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Navigating Through Surgical Implications of *Helicobacter pylori*: An Up-to-Date Comprehensive Literature Review

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Abbreviations:
H. pylori: Helicobacter pylori;
MALT: mucosa-associated lymphoid tissue;
PUD: peptic ulcer disease;
TLR:toll-like receptors;
NSAID: nonsteroidal anti-inflammatory drug;
GOO: gastric outlet obstruction;
EBD: endoscopic pneumatic dilation;
PPU: Perforated peptic ulcer;
PG: proximal gastrectomy;
DG: distal gastrectomy;
PPI: proton pump inhibitor;
B-I: Billroth-I;
RY: Roux-en-Y;
EGC: early gastric cancer;
GC: gastric cancer;
AGC: advanced gastric cancer;
PNI: peripheral nerve invasion;
CEA: carcino-embryonic antigen;
VEGF: vascular endothelial growth factor;
MMP-9: metalloproteinase-9;
ICIs: immune checkpoint inhibitors;
PD1: programmed cell death-1;
PDL1: programmed cell death-ligand 1;

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Rezumat

Investigarea implicațiilor chirurgicale ale Helicobacter pylori: o recenzie exhaustivă și actualizată a literaturii

Helicobacter pylori, o bacterie gram-negativă, a fost identificată ca un factor major în etiologia şi patogenia afecțiunilor gastro-intestinale, variind de la gastrită şi ulcere peptice la patologii mai grave precum adenocarcinomul gastric şi limfomul tisular asociat mucoasei (MALT). Deşi terapiile farmacologice de eradicare au avut succes în tratarea bolilor asociate cu infecția cu *H. pylori*, influențele acestei bacterii asupra intervențiilor chirurgicale sunt încă subiect de cercetare continuă şi de considerare clinică. Această recenzie exhaustivă îşi propune să clarifice implicațiile complexe ale infecției cu *H. pylori* în contextul intervențiilor chirurgicale. Astfel, sunt analizate datele recente referitoare la relația bine-cunoscută între bacteria gram-negativă şi apariția bolilor gastro-duodenale, inclusiv ulcerele peptice şi cancerul gastric. Totodată, colonizarea cu *Helicobacter pylori* poate juca un rol în promovarea carcinogenezei colonică şi, mai interesant, a fost asociată şi cu neoplasmele căilor biliare. Prezentul studiu al literaturii evidențiază progresul evolutiv al managementului infecției cu *H. pylori* în contextul intervențiilor chirurgicale, subliniind necesitatea unor cercetări suplimentare pentru a stabili strategii optime pentru screening-ul preoperator, terapiile de eradicare şi impactul acestora asupra rezultatelor chirurgicale şi prognosticului pe termen lung al pacienților. Înțelegerea implicațiilor chirurgicale ale infecției cu *H. pylori* rămâne esențială pentru accentuarea importanței managementului interdisciplinar şi a eforturilor continue de cercetare menite să îmbunătățească îngrijirea pacientului.

CTLA-4: cytotoxic T-lymphocyte antigen 4;
EGD: esophagogastroduodenoscopy;
CRC: colorectal cancer;
CagA: cytotoxin-associated gene A;
AP: denomatous polyps;
HP: hyperplastic polyps;
RNA: ribonucleic acid;
HCC: hepatocellular carcinoma;
HCV: hepatitis C virus;
CCA: cholangiocarcinoma;
PBC: primary biliary cholangitis;
PSC: primary sclerosing cholangitis;
VSG: vertical sleeve gastrectomy;
LSG: laparoscopic sleeve gastrectomy;
VSG: vertical sleeve gastrectomy.

Cuvinte cheie: Helicobacter pylori, carcinogeneza, strategii, screening, implicații chirurgicale, prognostic

Abstract

Helicobacter pylori, a gram-negative bacterium, has been identified as a major contributor to gastrointestinal diseases, ranging from gastritis and peptic ulcers to more severe complications such as gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma. While pharmacological eradication therapies have been successful in managing *H. pylori*-associated diseases, the implications of this bacterium on surgical interventions remain a topic of ongoing research and clinical consideration. This comprehensive review aims to elucidate the intricate surgical implications of *H. pylori* infection. Recent data on the well-known relationship between *H. pylori* and the development of gastroduodenal diseases, including peptic ulcers and gastric cancer, is analyzed. Concurrently, Helicobacter pylori infection may have a role in promoting colonic carcinogenesis and, more interestingly, it has also been linked to biliary tract cancers. The review highlights the evolving landscape of *H. pylori* management in the context of surgical interventions, accentuating the need for further research to delineate optimal strategies for preoperative screening, eradication therapies, and their impact on surgical outcomes and long-term patient prognosis. Comprehending the surgical ramifications of *H. pylori* infection remains crucial, emphasizing the significance of interdisciplinary approaches and ongoing research effort aimed at enhancing patient care.

Key words: *Helicobacter pylori*, carcinogenesis, strategies, screening, surgical implications, prognosis

Introduction

The pivotal discovery of *Helicobacter pylori* (*H. pylori*) in 1982, by Warren and Marshall, marked a milestone in medical history by identifying a bacterial infection as the underlying cause of chronic gastritis and successfully isolating the responsible microorganism. The authors conducted self-administered experiments involving the ingestion of a bacterial broth and subsequent resolution of gastritis upon *H. pylori* eradication, thereby meeting the criteria outlined in Koch's postulates (1).

This groundbreaking achievement led to their recognition and subsequent award of the Nobel Prize in Physiology or Medicine in 2005. Since then, ongoing scientific advancements and novel clinical findings have necessitated frequent revisions and updates in the clinical approach to managing *H. pylori*-related conditions (2).

H. pylori infection represents a widespread bacterial infection targeting the gastric

mucosa, affecting approximately half of the global population. However, its prevalence fluctuates based on geographic location and sanitation conditions. In Europe it exhibits a heterogeneous distribution. While rates have significantly declined over recent decades due to improved living conditions and widespread use of antibiotics, infection rates still vary within and between European countries. For instance, Southern and Eastern Europe generally showcase higher prevalence rates compared to Northern and Western Europe. Countries such as Italy, Romania, and Greece have reported higher *H. pylori* prevalence due to historical socioeconomic factors and varied healthcare access (3).

Despite the acidic reflux of gastric juice, low pH, and proteolytic activity, which typically create an inhospitable environment for microorganisms, the gram-negative bacterium *H. pylori* contradicts the concept of gastric sterility by thriving in this milieu. The equilibrium in the gastric mucosa is maintained through intricate immune and autoimmune regulatory mechanisms. In contrast to the intestinal environment, the gastric microenvironment lacks MALT, but orchestrates an immune response largely governed by the behavior of its epithelial layer (4).

Consequently, gastric epithelial cells serve a dual purpose: fortifying a physical barrier through mucous secretion and actively participating in the production of inflammatory cytokines, chemokines, antigen-presenting cells, and co-stimulatory molecules during instances of inflammation and tissue injury. Gastric immunological defense mechanisms involve humoral and cellular immunity. Numerous clinical studies emphasize the crucial role of gastric cellular immunity in initiating and sustaining immune equilibrium within the gastric milieu, underscoring the essentiality of epithelial cell integrity in mucosal autoimmunity (5).

The pathogenesis of *H. pylori* infection relies on intricate bacterial virulence mechanisms interacting with the host's immune system and environmental elements, culminating in diverse gastritis phenotypes that dictate potential progression toward various gastroduodenal pathologies. It stands as the primary causative factor for chronic gastritis and exhibits variable progression toward severe gastroduodenal pathologies in certain individuals, clustering conditions such as gastric and duodenal peptic ulcer disease (PUD), gastric MALT lymphoma, and gastric cancer (6).

The clinical implications of *H. pylori* infection are primarily influenced by the pattern and severity of *H. pylori* induced gastritis (7). An antral-predominant pattern, characterized by heightened acid secretion and relative sparing of the gastric corpus with its abundant parietal cell mass, increases the likelihood of peptic ulcers leading to complications such as hemorrhage, perforation, and gastric outlet obstruction. In contrast, the development of gastric cancer is associated with corpus-predominant gastritis, gastric atrophy, and a substantial loss of acid secretory capacity (8). Experimental animal investigations propose that transplanting the gastric microbiota from individuals with intestinal metaplasia or gastric cancer into germ-free mice induces the formation of precancerous gastric alterations (9).

Nevertheless, the impact of *H. pylori* on the survival rates of patients with gastric cancer remains to be elucidated (10). The correlation between *H. pylori* infection and the onset of gastric carcinoma has been extensively substantiated, resulting in the classification of Helicobacter pylori as a human carcinogen by the World Health Organization. Consequently, chronic infection with *H. pylori* was officially affirmed in 2021 within the list of substances identified or anticipated to induce cancer in humans in the National Toxicology Program's 15th Report on Carcinogens (11).

Beyond the gastric site of colonization, an elevated risk of colorectal cancer has been documented in correlation with a positive infection status. There have been indications of an association between *H. pylori* infection and the presence of hypergastrinemia, leading to increased proliferation of the colorectal mucosa. Potential pathological mechanisms

underlying this association include the direct mucosal stimulation, modifications in the gut microbiome and the induction of low-grade systemic inflammation (12,13). Multiple studies have explored the plausible link between *H. pylori* infection and colorectal polyps (14). Recent evidence suggests that individuals positive for this bacterial infection exhibit nearly twice the risk of developing colorectal cancer compared to those negative for *H. pylori* infection (15).

The hepato-biliary tract represents an additional anatomical site susceptible to colonization by this bacterium, potentially resulting in severe illnesses such as cirrhosis, hepatocarcinoma, cholangiocarcinoma or cholelithiasis. Multiple hypotheses aim to elucidate the mechanisms underlying the impact of *H. pylori* infection on the pathogenesis of hepatobiliary diseases (16). Among these theories, one postulates that the disruption of the epithelial barrier of the gastrointestinal tract allows the migration of microbiota and their byproducts into the portal system, triggering an inflammatory cascade mediated by toll-like receptors (TLR) present in hepatocytes (17).

Furthermore, *H. pylori* infection prompts the secretion of vasoactive and pro-inflammatory molecules and acute phase proteins (18). This infection is proposed to have systemic repercussions mediated by these cytokines, exacerbating diverse inflammatory responses (19). Ultimately, *H. pylori* significantly contributes to the onset of perioperative complications such as marginal ulcers, anastomotic leaks, or abscesses. These occurrences have been reported in academic literature concerning individuals who have undergone bariatric surgical interventions.

Considering the abundant data available on this comprehensive topic, our aim in conducting this literature review is to synthesize the latest advancements associated with the activity of this gram-negative bacterium within the gastrointestinal tract that might correlate with surgical consequences.

Helicobacter Pylori and Gastric Pathologies

Gastritis

Colonization of the gastric mucosa by *H. pylori* prompts a pro-inflammatory reaction within gastric epithelial cells, leading to the recruitment of various immune cells into the submucosal layer. This culminates in chronic gastritis, which typically remains asymptomatic for extended periods of time in the majority of patients. The degree of inflammation greatly varies among individuals, influenced by multiple factors such as bacterial morphology, host characteristics, and environmental features. The primary determinant of the pro-inflammatory capability of an *H. pylori* strain is the presence of a functional virulence determinant cag pathogenicity island (cagPAI) (20).

Atrophic gastritis denotes the disappearance of gastric glands, often arising from autoimmunity or chronic inflammation of the stomach mucosa, particularly linked to *H. pylori* infection. Diagnosis relies on histopathological examination, regardless of the underlying cause. Gastric atrophy marks the initial precancerous phase, succeeded by gastric intestinal metaplasia, dysplasia, and eventually gastric adenocarcinoma. It is recommended to screen all patients with atrophic gastritis for *H. pylori* infection, and if positive, eradication therapy is advised. Research indicates a substantial association between *H. pylori* infection and gastric atrophy, with a 5% incidence rate among Hp-positive individuals compared to less than 1% among *H. pylori*-negative individuals (21). For patients with H pylori-positive atrophic gastritis, endoscopic surveillance every three years is recommended, alongside evaluations for deficiencies in iron and vitamin B12.

For certain individuals, the potential for gastric mucosa restoration exists subsequent to the eradication of *H. pylori* infection, contingent upon the extent of mucosal damage. However, in cases involving extensive or severe atrophy, despite successful eradication of *H. pylori*, there remains an augmented risk of gastric cancer, necessitating ongoing

endoscopic surveillance. Nevertheless, there are findings supporting a decline in gastric cancer incidence subsequent to *H. pylori* treatment, even in instances characterized by persistent atrophic conditions (22).

Peptic ulcer disease (PUD)

Despite evolving patterns of debate on PUD globally, *H. pylori* infection and use of NSAID remain the predominant etiological factors underlying its prevalence (23). Globally, the incidence of PUD has decreased, attributed to enhanced hygiene, effective treatments, and cautious administration of NSAIDs (24). Duodenal ulcers exhibit a prevalence four times greater than gastric ulcers and they tend to occur more frequently in male population than in females (25).

The estimated lifetime prevalence of PUD among individuals with *H. pylori* infection is approximately 10%. Over a 10-year period, more than 11% of those infected develop PUD, contrasting with a 1% occurrence rate in uninfected individuals. Schöttker et al conducted a study encompassing a cohort of nearly 10,000 individuals, revealing in their cross-sectional analysis that infection with cagA-positive strains of *H. pylori* was linked to a 1.75-fold higher risk of PUD. In longitudinal analyses, the study unveiled an 18.4-fold escalated risk for duodenal ulcer and a 2.9-fold escalated risk for gastric ulcer, respectively (26).

Regarding the morphology of this condition, lesions measuring less than 5 mm in diameter are termed erosions, while those exceeding 5 mm in diameter are referred to as ulcers. Notably, Zollinger-Ellison syndrome, caused by gastrin-producing endocrine tumors or gastrinomas, leads to multiple ulcers in the duodenum and jejunum. Assessing gastrin serum levels stands as the gold-standard diagnostic approach for this condition.

Since the groundbreaking identification of *H. pylori* infection, the approach to managing PUD has undergone a profound transformation, shifting from predominantly surgical interventions to medical therapies (27).

The successful eradication of *H. pylori* demonstrates ulcer healing rates exceeding 90% (28). Healing gastric ulcers typically necessitates prolonged acid suppression and endoscopic monitoring remains essential to ensure complete restoration of tissue integrity and to rule out underlying related digestive malignancies.

Surgical intervention is recommended in cases where patients do not respond to medical therapy, demonstrate noncompliance, or present a high risk of complications. The complications associated with PUD incorporate hemorrhage, gastric outlet obstruction (GOO), perforation, penetration, and the development of gastric malignancies such as adenocarcinoma and MALT lymphoma.

Significantly, hemorrhaging surfaces as the predominant complication, impacting roughly 15-20% of patients, constituting approximately 40-60% of the overall instances of acute upper gastrointestinal bleeding (23). Notably, the immediate management of bleeding peptic ulcers, whether gastric or duodenal, requires prompt stabilization of cardiocirculatory and respiratory functions, immediate intravenous PPI therapy, emergency evaluation endoscopy providing diagnostic and therapeutic results (29). *H. pylori* eradication treatment should start once the active bleeding phase is managed. Repetitive hemorrhaging correlates with elevated mortality rates and may necessitate subsequent endoscopic procedures, interventional radiology-guided angiographic embolization, or surgical interventions (23).

Gastric outlet obstruction, a debilitating complication of PUD, can be effectively managed through surgical interventions, either as an initial therapeutic intervention or following the inadequacy of conservative approaches like medical treatment and endoscopic pneumatic dilation. Zare et al showed on 22 individuals that EBD is a safe approach in the treatment of GOO, delivering positive and enduring outcomes. Nearly three quarters (73%) of patients had relief in clinical symptoms following 2 sessions of EBD, while 27% required 3 sessions (30).

Perforated peptic ulcer (PPU) represents a surgical emergency, retaining an elevated

mortality rate estimated within the range of approximately 8.55% to 30.0% (31).

Conservative treatment with nasogastric suction, acid suppression and antibiotics can be a treatment option for poor surgical candidates with a contained perforation debuted more than 24 hours. The laparoscopic surgery for PPU has proven to be a safe procedure being recommended as the 2020 WSES guidelines, in experimented centers (32).

Gastric carcinoma

Gastric cancer represents a substantial global health concern, comprising around 5.5% of newly diagnosed cancer cases worldwide in 2020 (33). Its impact on mortality is notable, contributing to almost 7.5% of cancer-related deaths globally. The prognostic outlook for gastric cancer remains bleak, marked by a considerable decline in the 5-year survival rate, dropping from 70% for localized cases to a mere 6% for those diagnosed at an advanced stage (34).

Approximately 90% of gastric cancer occurrences are linked to *H. pylori* infection, establishing *H. pylori* as the predominant pathogen implicated in carcinogenesis (35). *H. pylori* has been classified as a Group 1 carcinogen specifically associated with gastric cancer by IARC (International Agency for Research on Cancer) (36). Variations in gastric cancer incidence and mortality across regions are prominent, with notably elevated rates observed in Asia and Eastern Europe (37). Socioeconomic status, dietary preferences, and lifestyle behaviors, including smoking habits and levels of salt consumption, contribute to gastric cancer development. However, these factors are considered secondary to the decisive influence exerted by the presence of *H. pylori* infection (3).

In a recent publication dated 2023, on a large cohort of more than 6,000,000 individuals, Wong et al introduced an algorithm designed for predicting gastric carcinoma in symptomatic patients, incorporating a scoring system that includes the presence of Helicobacter pylori infection among its constituents (38). While *H. pylori* is acknowledged for its potential in assessing the risk of gastric cancer, prior studies that constructed risk prediction models for gastric cancer predominantly relied on lifestyle habits and demographic elements (38).

H. pylori infection triggers the activation of oncogenes and the inhibition of tumor suppressor genes via genetic and epigenetic mechanisms. Given the absence of distinct clinical indicators and early diagnostic biomarkers, the diagnosis of gastric cancer typically occurs at an advanced stage, limiting the opportunity for optimal therapeutic interventions. Presently, the correlation between chronic inflammation and cancer has emerged as a fundamental attribute of malignancy. Chronic inflammation establishes an environment that suppresses the immune system, facilitating the genesis and progression of tumors as well as metastases (39).

As per findings from multiple studies, the Hippo pathway emerges as a potential diagnostic marker for gastric cancer, significantly influencing numerous biological processes encompassing cell proliferation, apoptosis, tissue differentiation, organ development, and tumorigenesis (40,41). This pathway, comprised of a kinase cascade and a suite of effector molecules, represents an evolutionarily conserved signaling mechanism. Numerous cellular signaling cascades, among them HippoYAP, are involved in overseeing the disruption of gastric epithelial cell balance induced by *H. pylori*. The results of a recent study suggest that elevated expression levels of YAP/TAZ-TEAD and their respective target genes frequently correlate with a more aggressive manifestation of gastric cancer, indicating a less favorable prognosis for affected patients (42).

Although specific retrospective studies have suggested the potential impact of eradicating *H. pylori* following partial gastrectomy on long-term prognosis, consensus in this area remains elusive (10). In a recent 2023 study from Korea, Yanagawa S. et al assessed the spontaneous disappearance rate of *H. pylori* post-partial gastrectomy in 80 patients with gastric carcinoma, 9 having undergone proximal gastrectomy (PG) and the remainder

distal gastrectomy (DG), findings revealing a degree of resolution of *H. pylori* infection was confirmed through stool antigen tests one year after the operation. Of the cohort, *H. pylori* infection disappeared in 34 patients (42.5%). While potential explanations such as residual stomach acidity from environmental factors, postoperative proton pump inhibitor (PPI) utilization, or alterations in the intestinal microbiota due to chemotherapy may account for the spontaneous resolution, the precise underlying mechanism remains uncertain. When comparing surgical techniques, there was no statistically significant distinction in the spontaneous resolution rate of *H. pylori* infection between PG and DG. Similarly, among the DG patients, there was no statistically significant difference in the surgical approaches between individuals who had Billroth-I (B-I) and Roux-en-Y (RY) reconstruction. The spontaneous disappearance of *H. pylori* after partial gastrectomy should be analyzed on larger prospective randomized studies in order to establish the underlying mechanism. In this way, unnecessary *H. pylori* eradication can be avoided and the incidence of *H. pylori*-related GC can be reduced (43).

The impact of Helicobacter pylori infection upon the survival of the individuals diagnosed with GC is under debate. While some studies have reported *H. pylori* negative status as independent predictive factor for poorer outcomes after gastrectomy, it is widely accepted that *H. pylori* eradication decreases tumor recurrence and enhances survival in individuals under-going endoscopic resection for early gastric cancer (EGC) (44). Additionally, the presence of premalignant GC lesions, like atrophic gastritis and intestinal metaplasia, is associated with a 4-6 times higher risk of GC among *H. pylori*-positive patients compared to *H. pylori*-negative individuals (45,46).

Guidelines advocate for *H. pylori* eradication following endoscopic treatment for early gastric cancer (EGC). However, the advantageous effect of *H. pylori* eradication on survival in patients undergoing gastrectomy remains inconclusive. In advanced gastric cancer (AGC), survival is primarily influenced by TNM classification. Further investigation is warranted to assess *H. pylori* positivity and cancer stage as distinct risk factors for recurrence and survival. The study conducted by Choi et al in 2020 examined the impact of *H. pylori* eradication after subtotal gastrectomy in a large cohort with extended follow-up period. Firstly, improved overall and GC-specific survival benefits were observed in the *H. pylori*-eradicated group. Secondly, *H. pylori* positivity remained an independent risk factor for GC-specific mortality and cancer recurrence. Moreover, concerning AGC, *H. pylori* positivity and final cancer stage were identified as independent risk factors for GC-specific mortality and cancer recurrence in both univariate and multivariate Cox proportional hazards analyses. These findings of this study, the first of its kind, suggest potential extensions to future *H. pylori* eradication guidelines and emphasize the importance of intensive screening and treatment for *H. pylori* infection in patients undergoing surgical treatment for both EGC and AGC (10).

The proposal of eradicating Helicobacter pylori as a preventative measure against gastric cancer has emerged naturally, previous retrospective investigations suggesting potential involvement of *H. pylori* along with other synergistic elements in the development of gastric cancer. Recent research has revealed that *H. pylori* infection significantly impacts gastric microbial dysbiosis, possibly contributing to carcinogenesis. However, successful eradication of the infection reinstates the gastric microbiota to a condition resembling that of uninfected individuals, thereby exhibiting beneficial effects on the gut microbiota (47).

A primary concern surrounding anti-*H. pylori* therapy revolves around antibiotic resistance. One recent study from Korea published in 2020 by Guo et al identified several upregulated drug resistance-related functional orthologs in cases where tetracycline-containing treatments have failed. This discovery contributes to unsuccessful treatment outcomes, which can also result in intricate impacts on the gut microbiota due to antibiotic use. However, following successful

eradication, a majority of the notably altered drug resistance functional orthologs demonstrated a decrease in expression, indicating that successful eradication might exert beneficial effects on enrichment of probiotics and suppression of drug-resistant mechanism related to gut microbiota. Moreover, interactions between other bacteria (which are influenced by gastric dysbiosis) and *H. pylori*-associated gastric lesions might contribute to the development of gastric carcinogenesis, yet further validation is required (47).

The combination of immunotherapy and surgical intervention stands as a predominant and aggressive therapeutic approach for individuals suffering from gastric carcinoma. However, despite this treatment regimen, certain patients display unfavorable prognoses. In a 2023 study, Liu et al conducted an analysis of mortality risk factors among patients undergoing radical surgery and immunotherapy for gastric cancer. On a cohort of 1,015 patients, 39 variables comprising diverse characteristics were studied. The findings indicated that advanced age, tumor invasion, lymph node metastasis, peripheral nerve invasion (PNI), multiple tumors, tumor size, specific tumor markers - such as carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), and carbohydrate antigen 72-4 (CA72-4), along with *H. pylori* infection were associated with a negative prognosis (48). Several mechanisms contribute, including the acceleration of vascular endothelial growth factor (VEGF) expression, fostering new blood vessel formation in the tumor microenvironment and the upregulation of metalloproteinase-9 (MMP-9) expression, an enzyme involved in extracellular matrix degradation. These mechanisms collectively enhance tumor proliferation, migration and elevate the likelihood of an unfavorable prognosis (49,50).

Regarding immunotherapy, the implementation of immune checkpoint inhibitors (ICIs) targeting programmed cell death-1 (PD1), programmed cell death-ligand 1 (PDL1), and cytotoxic T-lymphocyte antigen 4 (CTLA-4) has revolutionized the approach to gastric cancer treatment, whether administered individually or alongside chemotherapy (51). *H. pylori* infection was associated with elevated PD-L1 expression, possibly representing a beneficial aspect in individuals undergoing ICI treatment (52). However, recent investigations indicate that this infection might negatively impact outcomes in patients treated with immunotherapy (53).

As per current literature, Magahis et al conducted the most extensive study in this domain. Their findings revealed a notable correlation: patients with metastatic gastric cancer undergoing ICI therapy displayed significantly reduced progression-free survival and overall survival when affected by *H. pylori* infection. Notably, both prior and current infection showed comparable adverse responses to immunotherapy, making HP status an important predictive marker responsiveness to ICI treatment (54).

Even though the eradication of *H. pylori* might confer enduring protection against gastric cancer, therapeutic measures targeting *H. pylori* could potentially delay the identification of malignancies that might manifest as nonspecific gastrointestinal symptoms. In a previous study conducted in Finland, the elimination of *H. pylori* extended the time to diagnose gastric cancer, with a median delay of 7.5 months (36). Consequently, it is crucial to underline that the diagnostic assessment for malignancies should persist even upon the detection and treatment of *H. pylori* infection.

Gastric mucosa-associated lymphoid tissue (MALT) lymphoma

First described by Isaacson and Wright in 1983, MALT lymphoma signifies the transformation of B cells located within the marginal zone of mucosa-associated lymphoid tissue into a malignant state. The stomach predominantly represents the primary location linked to MALTomas, although other extranodal sites encompass the lung (14%), ocular adnexa (12%), thyroid (4%), and the small intestine (55, 56). Complications stemming from gastric MALT lymphoma, such as obstruction,

perforation, or bleeding, have become infrequent since the introduction of screening esophagogastroduodenoscopy (EGD), although there are instances where surgical intervention may be necessary. Moreover, individuals diagnosed with gastric MALT lymphoma exhibit a heightened susceptibility to the metachronous occurrence of gastric adenocarcinoma. Palmela et al documented that the relative risk for gastric adenocarcinoma in patients previously diagnosed with gastric MALT lymphoma stood at 4.32 (95% CI 2.64–6.67) (57).

A gastric MALT lymphoma typically exhibits an indolent nature and expresses favorable response rates to standard *H. pylori* eradication therapy, particularly when detected early. In a systematic review conducted by Zullo et al encompassing almost 1,400 patients diagnosed with low-grade stage I or stage II lymphoma, remission was observed in 77.5% of cases (58). However, Kim et al reported that approximately 25% of gastric MALT lymphomas demonstrate resistance to *H. pylori* eradication therapy (59). In another investigation conducted by Zullo et al, a pooled-data analysis involving 315 patients resistant to *H. pylori* eradication therapy was performed. The study revealed that among the second-line therapeutic options, radiotherapy was most commonly employed, followed by surgical intervention and chemotherapy. Notably, patients subjected to radiotherapy exhibited a comparable remission rate to those undergoing surgical resection (97% vs. 93%; p = 0.2) and a notably higher remission rate in comparison to individuals receiving chemotherapy (97% vs. 85%; p = 0.007) (60).

Gu et al documented, in 2023, an uncommon instance of gastric MALT lymphoma manifesting as gastric outlet obstruction occurring two years subsequent to *H. pylori* eradication therapy. In response to the gastric outlet obstruction, imperative palliative surgery was deemed necessary, wherein laparoscopic distal gastrectomy with a D1 lymph node dissection and partial omentectomy were conducted. Concurrently, systemic chemotherapy utilizing a CHOP regimen (comprising cyclophosphamide, doxorubicin, vincristine, and prednisone) was initiated. Over the subsequent five-year follow-up period no recurrence was detected, and the state of remission was sustained (55).

An infrequent discovery pertains to intestinal MALToma. While conventionally perceived as unrelated to *H. pylori* infection, select case reports have documented lymphoma regression subsequent to the initiation of eradication therapy targeting *H. pylori*. Badwaik et al presented a case involving MALToma in the ileum, complicated by intussusception—an occurrence characterized by the telescoping of a proximal segment of the intestine into the lumen of an adjacent section. The patient underwent resection and anastomosis of the ileal segment, with no recurrence observed during the follow-up period (61).

Relationship between Helicobacter pylori and Colorectal Cancer

Apart from serving as the primary risk factor in the development of gastric cancer, epidemiological investigations and meta-analyses indicate that individuals infected with this pathogen bear a nearly doubled risk of developing colorectal cancer (CRC) (62). Nonetheless, a direct causal and functional relationship between *H. pylori* infection and colon cancer remains inconclusive (63).

Multiple potential causal connections exist between the presence of *H. pylori* and the identification of CRC (64). A topic under great debate in specialized literature involves the potential carcinogenic impact of *H. pylori* on the mucosal lining of the colon. Furthermore, there have been documented instances wherein the identification of *H. pylori* in resected specimens for colorectal carcinoma was achieved using diverse histopathological diagnostic techniques. Moreover, the heightened production of gastrin resulting from *H. pylori* infection could potentially induce carcinogenesis by triggering proliferative impacts on the colonic mucosa.

In addition to the potential direct carcinogenic impact of *H. pylori* on the colorectal

mucosa, there have been deliberations regarding its indirect effects (15). First of all, changes in microbiota composition and the anomalous presence of specific bacterial strains in the small intestine have been linked to CRC development. This potentially presents an additional pathway through which *H. pylori* might influence intestinal carcinogenesis, considering its documented capability to modify microbiota profiles (47). Particular pathogens like Bacteroides fragilis and Enterococcus faecalis, alongside a general impact on colorectal dysbiosis, have been considered as potential causal connections (65).

Second of all, notably virulent strains of *H. pylori* characterized by the presence of the cytotoxin-associated gene A (CagA) gene might facilitate colorectal carcinogenesis through subclinical inflammation and heightened expression of proinflammatory cytokines (64).

Thirdly, host genes and their variations play a role in the response to *H. pylori*, potentially acting as susceptibility genes not only for gastric cancer development but also for CRC (66).

Conversely, CRC and *H. pylori* infection exhibit shared risk factors. Both conditions are correlated with cardiometabolic risk factors such as obesity, dietary patterns involving increased meat consumption, and tobacco usage (67). Moreover, there exists an association between low income and the prevalence of both *H. pylori* infection and CRC (68).

In a recent meta-analysis conducted by Lu et al, a cohort comprising over 300,000 participants from 17 observational studies was examined, revealing an independently correlation between *H. pylori* infection and the occurrence of colorectal polyps, but not serrated polyps. The combined outcomes utilizing a random-effects model indicated an independent association between *H. pylori* infection and overall colorectal polyps. For example, *H. pylori* infection was independently linked with adenomatous polyps (AP) (OR: 1.71, $p < 0.001$), advanced AP (OR: 2.06, $p < 0.001$), and hyperplastic polyps (HP) (OR: 1.54, $p = 0.04$). These findings imply that *H. pylori* infection might constitute a potential risk factor for colorectal polyps, highlighting its significance in preventive measures against colorectal polyps in the adult population (12).

Wernly et al conducted a study involving a cohort exceeding 5,000 asymptomatic patients who underwent screening colonoscopy and upper gastrointestinal endoscopy. The study aimed to evaluate the correlation between the presence of *H. pylori* infection and CRC. The outcomes of univariate and multivariate regression analysis revealed a significant association, wherein the diagnosis of *H. pylori* positivity was linked with the concurrent diagnosis of any CRC neoplasia, even after correction for common cardiometabolic risk factors (aOR 1.20; 95% CI 1.10–1.31; $p < 0.001$) (15).

Sonnenberg et al conducted a case-control study involving 300,000 patients, with over half presenting colonic polyps. Their findings suggested that the compromise of the gastric acid barrier might facilitate bacterial invasion of the lower intestinal tract, potentially fostering the progression of colonic carcinogenesis. However, this study did not incorporate corrections for variables beyond age and sex (69).

Nevertheless, these epidemiological observations have not yet received experimental validation, and the precise molecular mechanism through which *H. pylori* might facilitate CRC has remained volatile. Ralser A et al conducted a study employing two Apc-mutant mouse models and C57BL/6 mice infected with *H. pylori*. The authors conducted an extensive analysis of *H. pylori*-induced alterations in intestinal immune responses and epithelial characteristics using techniques such as flow cytometry, chip cytometry, immunohistochemistry, and single-cell RNA sequencing. The findings indicated an acceleration in tumor development due to *H. pylori* infection in Apc-mutant mice. They identified a distinctive immune alteration signature instigated by *H. pylori*, characterized by a decline in regulatory T cells and an increase in proinflammatory T cells. Additionally, within the intestinal and colonic epithelium, *H. pylori*

triggered pro-carcinogenic STAT3 signaling and a reduction in goblet cells. These changes, along with pro-inflammatory and mucus-degrading microbial signatures, were shown to contribute collectively to tumor development. Similar immune and epithelial modifications were discerned in a cohort of 154 human colon biopsies obtained from patients infected with *H. pylori* (70).

These discoveries imply that *H. pylori* infection might constitute a potential risk factor for colorectal cancer, providing important experimental confirmation that this infection promotes colorectal carcinogenesis.

The Link Between Helicobacter pylori Infection and Hepato-Biliary Tract Diseases

Primarily establishing colonization within the gastric mucosa, *H. pylori* has been identified within the biliary system, gaining access through either retrograde reflux from the sphincter of Oddi or hematologically via the portal circulation (71).

Multiple investigations have indicated a higher frequency of gastric and/or duodenal ulcers attributed to *H. pylori* among individuals with liver cirrhosis. For example, Feng et al, in their meta-analysis, delineated that within cirrhotic cohorts, the prevalence of *H. pylori* infection is notably elevated compared to control groups (OR=2.05, p<0.0001) (72).

Moreover, an association between liver cirrhosis and hepatocellular carcinoma (HCC) among individuals infected with *H. pylori* was established by Abdel-Razik et al. Notably, *H. pylori* emerged as an independent risk factor for portal vein thrombosis and HCC (p=0.043, p=0.037). Following *H. pylori* eradication, a decline in markers indicating inflammation and complications associated with cirrhosis was observed within one year (19).

In a recent extensive meta-analysis conducted by Madala et al, encompassing 26 studies, a noteworthy discrepancy in *H. pylori* infection rates emerged between patients with HCC and control groups. Notably, the prevalence of *H. pylori* infection was significantly higher in patients with HCC (OR= 4.75, 3.06-7.37). These findings suggest an elevated risk of HCC development in the presence of Helicobacter infection, particularly accentuated in cases of co-infection involving hepatitis C virus (HCV) and *H. pylori*. However, further prospective cohort studies are imperative to establish a conclusive causal relationship (73).

Given successful isolation of Helicobacter spp from the biliary system, an intriguing hypothesis surfaces concerning the potential involvement of these organisms in biliary tract diseases pathogenesis (17).

Although less recognized, *H. pylori* infection has been linked to cholelithiasis and cholecystitis. Investigations into the potential role of *H. pylori* in the development of gallstones have elucidated three plausible pathogenic mechanisms. Initially, the bacterium might serve as a focal point for the initiation of stone accumu-lation. Secondly, active infection within the bile vesicle heightens oxidative stress, escalating the generation of reactive oxygen and nitrogen species. This effect disrupts both the absorptive and secretory functions of the gallbladder, resulting in an elevated bile supersaturation within the organ, thereby fostering stone formation. Additionally, urease production increases the intra-gallbladder pH and stimulates enzymes responsible for bile deconjugation, ultimately leading to the precipitation of calcium bilirubinate (74,75).

Zhang et al, examining almost 15,500 participants, observed a significantly reduced gallstone occurrence among individuals whose *H. pylori* infection had been eradicated compared to those *H. pylori*-positive individuals without prior eradication (9.02% vs 9.47%; p< 0.0001) (76). Similarly, Takahashi et al, with a similar cohort size, noted comparable outcomes (6.08% vs 4.73%; p < 0.001) (77). Therefore, further exploration into the potential impact of *H. pylori* eradication on the management of gallbladder diseases is justified.

The reliability of these studies might be impacted due to the detection methodology utilized. Present diagnostic methods including urea breath tests and serology possess limitations as they cannot precisely identify

H. pylori infection within the gallbladder. More targeted detection approaches like PCR entail invasiveness, necessitating tissue samples, thereby restricting their application unless there are compelling indications for invasive biliary tract procedures. Despite the high specificity of PCR in detection, it fails to differentiate between active and inactive infections, potentially resulting in false-positive outcomes (78,79).

The capacity of *H. pylori* to generate pro-oncogenic agents such as CagA and VacA, along with its role in fostering chronic inflammatory conditions, can activate and instigate diverse carcinogenic pathways, resulting in increased cellular turnover. Persistent inflammatory processes predispose individuals to the development of both gallbladder cancer and cholangiocarcinoma (CCA) (80). In a case-control investigation conducted by Hassan et al, gallbladder mucosal histology was compared between non-infected and *H. pylori*-infected gallbladders. The findings indicated a substantial increase in mucosal hyperplasia ($p = 0.028$), along with metaplasia and dysplasia ($p = 0.049$) in *H. pylori*-infected gallbladders when contrasted with non-infected counterparts (81,82). These alterations are recognized as precursor lesions contributing to the development of gallbladder cancers.

Boonyanugomol et al reported a notably higher prevalence of *H. pylori* in bile samples obtained from cholangiocarcinoma (CCA) patients (66.7%) in comparison to those with cholelithiasis (41.5%) and the control group (25.0%), as determined by PCR analysis ($p < 0.05$ in both comparisons). Additionally, the study indicated a significantly elevated presence of the CagA gene in CCA patients compared to those with cholelithiasis (36.2% vs. 9.1%, $p < 0.05$), proposing its potential involvement in the pathogenesis of CCA (83).

It has been hypothesized that *H. pylori* might act as an etiological factor in primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) (84). However, findings in this area are conflicting. While Nilsson et al established a significant correlation between *H. pylori* infection and PSC/PBC, Boomkens et al found no disparities in the prevalence of PSC or PBC between *H. pylori*-positive and control groups. This presents an intriguing area for further investigation given the limited effective management strategies for PSC and PBC, both of which exhibit suboptimal outcomes (85,86).

In the past decade, numerous recent studies have explored the potential link between *H. pylori* infection and the development of pancreatic cancer, yielding inconsistent conclusions (87,88). However, a recent meta-analysis conducted by Zhou BG et al, comprising 20 observational studies involving over 67,000 participants, indicated that there exists no statistically significant association between *H. pylori* infection and the risk of pancreatic cancer ($OR = 1.20$, $p = 0.13$).

Moreover, the findings did not demonstrate any substantial correlation between CagA-positive and negative strains or VacA-positive strains of *H. pylori* infection and the likelihood of pancreatic cancer (89).

Currently, surgical intervention stands as the sole potential curative approach for biliary tract cancer, with a considerable recurrence rate despite the application of adjuvant chemotherapy (79). The efficacy of current *H. pylori* eradication regimens in eliminating the bacterium from the biliary tract remains uncertain. Considering the unfavorable prognosis associated with such conditions, further clarifications are required regarding detection methodologies, the etiological association between *H. pylori* and hepato-biliary tract diseases and the potential influence of *H. pylori* eradication on managing hepatobiliary tract diseases.

Helicobacter pylori and Perioperative Complications

It has been postulated that *H. pylori* infection may heighten the likelihood of postoperative complications subsequent to bariatric procedures due to its impact on the gastric mucosa (90,91). However, owing to the limited availability of data, the clinical practice guidelines on bariatric surgery issued by the

European Association for Endoscopic Surgery refrain from making a recommendation regarding preoperative eradication of *H. pylori* (92).

Prior meta-analyses examining the influence of *H. pylori* infection on outcomes of bariatric surgery have been documented. For instance, Mocanu et al conducted a meta-analysis comprising 255,435 patients who underwent various types of surgical bariatric procedures. The findings suggested a tenfold increase in marginal ulceration among *H. pylori* positive patients undergoing Roux-en-Y gastric bypass when compared to *H. pylori*-negative individuals. Nonetheless, similar rates of bleeding, leak incidents, hospital duration, and weight loss were observed between *H. pylori*-positive and *H. pylori*-negative patients (93).

Vertical sleeve gastrectomy (VSG) has emerged as the fastest-growing bariatric procedure globally, entailing the resection of the almost entire greater curvature of the stomach. This procedure significantly reduces the amount of tissue potentially colonized by *H. pylori* and, unlike gastric bypass, mitigates the risk of marginal ulceration. Despite this, there remains a dearth of definitive data concerning the management of *H. pylori* post VSG.

Information available in the specialized literature proposes that inflammation and edema within the gastric mucosa, consequent to *H. pylori* infection, might impede staple line formation, potentially elevating the risk of postoperative complications such as leakage, bleeding, or infection (94). Conversely, research indicates a low postoperative prevalence of *H. pylori* detected by urea breath tests despite a notable presence in immunohistochemical staining of excluded stomachs (95).

A meta-analysis conducted by Patrícia Marcolin focusing on laparoscopic Sleeve Gastrectomy (LSG), encompassing 6,199 patients, indicated a correlation between *H. pylori* infection and elevated rates of overall postoperative complications (OR 1.56, p=0.007) as well as staple line leak (OR 1.89, p = 0.03). Nonetheless, it is crucial to acknowledge that while such a correlation exists, other contributing factors may play substantial roles in the occurrence of this complication (96). Thus, the study does not establish a direct cause-and-effect relationship (97).

However, Brownlee et al have found that, among 480 patients undergoing primary vertical sleeve gastrectomy (VSG), 52 were identified as *H. pylori* positive based on pathological findings, thus creating two cohort groups. Within the initial 30-day postoperative period, 17 readmissions were recorded, with fewer than 30% occurring in the *H. pylori* positive cohort. Among those cases, 2 were classified as severe, involving occurrences of anastomotic leak and intra-abdominal abscess. Nevertheless, a definitive causal association with *H. pylori* infection status could not be established, as there was no statistically significant distinction in the rates of severe complications between the two groups (p = 0.67) (98).

Conclusion

In summary, the literature indicates that the surgical implications associated with *H. pylori* infection constitute a complex and continuously evolving subject of discussion. While extensive research has established its link with gastric disorders such as peptic ulcer disease, gastric cancer, and gastric MALT lymphoma, unraveling precise mechanisms and optimizing therapeutic interventions remains an ongoing challenge.

The observed correlations between *H. pylori*, colorectal polyps, and certain micro-biota alterations highlight its potential indirect impact on colorectal cancer. The association of *H. pylori* infection with hepato-biliary diseases is hypothesized through various theories involving gastrointestinal epithelial violation, microbial translocation, and immune stimulation. However, direct evidence establishing a pathogenic connection with pancreatic issues is still lacking.

Concerning bariatric surgery, the role of *H. pylori* in postoperative complications like staple line leaks is under ongoing investigation and scrutiny. The consideration of *H. pylori* infection in preoperative assessments is a subject of interest, with various diagnostic

methods available, including serological tests, urea breath tests, gastric endoscopy, and stool antigen tests.

However, much of the evidence comes from epidemiological studies where a comprehensive analysis of confounding factors is often lacking, making it challenging to establish causal relationships. Nonetheless, advancements in this field hold promise for refining preoperative management strategies, potentially improving patient outcomes. Interdisciplinary collaboration among surgical, clinical, and microbiological domains remains crucial for advancing our comprehension and refining treatment modalities. This collaboration aims to alleviate the surgical burden of *H. pylori* related diseases and enhance therapeutic strategies, ultimately improving patient care outcomes.

Author's Contributions

Conceptualization: R.C., T.P.; methodology, investigation: R.C., A.E., D.E.G.; writing - review & editing: D.E.G.; supervision: T.P.; All authors have read and agreed to the published version of the manuscript.

Conflicts of Interests

The authors declare no conflict of interest.

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References

1. Malfertheiner P, Constanza Camargo M, El-Omar E, Liou JM, Peek R, Schulz C, et al. Helicobacter pylori infection. Nat Rev Dis Primers. 2023;9(1):19.
2. Malfertheiner P, Link A, Selgrad M. Helicobacter pylori: perspectives and time trends. Nat Rev Gastroenterol Hepatol. 2014;11(10):628-38.
3. Venneman K, Huybrechts I, Gunter MJ, Vandendaele L, Herrero R, Van Herck K. The epidemiology of Helicobacter pylori infection in Europe and the impact of lifestyle on its natural evolution toward stomach cancer after infection: a systematic review. Helicobacter. 2018;23(3):e12483.
4. Yang I, Nell S, Suerbaum S. Survival in hostile territory: the microbiota of the stomach. FEMS Microbiol Rev. 2013;37(5):736-61.
5. Cortez V, Schultz-Cherry S. The role of goblet cells in viral pathogenesis. FEBS J. 2021;288(24):7060-7072.
6. Sugano K, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, et al. Kyoto global consensus report on Helicobacter pylori gastritis. Gut. 2015; 64(9):1353-67.
7. Hunt RH, Camilleri M, Crowe SE, El-Omar EM, Fox JG, Kuipers EJ, et al. The stomach in health and disease. Gut. 2015;64(10):1650-68.
8. Amieva M, Peek RM. Pathobiology of Helicobacter pylori-induced gastric cancer. Gastroenterology. 2016;150(1):64-78.
9. Kwon SK, Park JC, Kim KH, Yoon J, Cho Y, Lee B, et al. Human gastric microbiota transplantation recapitulates premalignant lesions in germ-free mice. Gut. 2022;71(7):1266-1276.
10. Choi Y, Kim N, Yun CY, Choi YJ, Yoon H, Shin CM, et al. Effect of Helicobacter pylori eradication after subtotal gastrectomy on the survival rate of patients with gastric cancer: follow-up for up to 15 years. Gastric Cancer. 2020;23(6):1051-1063.
11. Lunn R, Mehta S, Jahnke G, Wang A, Wolfe M, Berridge B. Cancer Hazard Evaluations for Contemporary Needs: Highlights From New National Toxicology Program Evaluations and Methodological Advancements. J Natl Cancer Inst. 2022;114(11):1441-1448.
12. Lu D, Wang M, Ke X, Wang Q, Wang J, Li D. Association between H. pylori infection and Colorectal Polyps: A Meta-Analysis of Observational Studies. Front Med (Lausanne). 2022:8:706036. eCollection 2021.
13. Constantin G, Firescu D, Voicu D, Stefanescu B, Serban R, Panaitescu E, et al. The Importance of Systemic Inflammation Markers in the Survival of Patients with Complicated Colorectal Cancer, Operated in Emergency. Chirurgia (Bucur). 2020;115(1):39-49.
14. Nam JH, Hong CW, Kim BC, Shin A, Ryu KH, Park BJ, et al. Helicobacter pylori infection is an independent risk factor for colonic adenomatous neoplasms. Cancer Causes Control. 2017;28(2):107-115.
15. Wernly S, Semmler G, Flamm M, Rezar R, Aigner E, Datz C, et al. The Association between Helicobacter pylori and Colorectal Neoplasia. Med Princ Pract. 2023;32(1):77-85.
16. Sharndama HC, Mba IE. Helicobacter pylori: an up-to-date overview on the virulence and pathogenesis mechanisms. Braz J Microbiol. 2022;53(1): 33-50.
17. Kugler T, Taradin G. Helicobacter and hepatobiliary diseases: update 2023 Arq Gastroenterol. 2023;60(2):271-281.
18. Doulberis M, Srivastava S, Polyzos SA, Kountouras J, Papaefthymiou A, Klukowska-Rötzler J, et al. Active Helicobacter Pylori infection is independently associated with nonalcoholic steatohepatitis in morbidly obese patients. J Clin Med. 2020;9(4):933.
19. Abdel-Razik A, Mousa N, Elhelaly R, Elzehery R, Hasan AS, Abdelsalam M, et al. Helicobacter pylori as an initiating factor of complications in patients with cirrhosis: a single-center observational study. Front Med (Lausanne). 2020;7:96.
20. Backert S, Haas R, Gerhard M, Naumann M. The Helicobacter pylori type IV secretion system encoded by the cag pathogenicity island: architecture, function and signaling. Curr Top Microbiol Immunol. 2017:413:187-220.
21. Annibale B, Esposito G, Lahner E. A current clinical overview of atrophic gastritis. Expert Rev Gastroenterol Hepatol. 2020;14(2):93-102.
22. Kato M, Hayashi Y, Nishida T, Oshita M, Nakanishi F, Yamaguchi S, et al. Helicobacter pylori eradication prevents secondary gastric cancer in patients with mild-to-moderate atrophic gastritis. J Gastroenterol Hepatol. 2021; 36(8):2083-2090.
23. Narayanan M, Reddy K, Marsicano E. Peptic Ulcer Disease and Helicobacter pylori infection. Mo Med. 2018;115(3):219-224.
24. Lanas A, Chan FKL. Peptic ulcer disease. Lancet. 2017;390(10094): 613-624.
25. Malik T, Gnanapandithan K, Singh K. Peptic Ulcer Disease. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan.
26. Schöttker B, Adamu MA, Weck MN, Brenner H. Helicobacter pylori infection is strongly associated with gastric and duodenal ulcers in a large prospective study. Clin Gastroenterol Hepatol. 2012;10(5):487-93.e1.
27. Kempenich J, Sirinek K. Acid Peptic Disease. Surg Clin North Am. 2018; 98(5):933-944.
28. Malfertheiner P, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, et al. Management of Helicobacter pylori infection — the Maastricht V/Florence consensus report. Gut. 2017;66(1):6-30.
29. Gralnek I, Stanley AJ, Morris AJ, Camus M, Lau J, Lanas A, et al. Endoscopic diagnosis and management of nonvariceal upper gastrointestinal hemorrhage (NVUGIH): European Society of Gastrointestinal

Endoscopy (ESGE) Guideline - Update 2021. Endoscopy. 2021;53(3): 300-332.
30. Zare E, Raeisi H, Honarvar B, Lankarani K. Long-term Results of Endoscopic Balloon Dilatation for Gastric Outlet Obstruction Caused by Peptic Ulcer Disease. Middle East J Dig Dis. 2019;11(4):218-224.
31. Chung KT, Shelat VG. Perforated peptic ulcer - an update. World J Gastrointest Surg. 2017;9(1):1-12.
32. Li ZW, Tong Y, Liu F, Liu XR, Lv Q, Tang KL. A comparative study on laparoscopic and open surgical approaches for perforated peptic ulcer repair: efficacy and outcomes analysis. Langenbecks Arch Surg. 2023;408(1):435.
33. Sung H, Ferlay J, Siegel R, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249.
34. U. D. o. H. a. H. S. NIoH, "Surveillance, Epidemiology, and End Results (SEER) Program," 2020. (Online). Available: https://seer.cancer.gov/about/.
35. Moss SF. The clinical evidence linking Helicobacter pylori to gastric cancer. Cell Mol Gastroenterol Hepatol. 2016;3(2):183-191.
36. Kosunen T, Nieminen A, Kokkola A, Arkkila P, Pukkala E, Rautelin H. Incidence of gastrointestinal malignancies increases in persons received eradication therapy for Helicobacter pylori: A cohort study. Helicobacter. 2023;28(3):e12979.
37. de Martel C, Georges D, Bray F, Ferlay J, Cliford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health. 2020;8(2):e180-e190.
38. Wong MCS, Yee-Man Leung E, Yau STY, Chan SC, Xie S, Xu W, Huang J. Prediction algorithm for gastric cancer in a general population: A validation study. Cancer Med. 2023;12(21):20544-20553. Epub 2023 Oct 19.
39. Hanahan D. Hallmarks of Cancer: New Dimensions. Cancer Discov. 2022; 12(1):31-46.
40. Masliantsev K, Karayan-Tapon L, Guichet PO. Hippo Signaling Pathway in Gliomas Cells. 2021;10(1):184.
41. Zheng A, Chen L, Zhang L. The Hippo-YAP pathway in various cardiovascular diseases: Focusing on the inflammatory response. Front Immunol. 2022;13:971416.
42. Liu Y, Zhang B, Zhou Y, Xing Y, Wang Y, Jia Y, et al. Targeting Hippo pathway: A novel strategy for Helicobacter pylori-induced gastric cancer treatment. Biomed Pharmacother. 2023;161:114549. Epub 2023 Mar 21.
43. Yanagawa S, Fujikuni N, Tanabe K, Nakahara M, Noriyuki T. The influence of partial gastrectomy for gastric cancer on the spontaneous disappearance of Helicobacter pylori: A single-center prospective study. Cancer Rep (Hoboken). 2023:e1903.
44. Choi IJ, Kook MC, Kim YI, Cho SJ, Lee JY, Kim CG, et al. Helicobacter pylori therapy for the prevention of metachronous gastric cancer. N Engl J Med. 2018;378(12):1085-1095.
45. Koulis A, Buckle A, Boussioutas A. Premalignant lesions and gastric cancer: current understanding. World J Gastrointest Oncol. 2019;11(9):665-678.
46. Cho SJ, Choi IJ, Kook MC, Yoon H, Park S, Kim CG, et al. Randomised clinical trial: the effects of Helicobacter pylori eradication on glandular atrophy and intestinal metaplasia after subtotal gastrectomy for gastric cancer. Aliment Pharmacol Ther. 2013;38(5):477-89.
47. Guo Y, Zhang Y, Gerhard M, Gao JJ, Mejias-Luque R, Zhang L, et al. Effect of Helicobacter pylori on gastrointestinal microbiota: a population-based study in linqu, a high-risk area of gastric cancer. Gut. 2020;69(9): 1598-1607.
48. Liu Y, Wang L, Du W, Huang Y, Guo Y, Song C, et al. Identification of high-risk factors associated with mortality at 1-, 3-, and 5-year intervals in gastric cancer patients undergoing radical surgery and immunotherapy: an 8-year multicenter retrospective analysis. Front Cell Infect Microbiol. 2023;13:1207235.
49. Bagheri N, Sadeghiani M, Rahimian G, Mahsa M, Shafigh M, Rafieian-Kopaei M, et al. Correlation between expression of mmp-9 and mmp-3 in helicobacter pylori infected patients with different gastroduodenal diseases. Arab J Gastroenterol. 2018;19(4):148-154.
50. Deng R, Zheng H, Cai H, Li M, Shi Y, Ding S, et al. Effects of helicobacter pylori on tumor microenvironment and immunotherapy responses. Front Immunol. 2022;13:923477.
51. Janjigian Y, Shitara K, Moehler M, Garrido M, Salman P, Shen L, et al. First-line Nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, Gastro-Oesophageal junction, and Oesophageal adenocarcinoma (Checkmate 649): a randomised, open-label, phase 3 trial. Lancet. 2021; 398(10294):27-40.
52. Zhang MJ, Chen DS, Li S, Chen L, Qi YX, Zhang CJ. Helicobacter Pylori infection as a potential favorable factor for immune Checkpoint inhibitor therapy for gastric cancer. Invest New Drugs. 2021;39(5):1436-1438.
53. Che H, Xiong Q, Ma J, Chen S, Wu H, Xu H, et al. Association of Helicobacter Pylori infection with survival outcomes in advanced gastric cancer patients treated with immune Checkpoint inhibitors. BMC Cancer. 2022;22(1):904.
54. Magahis P, Maron S, Cowzer D, King S, Schattner M, Janjigian Y, et al. Impact of Helicobacter pylori infection status on outcomes among patients with advanced gastric cancer treated with immune checkpoint inhibitors. J Immunother Cancer. 2023;11(10):e007699.
55. Gu H, Cheung DY, Seo YJ, Lee E, Lee HH, Kim JI, et al. Five-year Progress of Gastric MALT Lymphoma Presenting as Gastric Outlet Obstruction. Korean J Gastroenterol. 2023;81(6):265-269.
56. Troppan K, Wenzl K, Neumeister P, Deutsch A. Molecular pathogenesis of MALT lymphoma. Gastroenterol Res Pract. 2015:2015:102656.
57. Palmela C, Fonseca C, Faria R, Baptista RB, Ribeiro S, Ferreira AO. Increased risk for metachronous gastric adenocarcinoma following gastric MALT lymphoma - A US population-based study. United European Gastroenterol J. 2017;5(4):473-478.
58. Zullo A, Hassan C, Cristofari F, Andriani A, De Francesco V, Ierardi E, et al. Effects of Helicobacter pylori eradication on early stage gastric mucosa-associated lymphoid tissue lymphoma. Clin Gastroenterol Hepatol. 2010;8(2):105-10.
59. Kim JS, Park JC, Lee JY, Ahn JJ Y, Kang SH, Yang HJ, et al. Long-Term Clinical Outcomes of Gastric MALT Lymphoma: A Nationwide Multicenter Study in Korea. Front Oncol. 2021;11:681689.
60. Zullo A, Hassan C, Andriani A, Cristofari F, Bassanelli C, Spinelli GP, et al. Treatment of low-grade gastric MALT-lymphoma unresponsive to Helicobacter pylori therapy: a pooled-data analysis. Med Oncol. 2010; 27(2):291-5.
61. Badwaik N, Pankaj Gharde N, Lamture Y, Singh S, Shukla R. A Rare Case of Mucosa-Associated Lymphoid Tissue Lymphoma in the Ileum. Cureus. 2022;14(12):e32851.
62. Kim TJ, Kim ER, Chang DK, Kim YH, Baek SY, Kim K, et al. Helicobacter pylori infection is an independent risk factor of early and advanced colorectal neoplasm. Helicobacter. 2017;22(3).
63. Zuo Y, Jing Z, Bie M, Xu C, Hao X, Wang B. Association between helicobacter pylori infection and the risk of colorectal cancer: a systematic review and meta-analysis, Medicine (Baltimore). 2020;99(37):e21832.
64. Papastergiou V, Karatapanis S, Georgopoulos S. Helicobacter pylori and colorectal neoplasia: is there a causal link? World J Gastroenterol. 2016;22(2):649-58.
65. Irrazábal T, Belcheva A, Girardin S, Martin A, Philpott. The multifaceted role of the intestinal microbiota in colon cancer. Mol Cell. 2014;54(2):309-20.
66. He C, Tu H, Sun L, Xu Q, Gong Y, Jing J, et al. SNP interactions of Helicobacter pylori-related host genes PGC, PTPN11, IL1B, and TLR4 in susceptibility to gastric carcinogenesis. Oncotarget. 2015;6(22):19017-26.
67. Keum N, Giovannucci E. Global burden of colorectal cancer emerging trends, risk factors and prevention strategies. Nat Rev Gastroenterol Hepatol. 2019;16(12):713-732.
68. Coughlin SS. Social determinants of colorectal cancer risk, stage, and survival: a systematic review. Int J Colorectal Dis. 2020;35(6):985-995.
69. Sonnenberg A, Turner KO, Genta RM. Associations between gastric histopathology and the occurrence of colonic polyps. Colorectal Dis. 2020;22(7):814-817.
70. Ralser A, Dietl A, Jarosch S, Engelsberger V, Wanisch A, Janssen KP, et al. Helicobacter pylori promotes colorectal carcinogenesis by deregulating intestinal immunity and inducing a mucus-degrading microbiota signature. Gut. 2023;72(7):1258-1270.
71. Helaly GF, El-Ghazzawi EF, Kazem AH, Dowidar NL, Anwar MM, et al. Detection of Helicobacter pylori infection in Egyptian patients with chronic

calcular cholecystitis. Br J Biomed Sci. 2014;71(1):13-8.
72. Feng H, Zhou X, Zhang G. Association between cirrhosis and Helicobacter pylori infection: a meta-analysis. Eur J Gastroenterol Hepatol. 2014; 26(12):1309-19.
73. Madala S, MacDougall K, Surapaneni B, Park R, Girotra M, Kasi A. Coinfection of Helicobacter pylori and Hepatitis C Virus in the Development of Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis. J Clin Med Res. 2021;13(12):530-540.
74. Grigor'eva I, Romanova T. Gallstone disease and microbiome. Microorganisms. 2020;8(6):835.
75. Zhou D, Guan W, Wang Jd, Zhang Y, Gong W, Quan Zw, et al. A comparative study of clinicopathological features between chronic cholecystitis patients with and without Helicobacter pylori infection in gallbladder mucosa. PLoS One. 2013;8(7):e70265.
76. Zhang F, Yu CH, Chen HT, Shen Z, Hu FL, Yuan XP, et al. Helicobacter pylori infection is associated with gallstones: epidemiological survey in China. World J Gastroenterol. 2015;21(29):8912-9.
77. Takahashi Y, Yamamichi N, Shimamoto T, Mochizuki S, Fujishiro M, Takeuchi C, et al. Helicobacter pylori infection is positively associated with gallstones: a large-scale cross-sectional study in Japan. J Gastroenterol. 2014;49(5):882-9.
78. L. Cen, J. Pan, Zhou B, Yu C, Li Y, Chen W, et al. Helicobacter pylori infection of the gallbladder and the risk of chronic cholecystitis and cholelithiasis: a systematic review and meta-analysis. Helicobacter. 2018; 23(1).
79. Lim KPK, Loong Lee AJ, Jiang X, Jie Teng TZ, Shelat VG. The link between Helicobacter pylori infection and gallbladder and biliary tract diseases: A review. Ann Hepatobiliary Pancreat Surg. 2023;27(3):241-250.
80. Mishra S, Kumari N, Krishnani N. Molecular pathogenesis of gallbladder cancer: an update. Mutat Res. 2019:816-818:111674.
81. Hassan EH, Gerges SS, El-Atrebi KA, El-Bassyouni HT. The role of H. pylori infection in gall bladder cancer: clinicopathological study. Tumour Biol. 2015;36(9):7093-8.
82. Labib PL, Goodchild G, Pereira SP. Molecular pathogenesis of cholangiocarcinoma. BMC Cancer. 2019;19(1):185.
83. Boonyanugomol W, Chomvarin C, Sripa B, Bhudhisawasdi V, Khuntikeo N, Hahnvajanawong C, et al. Helicobacter pylori in Thai patients with cholangiocarcinoma and its association with biliary inflammation and proliferation. HPB (Oxford). 2012;14(3):177-84.
84. Lleo A, Leung P, Hirschfield GM, Gershwin EM. The pathogenesis of primary biliary cholangitis: a comprehensive review. Semin Liver Dis. 2020;40(1):34-48.
85. Nilsson HO, Taneera J, Castedal M, Glatz E, Olsson R, Wadström T. Identification of Helicobacter pylori and other Helicobacter species by PCR, hybridization, and partial DNA sequencing in human liver samples from patients with primary sclerosing cholangitis or primary biliary cirrhosis. J Clin Microbiol. 2000;38(3):1072-6.
86. Boomkens S, de Rave S, Pot RGJ, Egberink HF, Penning LC, Rothuizen J, et al. The role of Helicobacter spp. in the pathogenesis of primary biliary cirrhosis and primary sclerosing cholangitis. FEMS Immunol Med Microbiol. 2005;44(2):221-5.
87. Osaki T, Lin Y, Sasahira N, Ueno M, Yonezawa H, Hojo F, et al. Prevalence estimates of Helicobacter species infection in pancreatic and biliary tract cancers. Helicobacter. 2022;27(1):e12866.
88. Laya GB, Anandhi A, Gurushankari B, Mandal J, Kate V. Association between Helicobacter pylori and periampullary and pancreatic cancer: a case-control study. J Gastrointest Cancer. 2022;53(4):902-907.
89. Zhou BG, Mei YZ, Wang JS, Xia JL, Jiang X, Ju SY, et al. Is Helicobacter pylori infection associated with pancreatic cancer? A systematic review and meta-analysis of observational studies. Ther Adv Chronic Dis. 2023;14: 20406223231155119.
90. Gómez García de Las Heras S, Galindo Fernández C, Ruiz Tovar J, Fernández-Aceñero MJ. Preoperative management of obese patients undergoing bariatric surgery: role of endoscopy and Helicobacter eradication. Obes Res Clin Pract. 2021;15(3):289-290.
91. Almazeedi S, Al-Sabah S, Alshammari D, Alqinai S, Al-Mulla A, Al-Murad A, et al. The impact of Helicobacter pylori on the complications of laparoscopic sleeve gastrectomy. Obes Surg. 2014;24(3):412-5.
92. Di Lorenzo N, Antoniou SA, Batterham RL, Busetto L, Godoroja D, Iossa A. Clinical practice guidelines of the European Association for Endoscopic Surgery (EAES) on bariatric surgery: update 2020 endorsed by IFSO-ECEASO and ESPCOP. Surg Endosc. 2020;34(6): 2332-2358.
93. Mocanu V, Dang JT, Switzer N, Skubleny D, Shi X, de Gara 4 C, et al. The effect of Helicobacter pylori on postoperative outcomes in patients undergoing bariatric surgery: a systematic review and meta-analysis. Obes Surg. 2018;28(2):567-573.
94. Rasmussen J, Fuller W, Ali MR. Marginal ulceration after laparoscopic gastric bypass: an analysis of predisposing factors in 260 patients. Surg Endosc. 2007;21(7):1090-4.
95. D. Keren, I. Matter, Rainis T, Goldstein O, Stermer E, Lavy A. Sleeve gastrectomy leads to helicobacter pylori eradication. Obes Surg. 2009; 19(6):751-6.
96. Catchlove W, Liao S, Lim G, Brown W, Burton P. Mechanism of staple line leak after sleeve gastrectomy via isobaric pressurisation concentrating stress forces at the proximal staple line. Obes Surg. 2022;32(8):2525-2536.
97. Marcolin P, Machado Berleze M, Polettini J, Marchesan Rodrigues MA, Silveira DA. The Impact of Helicobacter pylori on Laparoscopic Sleeve Gastrectomy Postoperative Complications: a Systematic Review and Meta-analysis. Obes Surg. 2023;33(11):3649-3657. Epub 2023 Oct 6.
98. Brownlee A, Bromberg E, Roslin M. Outcomes in Patients with Helicobacter pylori Undergoing Laparoscopic Sleeve Gastrectomy. Obes Surg. 2015; 25(12):2276-9. doi: 10.1007/s11695-015-1687-6.