curative intent and where radical resection is possible (22). As survivorship increases, other issues than oncologic outcomes must be considered in long-term follow-up, including nutritional well–being, which has an important influence on the prognosis (22). Maintaining body weight after upper gastrointestinal cancer surgery is a recognized significant challenge, but despite the prevalence and importance of weight loss, the incidence, severity, and specific causes of malabsorption are not well understood (22).

Malnutrition prevalence varies across different tumour sites ranging from 80–85% in pancreatic cancer, up to 74% for gastric cancer and 30–60% in colorectal cancer (10, 34, 42). Studies revealed before major gastric cancer surgery approximately 80% of patients with esophagogastric cancer experience significant weight loss and up to 27% of patients are already malnourished (10). Cancer-related sarcopenia (i.e., low muscle quantity and quality) contributes independently to the rate of postoperative complications and overall survival in gastric cancer (10). A grading system based on BMI and per cent weight loss (% WL) among cancer patients has shown that patients with higher % WL and lower BMI have notably shorter median survival, increased rate of surgical and non-surgical complications and prolonged hospitalization (10). Malnutrition also impacts neoadjuvant treatment being an independent predictor of chemotherapy dose–reduction of toxicity as malnourished patients are more likely to have their starting chemotherapy dose reduced from standard published dose (10, 42).

Malnutrition is connected to a variety of mechanisms due to local and systemic aspects of gastric carcinoma. Locally advanced disease is related to early satiety, therefore reduced intake of food, vomiting and anaemia due to bleeding and nutrient deficiency (10). Systemically, pro-inflammatory cytokines and chronic inflammation, lead to muscle wasting, and metabolic dysregulation with additional weight loss, known as cancer-induced cachexia (42). Neo-adjuvant chemo/radiotherapy combined with psychosocial factors related to cancer (i.e., fear, anxiety, depression) also contribute to additional weight loss (10, 42). Another possible and potentially treatable cause of malnutrition is the possibility of developing complications, such as small intestinal bacterial overgrowth (SIBO) (34).

The type of surgical reconstruction influences the development of micronutrient deficiency (6). It is the passage of food through the duodenum that appears to influence the micronutrient deficiency (6). After surgery reconstruction there is an accelerated passage of the contents through the gastrointestinal tract as well as diminished gastric acid availability in the small intestine due to the accelerated passage (10). The most commonly described deficiencies are iron (40–70%), copper and zinc (10–75%) (10), as well as calcium deficiency, due to several mechanisms, which include insufficient dietary intake, decreased dissolution of calcium salts due to hypochlorhydria and vitamin D deficiency (10). Calcium deficiency is one of the main causes of bone disorders following gastrectomy (10). 75% of patients have diminished phosphate levels due to insufficient intake, bypass of the gastric absorption site, and vitamin D deficiency (10).

The jejunum and ileum are key absorption sites for fat-soluble vitamin, which includes vitamin A, D, E and K (6, 10). Undergoing gastrectomy patients are at risk of developing A, D and E deficiency (6, 10). After a total gastrectomy, there is an increased risk of lowered bone mineral density, probably due to vitamin D deficiency (10). Vitamin B_1 deficiency post-surgery is reported up to 49% resulting in duodenal and proximal jejunal exclusion as the primary absorption area (10). Vitamin B_{12} deficiency affects around one-third or more patients and is causing permanent megaloblastic anaemia. Folate deficiency also leads to megaloblastic anaemia and is far less common due to absorption across the entire small intestine (10). At lower incidence of B_{12} deficiency due to absorption across small intestinal areas (10).

Long-term changes in bowel function after gastric cancer surgical resection are common and are connected to decreasing the patient's quality of life (2). Also, altered microbiome pre- and post-surgery and neoadjuvant treatment contribute to the onset of clinical symptoms such as pain, diarrhoea and malabsorption, additional weight loss and cancer and malnutrition-related cachexia which is connected to poor life prognosis (2). Depending on which gastrointestinal functions are altered, a variety of different symptoms can present (43). Symptoms that are common in patients with SIBO condition are non-specific, such as non-specific abdominal pain, bloating, flatulence, obstipation, diarrhoea, malabsorption, and consequent unintentional weight loss (31). Non-specific abdominal symptoms are common after surgical resections of the upper gastrointestinal tract in patients with and without SIBO condition and they often trigger extensive diagnostic evaluation (31).

Careful evaluation of clinical symptoms in patients after total and subtotal gastrectomy presented, patients are more likely to manifest certain symptoms of SIBO. Besides, this study found that the symptoms were poor predictors of SIBO, as the symptom profiles were similar between SIBO negative and SIBO positive groups. We found that none of the symptoms were more frequent in the case of SIBO in symptomatic and asymptomatic patients after total and subtotal gastrectomy. In addition to the above, the recognition of symptoms in patients may also be subject to the patient's attitude towards knowledge of post-surgical complications. The extent to which the patient experiences these clinical symptoms certainly depends on the degree of symptom presence, knowledge of possible post-surgical complications, and assessment of quality of life. Targeted symptom-finding, considering the necessary nutritional treatment, could significantly improve treatment outcomes and also allow patients greater access to adjuvant treatment.

Literature reveals that symptoms are poor predictors for SIBO as most of the research did not find any connection to certain symptoms, with most of the research on symptomatic patients after RYGB surgery for morbid obesity treatment ((15, 18, 44)). Increasing evidence of microbiota involvement in different pathologies and disease burden offered new evidence-based data connecting gastric carcinoma and microbiota involvement (44). Besides, the characteristics of the microbial community play key roles as potential biomarkers and predictors of responses in cancer therapy (44).

Paik et al have found that abdominal fulness and borborygmus during glucose BT are positive predictive factors for SIBO (23). It is hard to compare their study with ours as we were trying to find the pretest symptoms that would help diagnose SIBO and not symptoms that are present during glucose BT. Paik et al suggested that SIBO could be associated with postprandial intestinal symptoms (23). Liang et al have proved that SIBO is connected to the severity or intensity of symptoms in patients with gastric cancer, also described and postulated with some other research groups; results are limiting due to a small number of included patients, poor description of observed groups or limited to SIBO detection preoperatively (36). Therefore, we have come to the conclusion that none of the pretest symptoms is connected to SIBO after total and subtotal gastrectomy, therefore having a glucose BT is necessary for such patients. Regarding Paik et al and Liang et al, it is possible that SIBO-positive patients have a higher intensity of symptoms or that their symptoms are more severe postprandial, but more research is needed to prove this hypothesis.

The integrity of the intestinal mucosa barrier is damaged by chemotherapy and radiotherapy used in treatment protocols for gastric cancer either through direct effects on the epithelial stem cell compartments or by causing diminished intestinal blood circulation (36). Both mechanisms provoke ischemic hypoxia resulting in the activation of the xanthine oxidase and subsequently oxygen-free radical production (36). The ionizing radiation triggers intestinal cell necrosis, and consequent reduced function and survival of enterocytes (36). Effects of chemo/radiotherapy therefore result in making enterocytes less capable of counteracting bacterial growth and invasion (36).

In this present study, we have not found statistically significant differences between SIBO positive and negative groups in treatment with (neo)adjuvant chemo/radiotherapy. To the best of our knowledge, this is the first research to have analysed the influence of chemo/radiotherapy treatment on SIBO in post-gastrectomy treatment. In terms of explaining the phenomenon, the data presented here would be significantly more relevant if patients were tested preoperatively and, secondly, if the microbiome of positive patients was analysed. We need to conclude that more research is needed to find out whether there is a connection between SIBO to dose and type of chemo/radiotherapy and any other correlation.

SIBO is a well-known cause of malabsorption and malnutrition; given the explained altered physiological circumstances after subtotal and total gastrectomy and the proven metabolic disturbances in the SIBO state, we expect a more rapid occurrence of deficiencies of minerals and some vitamins, especially those whose key resorption or mechanisms take place in the duodenum. Accelerated passage of contents through the alimentary canal and triggering factors influencing the exacerbation of SIBO further exacerbate metabolic deficiencies; the introduction of antimicrobial agents for SIBO-related clinical signs may further exacerbate or mask the often-combative clinical signs. In addition, in the presence of SIBO, due to the rapid passage of the contents through the gastrointestinal tract, lower plasma levels of chemotherapeutic agents can be expected in patients treated with oral chemotherapeutic agents in adjuvant treatment regimens, thus blunting the otherwise reasonable chances of a complete response to treatment. It should also be noted that the recognition of SIBO in the early postoperative period is also underestimated because of the altered dietary regimen that might explain the appearance of certain clinical signs. Literature reports that up to 74% of post-gastrectomy patients have a BMI < 18,5 kg/m^2 and up to 58% have hypoproteinaemia and albuminemia (< 3,5 mg/dl) ((34, 45)). Aisa et al have found a trend towards lower levels of prealbumin and vitamin D, although the differences were not statistically significant (46). Extended meta-

Table 3. (Neo)adjuvant chemo/radiotherapy and antibiotic treatment according to positive and negative breath test

Variable	**Positive breath test (n=11)**	**Negative breath test (n=26)**	**p**
Chemotherapy before S	1,455 ± 0,52	1,577 ± 0,50	0,501
Chemotherapy after S	1,364 ± 0,50	1,654 ± 0,49	0.108
Radiotherapy before S	1,909 ± 0,30	1,885 ± 0,33	0,829
Radiotherapy after S	1,818 ± 0,40	1,924 ± 0,27	0,354

The variables are expressed as mean ± SD (standard deviation). Statistical analysis was done using the Mann-Whitney U test and Fisher exact test bolic screening of patients has not been introduced in clinical protocols for post-operative follow-up, which could also account for the high incidence of late metabolic complications after gastrectomy.

In this present study SIBO positive and SIBO negative patients did not have important different eating patterns as eating profiles were similar in both groups. It is possible that eating patterns do not differ and that SIBO is one of the possible and treatable causes of malabsorption and malnutrition in patients after surgical removal of the gastrointestinal tract due to gastric cancer. Despite the rapid passage of contents through the gastrointestinal tract due to the tailored formula, ONS dietary treatment could have delayed the onset of metabolic disturbances; most patients in the observation group were prescribed pre-formulated formulas, but precise data on the actual consumption of fortified foods could not be obtained. At the same time, prescribing tailored nutritional formulas allows the patient to be able to resorb vitamins, minerals, and trace elements in a tailored way, which should be taken into account at least in the early postoperative period, until the adaptive environment has fully developed.

In conclusion regarding the high incidence of SIBO after total and subtotal gastrectomy, and its causal involvement in malabsorption and malnutrition it is necessary to diagnose and treat SIBO in such patients. Additional studies are needed to understand the exact connection between SIBO, malabsorption and its consequences in patients after gastrectomy and the impact of SIBO on the schemas of neoadjuvant treatment protocols for improved survival and QL.

The strength of this study is its focus on the connection between SIBO and surgical removal of the gastrointestinal tract after gastric cancer as this remains the mainstay treatment in these patients. We demonstrated the high incidence of SIBO after surgical resections for gastric carcinoma and mandatory early diagnosis and treatment.

The study had several limitations. First is the small number of participants, included in the study, but the interpretation of our results was based on significant data from the literature, therefore the importance of our study is increased even with the small cohort. The second limitation is the lack of a standardized methodology for diagnosing SIBO. The gold standard is a jejunal aspiration, which is very invasive and is therefore not suitable for our patients. The third limitation is the dose of glucose used for BT. In our study, we used 25 of glucose, because we wanted to avoid dumping symptoms in our patients. In the lite-

Table 4. Eating patterns according to positive and negative postoperative breathing tests after total and subtotal gastrectomy

Variable	Positive breath test (n = 11)	Negative breath test (n = 26)	p
Meals per day	4,636 ± 1,21	4,750 ± 0,97	0,958
Snacks per day	1,727 ± 1,01	2,000 ± 1,23	0,395
Sugars (n, (%))	0 (0,0)	2 (7,7)	0,744
Eating bread (n, (%))	9 (81,8 %)	20 (80,0%)	1,000
Drinking coffee (n, (%))	1 (9,1)	15 (57,7)	0,010*
Normal appetite	2 (22,2)	5 (19,2)	1,000
Fibres worsens symptoms	0,364 ± 0,67	0,2692 ± 0,83	0,300
Eating starch often	1,273 ± 1,49	1,423 ± 1,37	0,691
Starch worsens symptoms	0,546 ± 1,21	0,423 ± 0,95	0,808
Quit eating starch	0,636 ± 1,21	0,654 ± 1,02	0,938

rature, the glucose doses used in BT for the diagnosis of SIBO ranged from 25 to 100 g (15). There is a lack of standardization, but the North American consensus of 2017 suggests that a dose of 75 g of glucose appears to be the most practical dose for diagnosing SIBO (47). On the contrary, the European guideline on indications, performance, and clinical impact of hydrogen and methane breath tests in adult and paediatric patients of 2021 has suggested that this large dose is commonly associated with false positive diagnoses of SIBO (48). We are aware that due to smaller amounts of glucose, we could underestimate the prevalence of SIBO. The fourth limitation is that due to the study design, we did not have data on SIBO prevalence before surgical resection. The last limitation of our study is that we did not exclude patients with co-existing conditions, such as diabetes mellitus, connective tissue disease, chronic pancreatitis, thyroid disease, liver disease and some others that may be connected higher incidence of SIBO in our patients.

CONCLUSION

The incidence of SIBO in patients who underwent total and subtotal gastrectomy for gastric carcinoma is worryingly high, 30 and 29% respectively. The incidence of SIBO after total and subtotal gastrectomy is currently underestimated. SIBO is connected to systemic metabolic complications and their consequences. Symptoms are a poor predictor for SIBO, as the symptom profile is similar between SIBO positive and SIBO negative groups, therefore the diagnosis cannot be made based on clinical symptoms. Glucose BTs are useful and inexpensive tools for diagnosing SIBO but there is an urgent need for standardization.

The results of this observational study confirm there is an urgent need to systematically address SIBO after surgical resections of the gastrointestinal tract due to gastric cancer in subtotal and total gastrectomy to affect the clinical outcome and prevent the development of complications. Besides, SIBO as a clinical entity is implicated in the occurrence of gastric cancer, so there is also a diagnostic entity for disease confirmation and post-operative follow-up.

References

1. Zeng F, Chen L, Liao M, Chen B, Long J, Wu W, et al. Laparoscopic versus open gastrectomy for gastric cancer. World J Surg Oncol. 2020 Jan 27;18(1).
2. Gonsalves AR, Ambrogini O, Forones NM. NONINVASIVE BREATH TESTS FOR DIAGNOSIS OF SIBO AND LACTOSE INTOLERANCE IN PATIENTS ON CHEMOTHERAPY TREATMENT FOR COLORECTAL AND GASTRIC CÂNCER. Arq Gastroenterol (Internet). 2021 Apr 23 (cited 2023 Jan 26);58(1):26–31. Available from: http://www.scielo.br/j/ag/a/Nz8M67khQRDTW7dFfpc98Bt/?lang=en.
3. Pappas-gogos G, Tepelenis K, Fousekis F, Katsanos K, Pitiakoudis M, Vlachos K. The Implication of Gastric Microbiome in the Treatment of Gastric Cancer. Vol. 14, Cancers. MDPI; 2022.
4. Cummins J, Tangney M. Bacteria and tumours: Causative agents or opportunistic inhabitants? Vol. 8, Infectious Agents and Cancer. 2013.
5. Maekita T, Nakazawa K, Mihara M, Nakajima T, Yanaoka K, Iguchi M, et al. High levels of aberrant DNA methylation in Helicobacter pylori-infected gastric mucosae and its possible association with gastric cancer risk. Clinical Cancer Research. 2006 Feb 1;12(3 I):989-95.
6. Muszyński T, Polak K, Fratczaką A, Miziołek B, Bergler-Czop B, Szczepanik A. Vitamin D—The Nutritional Status of Post-Gastrectomy Gastric Cancer Patients—Systematic Review. Vol. 14, Nutrients. MDPI; 2022.
7. Ferreira RM, Pereira-Marques J, Pinto-Ribeiro I, Costa JL, Carneiro F, MacHado JC, et al. Gastric microbial community profiling reveals dysbiotic cancer-associated microbiota. Gut. 2018 Feb 1;67(2):226-36.
8. Aboona MB, Wong TW, Del Prado PR, Paley K, Goldberg RF, Weimer S, et al. Severe small intestinal bacterial overgrowth syndrome after jejunal feeding requiring surgical intervention: a case report and review of the literature. BMC Gastroenterol. 2022 Dec 1;22(1).
9. Schrope B, Coons B, Rosario V, Toledano S. Proximal gastrectomy is a viable alternative to total gastrectomy in early-stage proximal gastric cancer. Journal of the Society of Laparoendoscopic Surgeons. 2021 Jul 1;25(3).
10. Teixeira Farinha H, Bouriez D, Grimaud T, Rotariu AM, Collet D, Mantziari S, et al. Gastro-Intestinal Disorders and Micronutrient Deficiencies Following Oncologic Esophagectomy and Gastrectomy. Cancers (Basel) (Internet). 2023 Jul 9;15(14):3554. Available from: https://www.mdpi.com/2072-6694/15/14/3554
11. Lertpiriyapong K, Whary MT, Muthupalani S, Lofgren JL, Gamazon ER, Feng Y, et al. Gastric colonisation with a restricted commensal microbiota replicates the promotion of neoplastic lesions by diverse intestinal microbiota in the Helicobacter pylori INS-GAS mouse model of gastric carcinogenesis. Gut. 2014 Jan;63(1):54-63.
12. Villanueva-Millán MJ, Pérez-Matute P, Oteo JA. Gut microbiota: a key player in health and disease. A review focused on obesity. J Physiol Biochem. 2015 Sep 19;71(3):509-25.

13. Jandhyala SM, Talukdar R, Subramanyam C, Vuyyuru H, Sasikala M, Reddy DN. Role of the normal gut microbiota. World J Gastroenterol. 2015 Aug 7;21(29):8836-47.
14. Dixit K, Chaudhari D, Dhotre D, Shouche Y, Saroj S. Restoration of the dysbiotic human gut microbiome for homeostasis. Vol. 278, Life Sciences. Elsevier Inc.; 2021.
15. Mouillot T, Rhyman N, Gauthier C, Paris J, Lang AS, Lepers-Tassy S, et al. Study of Small Intestinal Bacterial Overgrowth in a Cohort of Patients with Abdominal Symptoms Who Underwent Bariatric Surgery. Obes Surg. 2020 Jun 1;30(6): 2331-7.
16. Madrid AM, Poniachik J, Quera R, Defilippi C. Small intestinal clustered contractions and bacterial overgrowth: A frequent finding in obese patients. Dig Dis Sci. 2011 Jan;56(1):155-60.
17. Coelho LK, Carvalho NS, Navarro-Rodriguez T, Marson FAL, Carvalho PJPC. Lactulose Breath Testing Can Be a Positive Predictor Before Weight Gain in Participants with Obesity Submitted to Roux-en-Y Gastric Bypass. Obes Surg. 2019 Nov 1;29(11):3457-64.
18. Sabaté JM, Jouët P, Harnois F, Mechler C, Msika S, Grossin M, et al. High prevalence of small intestinal bacterial overgrowth in patients with morbid obesity: A contributor to severe hepatic steatosis. Obes Surg. 2008 Apr;18(4):371-7.
19. Quigley EMM. The Spectrum of Small Intestinal Bacterial Overgrowth (SIBO). Vol. 21, Current Gastroenterology Reports. Current Medicine Group LLC 1; 2019.
20. Kim YJ, Paik CN, Jo IH, Kim DB, Lee JM. Serum gastrin predicts hydrogen-producing small intestinal bacterial overgrowth in patients with abdominal surgery: A prospective study. Clin Transl Gastroenterol. 2021 Jan 23;12(1).
21. Chen X, Xia C, Li Q, Jin L, Zheng L, Wu Z. Comparisons between bacterial communities in the mucosa in patients with gastric antrum ulcer and a duodenal ulcer. Front Cell Infect Microbiol. 2018 May 8;8(MAY).
22. Heneghan HM, Zaborowski A, Fanning M, Mchugh A, Doyle S, Moore J, et al. Prospective study of malabsorption and malnutrition after oesophageal and gastric cancer surgery. Ann Surg. 2015 Nov 1;262(5):803–8.
23. Kim DB, Paik CN, Kim YJ, Lee JM, Jun KH, Chung WC, et al. Positive glucose breath tests in patients with hysterectomy, gastrectomy, and cholecystectomy. Gut Liver. 2017 Mar 1;11(2):23-42.
24. Paik CN, Choi MG, Lim CH, Park JM, Chung WC, Lee KM, et al. The role of small intestinal bacterial overgrowth in postgastrectomy patients. Neurogastroenterology and Motility. 2011 May;23(5).
25. Chen X, Xia C, Li Q, Jin L, Zheng L, Wu Z. Comparisons between bacterial communities in the mucosa in patients with gastric antrum ulcer and a duodenal ulcer. Front Cell Infect Microbiol. 2018 May 8;8(MAY).
26. Bastos EL de S, Liberatore AMA, Tedesco RC, Koh IHJ. Gut Microbiota Imbalance Can Be Associated with Non-malabsorptive Small Bowel Shortening Regardless of Blind Loop. Obes Surg. 2019 Feb 15;29(2):369-75.
27. Jirapinyo P, Makuvire TT, Dong WY, Chan WW, Thompson CC. Impact of Oral-Cecal Transit Time on the Interpretation of Lactulose Breath Tests After RYGB: a Personalized Approach to the Diagnosis of SIBO. Obes Surg. 2019 Mar 15;29(3):771-5.
28. Liang W, Yang Y, Wang H, Wang H, Yu X, Lu Y, et al. Gut microbiota shifts in patients with gastric cancer in the perioperative period. Medicine (United States). 2019;98(35).
29. Gao JJ, Zhang Y, Gerhard M, Mejias-Luque R, Zhang L, Vieth M, et al. Association between gut microbiota and Helicobacter pylori-related gastric lesions in a high-risk population of gastric cancer. Front Cell Infect Microbiol. 2018 Jun 19;8(JUN).
30. Qi Y feng, Sun J ning, Ren L feng, Cao X ling, Dong J Hong, Tao K, et al. Intestinal Microbiota Is Altered in Patients with Gastric Cancer from Shanxi Province, China. Dig Dis Sci. 2019 May 15;64(5):1193-203.
31. Dolan RD, Baker J, Harer K, Lee A, Hasler W, Saad R, et al. Small Intestinal Bacterial Overgrowth: Clinical Presentation in Patients with Roux-en-Y Gastric Bypass. Available from: https://doi.org/10.1007/s11695-020-05032-y
32. Kim C, Chon HJ, Kang B, Kim K, Jeung HC, Chung HC, et al. Prediction of metachronous multiple primary cancers following the curative resection of gastric cancer. BMC Cancer. 2013 Aug 23;13.
33. Bagheri Z, Moeinzadeh L, Razmkhah M. Roles of Microbiota in Cancer: From Tumor Development to Treatment. Vol. 2022, Journal of Oncology. Hindawi Limited; 2022.
34. Pérez Aisa A, García Gavilán MC, Alcaide García J, Méndez Sánchez IM, Rivera Irigoin R, Fernández Cano F, et al. Small intestinal bacterial overgrowth is common after gastrectomy but with little impact on nutritional status. Gastroenterología y Hepatología (English Edition). 2019 Jan;42(1):1-10.
35. Brechmann T, Sperlbaum A, Schmiegel W. Levothyroxine therapy and impaired clearance are the strongest contributors to small intestinal bacterial overgrowth: Results of a retrospective cohort study. World J Gastroenterol. 2017 Feb 7;23(5): 842-52.
36. Liang S, Xu L, Zhang D, Wu Z. Effect of probiotics on small intestinal bacterial overgrowth in patients with gastric and colorectal cancer. Turkish Journal of Gastroenterology. 2016 May 1;27(3):227-32.
37. Lefere S, Onghena L, Vanlander A, van Nieuwenhove Y, Devisscher L, Geerts A. Bariatric surgery and the liver—Mechanisms, benefits, and risks. Vol. 22, Obesity Reviews. John Wiley and Sons Inc; 2021.
38. Rafiei R, Bemanian M, Rafiei F, Bahrami M, Fooladi L, Ebrahimi G, et al. Liver disease symptoms in non-alcoholic fatty liver disease and small intestinal bacterial overgrowth. Rom J Intern Med. 2018 Jun 1;56(2):85-9.
39. Ferro D, Baratta F, Pastori D, Cocomello N, Colantoni A, Angelico F, et al. New insights into the pathogenesis of non-alcoholic fatty liver disease: Gut-derived lipopolysaccharides and oxidative stress. Vol. 12, Nutrients. MDPI AG; 2020. p. 1-14.
40. Soleimanpour S, Hasanian SM, Avan A, Yaghoubi A, Khazaei M. Bacteriotherapy in gastrointestinal cancer. Vol. 254, Life Sciences. Elsevier Inc.; 2020.
41. Khachfe HH, Salhab HA, Fares MY, Chahrour MA, Jamali FR. Landscape of interventional clinical trials involving gastrectomy for gastric cancer. Ecancermedicalscience. 2021 Apr 1;15.

42. Klute KA, Brouwer J, Jhawer M, Sachs H, Gangadin A, Ocean A, et al. Chemotherapy dose intensity predicted by baseline nutrition assessment in gastrointestinal malignancies: A multicentre analysis. Eur J Cancer. 2016 Aug 1;63: 189-200.
43. Muls AC, Amyn Lalji A, Christopher Marshall B, Lewis Butler C, Clare Shaw D, Susan Vyoral E, et al. The holistic management of consequences of cancer treatment by a gastrointestinal and nutrition team: a financially viable approach to an enormous problem? Vol. 16, ORIGINAL RESEARCH Clinical Medicine. 2016.
44. Liu Y, Baba Y, Ishimoto T, Gu X, Zhang J, Nomoto D, et al. Gut microbiome in gastrointestinal cancer: a friend or foe? Vol. 18, International Journal of Biological Sciences. Ivyspring International Publisher; 2022. p. 4101-17.
45. Bushyhead D, Quigley EMM. Small Intestinal Bacterial Overgrowth Pathophysiology and its Implications for Definition and Management. Gastroenterology. 2022 Sep;
46. Pérez Aisa A, García Gavilán MC, Alcaide García J, Méndez Sánchez IM, Rivera Irigoin R, Fernández Cano F, et al. Small intestinal bacterial overgrowth is common after gastrectomy but with little impact on nutritional status. Gastroenterología y Hepatología (English Edition). 2019 Jan;42(1):1-10.
47. Rezaie A, Buresi M, Lembo A, Lin H, McCallum R, Rao S, et al. Hydrogen and Methane-Based Breath Testing in Gastrointestinal Disorders: The North American Consensus. American Journal of Gastroenterology. 2017 May 1;112(5):775-84.
48. Hammer HF, Fox MR, Keller J, Salvatore S, Basilisco G, Hammer J, et al. European guideline on indications, performance, and clinical impact of hydrogen and methane breath tests in adult and pediatric patients: European Association for Gastroenterology, Endoscopy and Nutrition, European Society of Neurogastroenterology and Motility, and European Society for Paediatric Gastroenterology Hepatology and Nutrition consensus. United European Gastroenterology Journal. John Wiley and Sons Inc; 2021.