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Review Article

Etiology, Therapeutic Challenges, Drug Interactions, and Future Directions of Gastric Ulcer Progression to Gastric Cancer

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ABSTRACT

Gastric cancer remains one of the leading causes of cancer-related mortality worldwide, and chronic gastric ulceration represents an important precursor lesion in a subset of patients. This narrative review aimed to synthesize evidence published between 2015 and 2026 on the etiology and pathogenesis of gastric ulcer, current therapeutic strategies, the preclinical roles of laboratory animals, treatment failures, and the transition from gastric ulcer to gastric cancer. The progression from chronic inflammation to malignancy is driven by a complex interplay of bacterial virulence factors, host responses, and molecular alterations. Laboratory animal models have provided important preclinical evidence for evaluating gastric mucosal injury, histopathological changes, diagnostic biomarkers, and carcinogenic progression. In particular, rodent and mouse models have supported the development of molecular and fluorescence-based imaging approaches for detecting ulcerative, dysplastic, and malignant gastric lesions. *Helicobacter pylori* (*H. pylori*) infection and prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs) are the primary etiological factors in the development of gastric ulcer, while host susceptibility, environmental influences, and microbial interactions further contribute to disease progression. Recent advances have improved understanding of the molecular mechanisms underlying gastric mucosal injury, ulcer healing, and carcinogenesis, including *CagA*-mediated signaling, the spermine oxidase (SMOX) pathway, and microbiota-derived metabolites. Despite the widespread use of proton pump inhibitors and *H. pylori* eradication diets, increasing antibiotic resistance and refractory ulcers continue to limit treatment success. Emerging biomarkers, innovative acid-suppressive agents, microbiome-based strategies, and advanced imaging technologies present promising strategies for improving diagnosis and treatment. Integrating findings from experimental animal models with clinical evidence could improve diagnostic timing, risk prediction, and the development of targeted strategies to prevent the progression of gastric ulcers to gastric cancer.

1. Introduction

Gastric ulcer is a significant global health problem despite substantial advances in the understanding and management of peptic ulcer disease over recent decades[1]. Gastric ulcer involves a deep mucosal defect that extends through the muscularis mucosae into the submucosa, resulting from an imbalance between aggressive factors such as gastric acid, pepsin, *Helicobacter pylori* (*H. pylori*) infection, and nonsteroidal anti-inflammatory drugs (NSAIDs) and the stomach's protective mechanisms. While many ulcers heal with adequate and proper treatment, some can cause serious problems such as bleeding, perforation, recurrence, and, most critically, gastric carcinoma[2].

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Helicobacter pylori is the main cause of gastric ulcers globally[3]. *Helicobacter pylori* contributes to chronic inflammation, epithelial damage, and mucosal disruption by producing urease and virulence factors such as *cytotoxin-associated gene A* (*CagA*) and *vacuolating cytotoxin A* (*VacA*)[4]. The second important cause of gastric ulcers is long-term NSAID use, which mainly functions by inhibiting cyclooxygenase enzymes and reducing prostaglandin-mediated cytoprotective mechanisms[5].

Additional risk factors, including smoking, alcohol consumption, advanced age, severe physiological stress, genetic susceptibility, and comorbid diseases, further contribute to disease development and impaired ulcer healing[6]. The lifetime prevalence is estimated to range between 5% and 10% of the adult population, with particularly high burdens reported in East Asia, South Asia, and the Middle East, where *H. pylori* infection remains highly prevalent[7]. Moreover, the emergence of antibiotic-resistant *H. pylori* strains has become a major obstacle to successful eradication, contributing to treatment failure, recurrent disease, and increased healthcare costs.

The importance of gastric ulcer goes beyond its direct clinical signs due to its strong link to gastric cancer development. Gastric cancer remains one of the leading causes of cancer-related mortality worldwide, accounting for nearly one million new cases annually[8]. Evidence suggested that chronic gastric inflammation and mucosal injury can initiate a multistep process known as Correa's cascade, leading from chronic gastritis to adenocarcinoma. Although not all gastric ulcers undergo malignant transformation, ulcer size, persistence, underlying *H. pylori* infection, and molecular alterations significantly influence cancer risk[9].

During the last decade, major advances have expanded understanding of the molecular pathways linking gastric ulceration to gastric cancer[10]. Novel mechanisms involving bacterial virulence factors, host genetic susceptibility, microbiome-derived metabolites, stem-cell signaling pathways, and inflammatory mediators have been identified[11]. Importantly, laboratory animal models have become a key component of preclinical investigations into and characterization of gastric ulceration. Experimental rat models, particularly ethanol- and indomethacin-induced gastric injury models, reproduce reproducible mucosal lesions that can be evaluated using complementary macroscopic and microscopic approaches[12]. Gross examination allows for the assessment of lesion number, extent, and hemorrhagic damage, while histopathological evaluation can detect inflammatory infiltration, epithelial disruption, apoptosis, necrosis, and submucosal injury that might not be visible during macroscopic examination[13]. These approaches provide standardized experimental endpoints to characterize gastric injury and validate potential diagnostic biomarkers or therapeutic interventions. A systematic comparison of experimental ulcer models has also shown that ethanol-induced gastric ulceration is among the most commonly used in vivo models due to its rapid development and ability to mimic different features of acute gastric mucosal damage[14]. Histopathological assessment further improved characterization of experimental ulcers by distinguishing superficial epithelial injury from deeper necrotic and inflammatory lesions[15].

Animal models have also contributed to the development of diagnostic approaches for gastric cancer and its precursor lesions. Mouse models, such as xenograft and genetically modified models, offer a controlled *in vivo* platform for assessing tumor-related molecular targets and imaging biomarkers[16]. Molecular imaging has become a promising noninvasive method for detecting and characterizing gastric tumors in experimental animals[17]. Fluorescent and near-infrared probes targeting carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6), a marker linked to gastric cancer development, in mouse models[18]. These anti-CEACAM6 probes successfully tracked primary tumors and metastatic sites *in vivo* and helped identify dysplastic gastric mucosa through fluorescence endoscopy[19]. These findings illustrated how animal models can serve as an intermediate platform for linking molecular biomarker discovery with endoscopic diagnostic technologies. Similarly, molecular imaging approaches targeting tumor-associated receptors and proteins have demonstrated the feasibility of fluorescence-based and other imaging modalities for visualizing gastric cancer *in vivo*[20,21].

The use of animal models is therefore particularly relevant to the diagnostic continuum spanning gastric mucosal injury, premalignant transformation, and established gastric cancer. By combining macroscopic evaluation, histopathology, immunohistochemistry, molecular biomarkers, and *in vivo* imaging, experimental models can help determine whether candidate diagnostic markers reliably distinguish normal gastric mucosa from ulcerative, inflammatory, dysplastic, and malignant lesions[13,19,22]. Nevertheless, important interspecies differences in gastric anatomy, immune responses, microbiota, and tumor biology should be considered when using findings from experimental animals in human clinical practice. Thus, animal models should be regarded as complementary preclinical platforms rather than substitutes for clinical endoscopy, biopsy, and histopathological diagnosis[23]. The present study aimed to comprehensively review evidence published from 2016 to 2026 on the progression from gastric ulcer to gastric cancer, focusing on experimental and clinical methods used to understand disease development, identify diagnostic biomarkers, and enhance early detection.

2. Search criteria

The present narrative review was conducted to summarize and synthesize current evidence regarding the progression from gastric ulcer to gastric cancer. Relevant literature published between 2015 and August 2026 was identified through searches of important scientific databases, including PubMed, Scopus, and Google Scholar. The search strategy incorporated combinations of specific keywords and controlled terms related to the primary objectives of the review, including gastric ulcer, peptic ulcer

disease, *Helicobacter pylori*, gastric cancer, gastric carcinogenesis, proton pump inhibitors (PPIs), antibiotic resistance, gastric ulcer diagnosis, gastric cancer diagnosis, biomarkers, animal models, endoscopy, and gastric ulcer management. The broad term drug interactions was not used as an independent search term because of its non-specificity and the risk of retrieving a large volume of literature unrelated to the central objectives of the present study. Priority was given to original research articles, systematic reviews, meta-analyses, clinical guidelines, and other relevant peer-reviewed publications that directly addressed ulcer etiology, diagnostic approaches, therapeutic challenges, *H. pylori*-associated disease, malignant transformation, gastric carcinogenesis, experimental animal models, biomarkers, and emerging diagnostic or therapeutic strategies. Additional relevant publications were identified through manual screening of the reference lists of selected articles. Of the 523 articles retrieved in the initial search, 424 were excluded due to not providing directly relevant evidence aligned with the predefined objectives of the review, leaving 99 articles for final inclusion and analysis. The selected studies were critically reviewed and thematically organized according to major topics, including the pathogenesis and etiology of gastric ulcer, diagnostic approaches, experimental animal models, *H. pylori*-associated carcinogenesis, progression from chronic gastric injury to malignancy, therapeutic challenges, and emerging diagnostic and management strategies.

3. Etiology and pathogenesis

Gastric ulcer results from a complex interaction among microbial, environmental, and host factors, leading to an imbalance between mucosal defense mechanisms and damaging agents[13]. Most ulcers heal with appropriate therapy, but persistent mucosal injury may initiate a cascade of inflammatory and molecular events that predispose susceptible individuals to gastric carcinogenesis[14]. In the past decade, major advances have expanded the understanding of the biological pathways linking gastric ulcers to gastric cancer, emphasizing the pivotal roles of *H. pylori* virulence factors, host genetic susceptibility, inflammatory signaling pathways, and the gastric microbiome.

3.1. Helicobacter pylori virulence factors and host interactions

Helicobacter pylori is the most important etiological factor in gastric ulcer disease and the main microbial driver of gastric carcinogenesis[15]. The bacterium possesses several adaptations that enable it to colonize the gastric mucosa for extended periods in the face of the hostile acidic environment[19]. Its characteristic helical shape and flagellar motility enable it to penetrate the mucus layer and adhere to epithelial cells, thereby establishing persistent infection and chronic inflammation[20]. Two bacterial virulence factors, *CagA* and *VacA*, have attracted considerable attention for their direct roles in epithelial injury and malignant transformation[21]. *CagA* is translocated into gastric epithelial cells and disturbs different intracellular signaling pathways involved in cell proliferation, apoptosis, and cellular polarity[22]. Persistent activation of these pathways leads to genomic instability and contributes to the progression from chronic gastritis to gastric cancer[23]. Recent studies have demonstrated the potential for *H. pylori* interactions with the gastric microbiome to affect cancer risk[24]. It has been demonstrated that short-chain fatty acids, especially propionate and butyrate produced by some commensal bacteria, increase CAPZA1 expression, which in turn reduces the degradation and accumulation of *CagA* in gastric epithelial cells[25]. This process promotes the formation of CD44v9-positive cancer stem-like cells and might help explain why only some *H. pylori*-infected individuals progress to gastric cancer[26]. Thus, the development of gastric cancer is affected not only by bacterial infection but also by the surrounding microbial community and the host response[27].

3.2. Host genetic and molecular determinants

Host genetic and molecular factors are important in disease progression, and clinical outcomes of *H. pylori* infection vary widely between individuals[28]. Recent evidence has identified several signaling pathways mediating the transition from chronic inflammation to neoplastic transformation[29]. One of the most studied pathways is the spermine oxidase (SMOX), an enzyme that participates in oxidative stress, DNA damage, and inflammatory responses[30]. Increased SMOX activity has been linked to increased β-catenin signaling, a principal pathway in cell proliferation and tumor development[31]. Experimental studies have indicated that inhibition of SMOX can reduce inflammation and the risk of malignant transformation, suggesting the potential of SMOX as a therapeutic target[30]. Another important mechanism is the gastrin-mediated regulation of gastric epithelial regeneration[31]. Gastrin stimulates the secretion of gastric acid and also affects stem and progenitor cell populations involved in mucosal repair[32]. Activation of the gastrin-CCK2 receptor axis has been demonstrated to promote epithelial regeneration and ulcer healing, whereas impaired gastrin signaling has been linked to delayed healing and increased susceptibility to chronic mucosal damage[33,34]. These findings suggest that pathways involved in physiological tissue repair may also influence long-term cancer risk when dysregulated[34].

3.3. Inflammation, mucosal injury, and the pathway to cancer

The progression of gastric ulcer to gastric cancer is generally accepted as a process of chronic inflammation and carcinogenesis[35]. Prolonged *H. pylori* infection and repeated mucosal injury cause an ongoing inflammatory reaction characterized by cytokine release, oxidative stress, epithelial damage, and repeated cycles of tissue destruction and regeneration[36]. These processes might eventually result in the stepwise histopathological changes described in Correa's cascade, such as chronic gastritis, mucosal atrophy, intestinal metaplasia, dysplasia and ultimately gastric

adenocarcinoma[37]. The risk of malignant change is influenced by a variety of factors including the duration of inflammation, bacterial virulence factors, host genetic susceptibility, persistence of ulcer, and size of lesion[38]. Recent molecular studies have identified pathways of cancer stem cell formation, beta-catenin activation, oxidative DNA damage, and microbiome-derived metabolites as important in this transition[39,40].

3.4. Experimental models and translational insights

Current knowledge of the pathogenesis of gastric ulcer and gastric carcinogenesis has been greatly advanced by experimental animal models[41]. Mice, rats, and Mongolian gerbils have been extensively used to investigate *H. pylori* colonization, ulcer healing, inflammatory signaling pathways, and cancer development[41]. These models have facilitated the identification of important molecular mechanisms, including the roles of *CagA*, *SMOX*, gastrin signaling, and microbiome-host interactions[42]. Animal models cannot fully mimic the complexity of human disease; however, they still provide significant translational insights and remain important tools for assessing novel treatments to prevent both ulcer recurrence and gastric cancer development.

4. Current therapeutic strategies

The main goals of therapy are to promote healing of the mucosa, to eliminate the underlying etiologic factors, to prevent complications, to reduce recurrence, and finally to reduce the risk of progression to gastric cancer[43]. Presently, treatment mainly focuses on reducing stomach acid, eradicating *H. pylori* infection, and modifying risk factors[43]. Clinical practice over the past decades has substantially improved treatment outcomes, but disorders such as antibiotic resistance, refractory disease, and long-term medication safety still present challenges[44].

4.1. Proton pump inhibitors

Proton pump inhibitors are the mainstay of therapy for gastric ulcer. The PPIs irreversibly inhibit the gastric H+/K+-ATPase proton pump in parietal cells, thereby suppressing gastric acid secretion and creating a favorable environment for mucosal repair and ulcer healing[45]. Examples of commonly prescribed agents include omeprazole, pantoprazole, lansoprazole, rabeprazole, and esomeprazole[46]. Aside from acid suppression, recent findings suggest that PPIs may have other biological effects important for mucosal regeneration[47]. Experimental studies have shown that PPI-induced hypergastrinemia may activate regenerative signaling pathways and stimulate epithelial repair mechanisms, thereby improving ulcer healing[29]. Although the clinical importance of these findings is still under investigation, previous studies suggest that the therapeutic benefits of PPIs may extend beyond simple acid control[48]. The PPIs are the first-line treatment for gastric ulcers associated with *H. pylori* and NSAIDs because of their efficacy and generally favorable safety profile[2]. However, issues of long-term use such as possible drug interactions and adverse effects have prompted continued investigations into alternative acid-suppressive therapies and improved treatment strategies[49].

4.2. Helicobacter pylori eradication therapy

One of the most important interventions to prevent ulcer recurrence and reduce the long-term risk of gastric cancer is the eradication of *H. pylori*[50]. For standard regimens, a PPI plus two or more antibiotics, such as amoxicillin, clarithromycin, metronidazole, tetracycline, or levofloxacin, is used according to local resistance patterns and treatment guidelines[51]. Successful eradication not only accelerates ulcer healing but also breaks the cycle of chronic inflammation that drives gastric carcinogenesis[52]. Many studies have demonstrated that eradication therapy reduces the incidence of gastric cancer, especially when used before the development of advanced precancerous lesions such as extensive intestinal metaplasia or dysplasia[52]. In recent years, treatment strategies have increasingly shifted toward individualized approaches based on regional patterns of antibiotic resistance. Potassium-competitive acid blockers (P-CABs), especially vonoprazan-based regimens, have also emerged as promising alternatives with the potential to achieve higher eradication rates in selected patient populations[53].

4.3. Emerging and complementary therapeutic approaches

Growing concerns about antibiotic resistance and the consequences of incomplete treatment have increased interest in alternative and adjunctive therapies[54]. Among these strategies were novel acid-suppressive drugs, microbiome-directed therapies, vaccine development, and natural compounds with gastroprotective activity[54]. The beneficial effects of several herbal formulations and bioactive compounds have been reported in experimental studies through mechanisms including suppression of inflammatory cytokines, enhancement of mucosal defense, stimulation of prostaglandin production, and promotion of epithelial regeneration[55]. For instance, the standardized herbal preparation Yeokwisan showed gastroprotective and anti-inflammatory effects in animal models of gastric injury[56]. Although many of these therapies remain in preclinical or early clinical development, they may provide valuable adjunctive options in the future, especially for patients with refractory ulcers, recurrent *H. pylori* infection, or intolerance to conventional treatment[57,58].

5. Therapeutic challenges

Despite progress in the treatment of gastric ulcer disease, there are still several therapeutic challenges that have limited the success of treatment and lead to recurrence of the disease, chronic inflammation, and progression to gastric cancer[59]. The main obstacles to optimal patient outcomes are increasing antibiotic resistance, refractory ulcer disease, interindividual variability in response to treatment, and gaps in translational studies[60].

5.1. Antibiotic resistance and the challenge of Helicobacter pylori eradication

The increasing prevalence of antibiotic-resistant strains of *H. pylori* is one of the most important challenges in contemporary gastroenterology[61]. Successful eradication of *H. pylori* is important not only for ulcer healing but also for reduction of long-term risk of gastric carcinogenesis. But in many areas, the success of standard eradication regimens has declined dramatically due to rising antibiotic resistance. High rates of clarithromycin and metronidazole resistance have been reported in several Asian countries, and intermediate rates of resistance have been observed in parts of the Middle East, including Iran[62,63]. The increasing prevalence of strains resistant to multiple drugs limits the success of therapy further.

5.2. Refractory gastric ulcers and host-related factors

The 5-10% of gastric ulcers that do not recover with appropriate therapy are designated as refractory and fail to heal despite adequate treatment[62]. Refractory disease is associated with longer symptom duration, increased healthcare utilization, and higher risk of complications[62]. Treatment failure is multifactorial, with persistent *H. pylori* infection, continued NSAID exposure, poor medication adherence, smoking, and underlying comorbid conditions all playing a role[63]. The variability of host genetic factors is also important. PPI metabolism is affected by polymorphisms in the *CYP2C19* gene, resulting in substantial variability in drug exposure and acid suppression[64]. Rapid metabolizers have lower intragastric pH, which can lead to delayed ulcer healing and reduced treatment efficacy[65]. Recent experimental studies have suggested a role for impaired gastrin-mediated mucosal regeneration in refractory disease[66]. Reduced gastrin activity is associated with delayed epithelial repair and a reduced response to acid-suppressive therapy, highlighting the importance of host biological factors in determining treatment outcome[67].

5.3. Translational gaps between experimental and clinical investigations

Experimental models have made significant progress in advancing understanding of the pathogenesis of gastric ulcer disease, but translating these findings into clinical practice remains challenging[68]. Animal models have provided useful insights into *H. pylori* colonization, inflammatory signaling pathways, ulcer healing, and gastric carcinogenesis[41]. However, animal models do not fully reflect the complexity of human infection, immune responses, interactions with the microbiome, and long-term disease progression[69]. Thus, many therapeutic interventions that showed promising results in preclinical studies failed to translate into similar success in human clinical trials[70].

6. Mechanisms and clinical implications

The link between gastric ulcer disease and gastric cancer is one of the most important clinical issuses in gastroenterology[71]. The majority of gastric ulcers heal without malignant sequelae, but a small group of patients develops persistent inflammation, progressive mucosal injury and molecular changes that eventually lead to carcinogenesis[72,73].

6.1. Risk of malignant transformation

The malignant potential of gastric ulcers is well known, but the magnitude of risk varies considerably between patients[74]. The risk of malignant transformation is influenced by a number of clinical and pathological factors, including ulcer size, duration, recurrence, *H. pylori* infection status, and the presence of premalignant mucosal changes[75]. Previous studies indicated that the risk of malignancy increased significantly with larger ulcer size, especially for lesions larger than 3 cm in diameter[76]. The risk was increased by the persistence of *H. pylori* infection, with its chronic inflammation and genomic changes[77]. Untreated *H. pylori* infection confers a three- to six-fold increased risk of developing gastric cancer compared to uninfected populations[78]. Observations emphasize the need for early diagnosis, appropriate treatment, and long-term surveillance in selected high-risk patients[79].

6.2. Molecular pathways linking ulceration to carcinogenesis

The transition from gastric ulceration to gastric adenocarcinoma is generally thought to be part of a broader process of inflammatory carcinogenesis[80]. The classical model of this progression is Correa's cascade, in which chronic gastritis progresses to mucosal atrophy, intestinal metaplasia, dysplasia, and finally invasive adenocarcinoma[81]. Ongoing inflammatory stimulation creates a favorable environment for DNA damage, abnormal cell growth, and accumulation of oncogenic mutations[82]. Several pathways that could drive this transition have recently been identified by molecular studies. Of these, the interactions between *H. pylori* virulence factors and the gastric microbiome have attracted particular interest[83]. The SCFA-Cag-CAPZA1A signaling axis indicated a mechanistic explanation for how microbial metabolites might enhance carcinogenic potential. Furthermore, certain microbial communities can promote intracellular accumulation of *CagA*, which can activate cancer-associated signaling pathways and generate stem cell-like populations that contribute to tumor initiation[25]. Another major pathway is via SMOX, leading to oxidative stress, chronic inflammation, and DNA damage. The increased SMOX activity has been linked to activation of β-catenin signaling, a master regulator of proliferation and tumor development[30]. These findings suggest that gastric carcinogenesis results from a complex interplay among bacterial virulence factors, host genetic susceptibility, inflammatory mediators, and the surrounding microbial environment[84].

6.3. Protective and reparative mechanisms

Not all biological responses associated with gastric ulceration are implicated in cancer development[85]. Several physiological repair mechanisms with protective roles promote mucosal regeneration and limit chronic tissue damage[86]. One such protective mechanism is gastrin-mediated signaling, which is attracting increasing

attention[87]. Recent experimental evidence indicates that physiological gastrin responses are involved in epithelial regeneration, maintenance of mucosal integrity, and enhancement of ulcer healing[87]. Delayed healing, increased bacterial colonization, and worsening of inflammatory changes have been linked to impaired gastrin signaling. These results indicated that the balance between tissue injury and repair is a critical determinant of disease outcome[88].

6.4. Clinical implications for cancer prevention

Gastric ulcer is a potential precursor lesion, highlighting the necessity of cancer prevention strategies[89]. Timely eradication of *H. pylori*, effective ulcer treatment, endoscopic surveillance of high-risk lesions, and identification of molecular biomarkers associated with malignant transformation may significantly reduce the incidence of gastric cancer[90]. Precision medicine approaches may facilitate earlier detection of individuals at the highest risk and enable targeted preventive interventions prior to the onset of irreversible neoplastic changes[90].

7. Drug interactions in gastric ulcer management

Management of gastric ulcer disease often involves long-term pharmacological therapy and is often in patients with multiple chronic conditions[1]. Drug interactions and comorbidities are important considerations that may affect treatment efficacy, safety, and long-term outcomes[91].

7.1. Long-term safety of acid-suppressive therapy

Proton pump inhibitors are still among the most prescribed drugs worldwide and are generally considered safe and effective[92]. However, there have been concerns about possible adverse effects of long-term use of these medicines, including nutritional deficiencies, enteric infections, renal complications, and possible associations with extra-gastrointestinal diseases[93]. Some observational analyses have suggested associations, but follow-up experimental studies have not consistently demonstrated a causal relationship[94]. Existing evidence suggests that PPIs are safe in the majority of patients, when used according to established clinical indications, although periodic reassessment of long-term therapy is still advisable[95].

7.2. Drug-drug interactions

Drug-drug interactions are particularly important in those on long-term acid-suppressive therapy with gastric ulcers[44]. Proton pump inhibitors may alter the absorption, bioavailability, or metabolism of concomitant medications by changing gastric pH or modulating cytochrome P450 enzymes, especially CYP2C19[96]. In clinical practice, interactions have been reported with antiplatelet agents, anticoagulants, antifungal agents, some antiretroviral agents, and other medications that require an acidic gastric pH for optimal absorption[97].

7.3. Impact of comorbidities

Gastric ulcers are often complicated by comorbid diseases that influence their development and treatment[1]. Altered ulcer risk, healing potential, and drug choice may be caused by cardiovascular disease, chronic kidney disease, diabetes mellitus, chronic liver disease, and autoimmune disorders[1]. Furthermore, many patients have to take NSAIDs, antiplatelet agents, or anticoagulants for long periods, which can increase the chances of developing ulcers and gastrointestinal bleeding[98]. Systemic conditions can also influence biological pathways involved in mucosal repair and immune regulation, and this may affect response to treatment[98]. Management of gastric ulcer disease is frequently successful when individualized and tailored to the gastrointestinal pathology and overall clinical context[98].

8. Conclusion

Gastric ulcer is still an important clinical entity in the evolution of gastric carcinogenesis. Laboratory animal models have played an important role in understanding gastric ulcer and cancer by enabling controlled evaluation of mucosal injury, histopathological changes, biomarkers, carcinogenesis, and novel molecular imaging approaches. These models have been an important preclinical bridge for the development and validation of new diagnostic strategies, but their findings need to be validated in clinical settings. The mainstays of treatment continue to be PPIs and eradication of *H. pylori*, but therapeutic challenges remain, including antibiotic resistance, refractory disease and patient-specific factors. New molecular pathways, such as the SCFA-CAPZA1-*CagA* axis and SMOX signaling, may offer new possibilities for more precise risk assessment and targeted treatments. Future studies must incorporate animal models with human biomarker studies, advanced imaging, and precision medicine for earlier detection and prevention of progression from gastric ulcer to gastric cancer.

Declarations

Authors' contributions

Hadis Farokhmoradi conceived and designed the study, supervised the entire study process, and critically revised the manuscript to ensure critical intellectual content was accurately addressed. Parsa Jahani and Sima Saravani were primarily responsible for data acquisition and contributed to the interpretation of the findings. Seyedeh Maryam Moallem and Mohammad Amin Ghasemzadeh drafted the initial manuscript and conducted the literature review. Parsa Taher assisted with data collection and validation, and provided administrative and technical support. All authors reviewed and approved the final edition of the manuscript and agreed to be accountable for all aspects of this study.

Availability of data and materials

The data are available upon reasonable request.

Competing interests

The authors declared no competing interests.

Ethical considerations

During manuscript preparation, the authors used Gemini (an advanced language model developed by Google) solely for language polishing, improving structural flow, and verifying academic nomenclature and formatting in the technical text. After using this tool, the authors thoroughly reviewed, verified, and edited the suggested content to ensure scientific accuracy and take full responsibility for the final integrity and factual correctness of the peer-reviewed text. The authors accept full responsibility for the originality of the study before submission and before publication.

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