RJNMSR
Review Journal of Neurological & Medical Sciences Review

Volume 3, Issue 3, 2025

PREVALENCE, RISK FACTORS, AND CURRENT DIAGNOSTIC APPROACHES FOR GASTROESOPHAGEAL REFLUX DISEASE: AN UPDATE REVIEW

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DOI: https:/doi.org/

Received	Accepted	Published
29 June, 2025	04 Aug, 2025	06 Aug, 2025

ABSTRACT

Gastroesophageal reflux disease (GERD) is a chronic gastrointestinal disorder characterized by the abnormal reflux of stomach contents into the esophagus, leading to symptoms like heartburn and regurgitation. GERD significantly impacts patients' quality of life and can result in complications such as esophagitis, Barrett's esophagus, and esophageal adenocarcinoma. This review provides a comprehensive overview of prevalence, risk factors, and current diagnostic approaches for GERD. Traditional diagnostic methods, such as endoscopy, pH monitoring, and manometry, remain crucial for identifying the disease. However, these invasive techniques often fail to detect non-erosive GERD (NERD) and atypical symptoms, limiting their diagnostic utility. Non-invasive diagnostic tools, including salivary biomarkers (e.g., pepsin) and miRNA testing, offer promising alternatives for diagnosing GERD, particularly in patients with atypical symptoms who do not show visible esophageal damage. Furthermore, artificial intelligence (AI) and advanced imaging technologies are emerging as valuable tools for enhancing diagnostic accuracy and personalizing treatment. These technologies could complement traditional diagnostic methods and improve early detection of GERD-related complications. This review emphasizes the need for standardized guidelines and the integration of advanced, non-invasive technologies into routine clinical practice to improve GERD diagnosis and management outcomes.

Keywords: *Gastroesophageal Reflux Disease (GERD), Non-invasive Diagnostic methods, pH monitoring, Salivary biomarkers, miRNA testing, Artificial Intelligence (AI)*

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a chronic gastrointestinal condition characterized by the abnormal reflux of stomach contents into the esophagus. This condition typically results in symptoms such as heartburn, regurgitation, and chest pain. The Disease caused when the lower esophageal sphincter (LES), which physiologically acts as a barrier to prevent stomach contents from backflow, becomes weakened or relaxed. As a result, stomach contents including acid can irritate the esophagus, leading to inflammation and other complications. However occasional acid reflux is common, but persistent or severe reflux that causes damage to the esophageal lining is classified as GERD. The condition can vary in severity on individual bases, with some patients experiencing mild symptoms while others suffer from more serious, life-disrupting issues such as esophagitis, ulceration, or even Barrett's esophagus. Persistent reflux can also result in complications like stricture formation, respiratory symptoms, and chronic cough (1) . Worldwide, one of the most prevalent chronic diseases, affecting millions of individuals. The disease can significantly affect daily functioning and quality of life. In its most severe form, the illness can lead to complications such as erosive esophagitis and Barrett's esophagus, a pre-cancerous condition that increases the risk of esophageal adenocarcinoma (2) . Recent studies have reported an increasing trend in the prevalence of GERD, particularly in Western countries, with a rising incidence in developing regions, associated with changing lifestyles and dietary habits (3) . Moreover, the economic burden of disease is growing, with a significant rise in both direct medical costs and indirect costs due to work absenteeism (4).

The clinical significance of disease cannot be overstated. In addition to its high prevalence, GERD is a major contributor to healthcare utilization and costs. Patients frequently present to primary care physicians and gastroenterologists, requiring ongoing management and follow-up. The symptoms of disease, such as heartburn and regurgitation, are often chronic and can severely affect a person's quality of life. Furthermore, the condition is associated with various comorbidities, including respiratory disorders, such as asthma and chronic cough, and cardiovascular symptoms, like chest pain. These overlapping symptoms can often lead to misdiagnosis, making effective treatment and management challenging (5) . Also exacerbate sleep disorders, with patients reporting difficulty sleeping due to nocturnal reflux, which significantly impacts their daily functioning and well-being (6).

The potential long-term consequences if left untreated can further increase its clinical complexity. Persistent acid reflux can cause esophageal damage, leading to complications like erosive esophagitis and Barrett's esophagus, a pre-cancerous condition that increases the risk of esophageal adenocarcinoma. Recent studies have suggested that untreated GERD may be linked to an increased incidence of esophageal cancer, a disease with high mortality rates (7) . Moreover, the progression

to more severe forms, such as strictures and esophageal perforations, can complicate treatment and lead to the need for surgical interventions (8) . This makes early detection and proper management vital in preventing disease progression and improving patient outcomes. Additionally, the disease represents a substantial economic burden, both directly and indirectly. Direct costs include medical expenses for diagnosis, treatment, and hospitalization, while indirect costs arise from productivity loss due to missed workdays and reduced workplace performance. A study found that hospitalizations and outpatient visits significantly contribute to healthcare expenditure. This combination of health and economic impacts underscores the critical need for efficient and accurate management strategies (8; 9) . The increasing burden on both healthcare systems and individuals calls for better prevention and management strategies to mitigate its adverse effects (10) . This review aims to provide a comprehensive overview of GERD, focusing on its prevalence, risk factors, and current diagnostic approaches. A systematic approach was employed to identify and synthesize peer-reviewed studies published in 2015 to 2025, using well-established databases such as PubMed, Scopus, and Google Scholar. Understanding the global and regional prevalence of disease is crucial for identifying high-risk populations and tracking its increasing incidence across different demographics. By reviewing epidemiological studies and systematic reviews, the review highlights the geographical and demographic variations in prevalence, including rising trends in both developed and under developing countries. The review emphasizes the importance of understanding these trends to help identify populations most at risk and implement appropriate public health strategies. In terms of risk factors, this review explores studies that examine lifestyle, genetic, and environmental contributors to GERD, including diet, obesity, and smoking. The methodology involved gathering findings from cohort studies, case-control studies, and cross-sectional studies, emphasizing those factors that can be mitigated through prevention strategies. The review also evaluates the current diagnostic methods used in clinical practice, such as endoscopy, pH monitoring, and manometry, focusing on their effectiveness, sensitivity, and limitations. Clinical guidelines and meta-analyses were reviewed to assess the diagnostic accuracy of these methods. Additionally, emerging diagnostic technologies, including wireless pH monitoring and non-invasive biomarkers, are discussed to offer a broader view for diagnostics. Their potential role in improving early detection and treatment is considered, with a focus on the evolving landscape of GERD diagnostics, drawing from clinical trial data, observational studies, and expert opinions published in recent literature.

PREVALENCE OF GERD

GLOBAL PREVALENCE STATISTICS

Gastroesophageal reflux disease is one of the most common chronic diseases worldwide, with a significant impact on healthcare systems and patients' quality of life. Studies have consistently shown that the global prevalence

ranges from 10% to 20% of the population in Western countries, with rates of up to 25% in some regions like the United States and Europe (11) . According to the World Gastroenterology Organization, GERD is a leading cause of morbidity and is frequently associated with other chronic diseases, including asthma, chronic cough, and sleep apnea (12). In high-income countries, the condition is a major contributor to healthcare utilization, accounting for millions of visits to general practitioners and gastroenterologists each year. This high prevalence is largely attributed to lifestyle factors such as the increased consumption of high-fat diets, alcohol, and smoking, in addition to rising obesity rates (13). In the United States, studies have estimated that nearly 20% of the adult population suffered, with heartburn or acid regurgitation being the most commonly reported symptoms (14).

However, the global prevalence of GERD is not uniform. Countries with lower socioeconomic status or limited access to healthcare may report lower prevalence rates, but recent evidence suggests an upward trend in these regions as Westernized lifestyle habits permeate (15) . A study in India showed that the illness affects nearly 7% of the urban population, which is a stark contrast to the 1-2% prevalence in rural areas (16). The global prevalence data highlights the growing burden and the need for widespread public health strategies aimed at its prevention and management.

REGIONAL PREVALENCE AND VARIATIONS

THE prevalence of GERD varies significantly across different regions of the world. In North America, particularly the United States, the prevalence is among the highest globally. Studies have found that up to 20% of the population in the United States is affected, with its prevalence increasing over the past few decades. This rise is attributed to lifestyle changes, including increased obesity rates and dietary patterns high in fat and sugar (17; 15) Similarly, countries in Europe, such as France and Germany, also report high prevalence, with some estimates suggesting that as much as 15-20% of the adult population is affected (18).In contrast, Asia has historically had lower prevalence rates, though recent studies indicate a rising trend. In China, the prevalence of disease has increased from around 5% in the early 2000s to approximately 10-15% in recent years, with urban populations experiencing higher rates than rural populations (19) . Factors contributing to this increase include changes in diet, stress levels, and lifestyle choices that are more aligned with Western patterns, such as increased fast food consumption and sedentary behavior (20; 21). Similarly, in India, the prevalence in urban centers is rising, with estimates ranging from 7% to 15% among the adult population, while rural areas report significantly lower rates of approximately 1-2% (22) . This disparity is largely due to lifestyle differences between urban and rural populations, with urban dwellers adopting more Westernized habits. Latin America also shows notable regional

variations. Countries like Brazil and Argentina reported prevalence rates was between 10% and 15%, while rural and remote areas of Latin America tend to have lower rates, in part due to different dietary habits and lifestyle factors (23). In Pakistan and its neighboring countries, including Iran, Afghanistan, and Kazakhstan, the prevalence has been steadily rising in recent years, largely driven by urbanization, changing diets, and increasing rates of obesity. In Pakistan, studies have shown that the prevalence ranges from 7% to 15% in urban populations, with lower rates in rural areas where traditional diets and lifestyles are more common (24) . Similarly, Iran reports a prevalence of around 18% among the adult population, with higher rates seen in urban regions due to lifestyle changes, including a high-fat diet and increased stress levels (25). In Afghanistan, although data is more limited, emerging studies suggest that the condition affects 5-10% of the population, with urbanization contributing to this rise. Kazakhstan also shows increasing rates, with some studies indicating that up to 12% of the population is affected, influenced by similar lifestyle factors such as diet and sedentary behavior (26; 27) . These trends highlight the growing burden of disease in South and Central Asia, with urbanization and lifestyle factors playing significant roles in the rise of the disease. In Africa, the prevalence is lower compared to other regions, though studies suggest an increase in urban populations, particularly in countries with more developed healthcare infrastructures such as South Africa (28) . The Middle East has a higher-than-expected prevalence in countries like Saudi Arabia, with rates ranging between 20.1% influenced by high rates of obesity and sedentary lifestyles (29) . These regional variations in GERD prevalence highlight the influence of socio-economic factors, diet, lifestyle, and access to healthcare in determining the burden of the disease.

PREVALENCE BY DEMOGRAPHICS

The prevalence also varies according to demographic factors such as age, gender, and socioeconomic status. In terms of age, most commonly affect adults aged 40 years and older, with the prevalence increasing significantly with age. Studies show that the incidence rises in individuals aged 45-60 years, with a peak in those over 60 years of age, as the lower esophageal sphincter tends to weaken with age (30).

Gender also plays a role in the prevalence of GERD. Historically, the disease has been more common in men during early adulthood, while in later years, women tend to report higher rates of the disease. The gender disparity is most pronounced in the middle-aged population, with women more likely to suffer from GERD post-menopause due to hormonal changes affecting the esophagus and LES function (31).

Obesity is a significant demographic factor that influences the prevalence, as overweight individuals have a higher likelihood of developing the condition due to increased intra-abdominal pressure. A recent study showed that 45% of obese individuals suffered, compared to 20% of those with normal weight

(32) . Furthermore, smoking and alcohol consumption increase the risk, especially in younger individuals (33).

RISK FACTORS FOR GERD

LIFESTYLE FACTORS

Lifestyle factors play a significant role in the development and exacerbation of gastric disorders. Among the most influential risk factors are obesity, diet, and smoking, all of which contribute to the weakening of the lower esophageal sphincter (LES) and increase intra-abdominal pressure, both of which are central to the condition pathophysiology. Obesity is one of the strongest lifestyle factors associated with the disease. Studies have shown that obese individuals are at a significantly higher risk of developing gastroesophageal related diseases, with obesity increasing the likelihood of GERD by up to threefold compared to individuals with normal body weight (34) . The primary mechanism linking obesity with the condition is increased intra-abdominal pressure, which can promote the reflux of gastric contents into the esophagus. Additionally, fatty tissue, particularly visceral fat, can increase the risk by exerting pressure on the diaphragm, which may further weaken the LES (35).

Dietary habits are another critical factor in the development and progression of GERD. High-fat diets, large meals, and the consumption of trigger foods like spicy foods, citrus fruits, chocolate, and caffeinated beverages have been shown to exacerbate the symptoms (36). These foods can directly irritate the esophageal lining or delay gastric emptying, leading to increased reflux events. Studies have demonstrated that a diet high in fats and sugars is particularly associated with an increased risk and its complications, as these foods can alter gastric motility and LES tone (37) . Smoking also significantly increases the risk. Nicotine in cigarettes can relax the LES, impair esophageal motility, and increase gastric acid production, making it easier for stomach contents to reflux into the esophagus (38) . Smokers have been shown to have a 50% higher risk of developing GERD compared to non-smokers. Furthermore, smoking can delay esophageal clearance of acid, which exacerbates the symptoms (39) . Smoking cessation has been shown to significantly reduce the frequency and severity of symptoms, highlighting the importance of lifestyle changes in the management of the disease.

Physical inactivity is another contributor to GERD. Lack of regular physical activity is linked to obesity and poor gastrointestinal motility, both of which exacerbate disease manifestation. Regular physical exercise can help reduce intra-abdominal pressure and promote healthy digestive function, thus improving symptoms in individuals affected by the disease (40).

MEDICAL CONDITIONS

Several medical conditions are closely linked to the development of the disease pathology, including hiatal hernia, pregnancy, and other gastrointestinal disorders. These conditions either predispose individuals to GERD or worsen its symptoms due to their impact on the esophagus and LES function. A hiatal hernia is one of the most common anatomical conditions associated with the condition. It

occurs when part of the stomach protrudes into the chest through the diaphragm, disrupting the normal function of the LES and promoting reflux. Hiatal hernias are found in a significant proportion of patients, with studies indicating that up to 60% of individuals with GERD also have a hiatal hernia (41) . The presence of a hiatal hernia can worsen the symptoms by reducing the LES's ability to prevent gastric reflux, as well as by contributing to abnormal esophageal motility. Pregnancy is another medical condition that significantly increases the risk of developing GERD. The prevalence is notably higher in pregnant women, with around 20% of pregnant individuals experiencing disease related symptoms during their pregnancy (42). Pregnancy-induced hormonal changes, such as increased levels of progesterone, relax the LES, allowing gastric contents to flow back into the esophagus more easily. Additionally, the growing uterus increases intra-abdominal pressure, further contributing to reflux symptoms. The symptoms often improve after pregnancy, but some women may continue to experience symptoms post-partum.

Other gastrointestinal conditions, such as gastroparesis (delayed gastric emptying), functional dyspepsia, and esophageal motility disorders, can also predispose individuals to the condition. In gastroparesis, the delayed emptying of the stomach increases the likelihood of gastric contents remaining in the stomach for prolonged periods, thereby raising the risk of reflux. Functional dyspepsia, a disorder characterized by abdominal discomfort and bloating, has also been found to overlap with GERD, as the symptoms of both diseases are often triggered by similar factors (43).

GENETIC AND ENVIRONMENTAL FACTORS

Genetic and environmental factors also contribute significantly to the development and progression of disease. While lifestyle and medical conditions play a dominant role, genetic predisposition cannot be overlooked, particularly in patients with a family history of GERD or esophageal cancer.

Genetics has been shown to play a role in disease, with studies suggesting that individuals with a first-degree relative who suffers from GERD are more likely to develop the disease themselves. A study reported that genetic polymorphisms affecting the lower esophageal sphincter (LES) tone and gastric acid secretion may predispose individuals to the condition. Additionally, specific genes involved in the regulation of the esophageal motility and acid production may influence susceptibility (44; 45). Moreover, the disease has been genetically link with different other types of diseases (46; 47; 48; 49). Research into these genetic links is ongoing, with the aim to identify individuals at higher risk due to their genetic makeup.

Environmental factors such as air pollution, dietary habits, and stress are increasingly being studied for their role in GERD development. Some studies suggest that exposure to certain environmental factors, such as fine particulate matter in urban areas, may exacerbate symptoms by irritating the respiratory and esophageal linings. Stress is another environmental factor that can impact GERD

by increasing gastric acid production and lowering LES pressure (50; 51; 52; 53; 54) . Chronic stress, often linked to modern work environments, has been identified as a risk factor for exacerbating symptoms, especially in individuals with other predisposing factors.

MEDICATIONS AND OTHER FACTORS

Certain medications can also increase the risk of developing GERD or exacerbate symptoms in individuals who already have the condition. Medications that relax the LES or delay gastric emptying are particularly implicated. Common classes of medications associated with the condition include calcium channel blockers, beta-blockers, and anticholinergic drugs. These medications are used for various conditions, including hypertension, heart disease, and gastrointestinal disorders, but they have the unfortunate side effect of promoting acid reflux by relaxing the LES, which normally serves as a barrier to prevent acid from entering the esophagus (55; 56; 57; 58; 59) . Non-steroidal anti-inflammatory drugs (NSAIDs) are another class of medications known to exacerbate GERD. Although commonly used to treat pain and inflammation, NSAIDs can irritate the stomach lining and increase gastric acid secretion, which in turn promotes reflux (60; 61) . Prolonged use of these medications can not only worsen GERD symptoms but also lead to complications such as gastritis and peptic ulcers.

TABLE.1: SHOW THE CHARACTERISTICS OF STUDIES RELATED TO RISK FACTORS

Risk Factor Category	Risk Factor	Description	References
	Obesity	Obesity increases intra-abdominal pressure, promoting gastric reflux. Studies show a higher prevalence of GERD in obese individuals.	34,35
Lifestyle Factors	Diet	High-fat diets, large meals, and spicy foods can exacerbate GERD symptoms by increasing gastric acid production and delaying gastric emptying.	36,37,38,39
	Smoking	Smoking relaxes the LES, increases gastric acid production, and reduces esophageal motility, all of which contribute to GERD.	39,103
	Physical Inactivity	Lack of regular exercise can lead to obesity and poor gastrointestinal motility, worsening GERD symptoms.	40,3
	Alcohol Consumption	Excessive alcohol consumption can impair LES function, promote gastric	104,7

		acid secretion, and delay gastric emptying.	
	Hiatal Hernia	A condition where part of the stomach pushes into the chest, weakening the LES and increasing the risk of GERD.	41,105,106
Medical Conditions	Pregnancy	Hormonal changes and increased intra-abdominal pressure during pregnancy can lead to GERD symptoms in up to 50% of pregnant women.	42,107
	Gastroparesis, Functional Dyspepsia, Esophageal Motility Disorders	A condition that delays gastric emptying, increasing the chance of acid reflux. Common in diabetic patients.	43,2,8
	Genetic Predisposition	A family history of GERD or esophageal cancer increases the likelihood of developing the disease.	44,45,46,47,48 .49
Genetic & Environmental	Air Pollution, Stress, Dietary Patterns	Exposure to air pollutants, particularly fine particulate matter, may exacerbate GERD symptoms by irritating the respiratory and esophageal linings. Chronic stress may contribute to GERD by increasing gastric acid secretion and decreasing LES pressure. A shift toward a Western diet, high in fats, sugars, and processed foods, is strongly linked to increasing GERD prevalence in developing countries.	50,51,52,53,54 ,9

CURRENT DIAGNOSTIC APPROACHES

CLINICAL EVALUATION

The clinical evaluation of GERD begins with obtaining a thorough patient history and assessing symptoms. A clinical diagnosis is often made based on heartburn, acid regurgitation, chest pain, and dysphagia. The frequency and intensity of these symptoms are important in determining the severity of the disease. Symptoms are usually meal-related and can be aggravated by certain lifestyle factors. Other symptoms such as chronic cough, hoarseness, and globus sensation (a sensation of a lump in the throat) are often associated with extra-esophageal reflux, which can complicate the diagnostic process.

Risk factors such as obesity, smoking, dietary habits, and medication use should be identified, as these factors contribute to LES relaxation and increased intra-abdominal pressure, both of which are contributed. Comorbidities like asthma, chronic cough, and sleep apnea are frequently seen in patients, making the diagnostic process challenging due to symptom overlap.

Clinical evaluation plays a key role in differentiating GERD from other conditions, such as cardiovascular disease and functional dyspepsia, which may present with similar symptoms. Validated symptom questionnaires like GERD-Q and Gerd-HRQL are useful in quantifying the severity and frequency of disease symptoms, which helps guide treatment decisions (62; 63).

MONITORING-BASED DIAGNOSTIC APPROACHES FOR GERD

Endoscopy is considered the gold standard for diagnosing GERD, particularly in patients with severe or complicated symptoms. Upper endoscopy allows for direct visualization of the esophageal mucosa, aiding in the detection of erosive esophagitis, ulcerations, and complications such as Barrett's esophagus. Endoscopy is also useful for ruling out other conditions, such as peptic ulcers and esophageal cancer. However, endoscopy does not detect non-erosive (NERD), where the esophageal lining appears normal despite chronic acid reflux (64; 65).

pH monitoring plays a crucial role in diagnosing the condition, especially in cases where symptoms are not clearly linked to acid reflux. 24-hour ambulatory pH monitoring is the gold standard for measuring acid exposure in the esophagus. A catheter inserted through the nose into the esophagus measures the pH levels over 24 hours, correlating reflux events with symptoms. This test is helpful in determining the frequency, duration, and severity of acid reflux, thereby guiding treatment decisions. However, wireless pH monitoring systems, such as the BRAVO capsule, are increasingly preferred due to their greater comfort and mobility for patients. The BRAVO system involves placing a small wireless capsule in the esophagus, which transmits data to an external receiver, making it a less invasive and more patient-friendly alternative (66; 67).

Manometry is used to assess esophageal motility and the function of the lower esophageal sphincter (LES). It involves passing a catheter through the esophagus to measure LES pressure and esophageal peristalsis. A hypotensive LES or disordered motility can contribute to GERD by allowing gastric contents to flow back into the esophagus. Manometry is especially useful in patients with atypical symptoms or those undergoing surgical treatments like fundoplication (68). Impedance monitoring measures the movement of liquids, gas, and mixed contents in the esophagus, detecting both acid and non-acid reflux. Unlike pH monitoring, which only measures acidic reflux, impedance can detect non-acid reflux, which is important for diagnosing non-erosive reflux disease (NERD). Impedance-pH monitoring, which combines both techniques, is increasingly used to assess the symptom-reflux relationship, particularly in patients

with atypical symptoms, such as chronic cough or laryngopharyngeal reflux (69; 70).

Together, these monitoring-based diagnostic approaches provide a holistic view of the disease and its complications. While endoscopy and pH monitoring are essential for visualizing esophageal damage and measuring acid reflux, manometry and impedance monitoring provide deeper insights into esophageal motility and the role of non-acid reflux in GERD symptoms.

NONINVASIVE DIAGNOSTIC APPROACHES FOR GERD

Salivary biomarkers, such as pepsin, have emerged as noninvasive diagnostic tools for the condition. Pepsin, a digestive enzyme normally found in the stomach, has been detected in saliva following acid reflux episodes. Salivary pepsin has shown promise as a diagnostic marker for non-erosive and laryngopharyngeal reflux, as it correlates with acid exposure and reflux episodes. Studies suggest that detecting pepsin in saliva can help identify GERD in patients with atypical symptoms who do not show visible damage in the esophagus (71; 72; 73; 74; 75).

miRNA (microRNA) biomarkers are being investigated for their role in gastric related disorders diagnosis. Specific miRNAs, such as miR-205 and miR-4668, have been shown to be differentially expressed in GERD patients, particularly those with eosinophilic esophagitis and esophageal cancer. These miRNAs are stable in saliva, making them attractive noninvasive diagnostic tools. The use of miRNA in saliva could provide a sensitive and specific method for diagnosing GERD, particularly in cases of non-erosive (76; 77; 78; 79; 80).

Hormonal markers, such as gastrin and ghrelin, are also being explored for their potential role in diagnosis. Gastrin, a hormone that regulates acid production in the stomach, is often elevated in patients. Ghrelin, involved in esophageal motility, could serve as a marker for LES function and reflux events (81; 82; 83; 84; 85; 86) . These noninvasive approaches offer significant advantages in routine screening and follow-up care, providing a patient-friendly, low-cost alternative to traditional diagnostic methods.

EMERGING DIAGNOSTIC METHODS FOR GERD

Emerging diagnostic methods are revolutionizing the management of diseases. Artificial Intelligence (AI) is being used to analyze endoscopic images and patient data to improve diagnostic accuracy. AI algorithms are being developed to detect Barrett's esophagus, erosive esophagitis, and other gastric-related complications by analyzing endoscopic findings and correlating them with patient symptoms. AI-based systems could assist clinicians in making data-driven treatment decisions for GERD patients (87; 88; 89; 90; 91).

Advanced imaging techniques, such as high-resolution ultrasound and magnetic resonance imaging (MRI), are also being explored for visualizing reflux events and esophageal motility. These techniques provide more detailed images of the esophagus compared to traditional endoscopy and may offer new insights into the condition pathophysiology (92; 93; 94; 95) . In addition to imaging,

biomarkers and genetic testing are being integrated into the diagnostic process. Genetic markers associated with Barrett's esophagus and esophageal adenocarcinoma are being studied to help identify high-risk individuals for earlier intervention. Biomarkers such as serum pepsinogen and gastric juice markers are also being explored to improve the diagnostic accuracy and early detection and its complications (96; 97; 98; 99; 100).

TABLE.2: SUMMARY OF CURRENT AND EMERGING DIAGNOSTIC APPROACHES FOR GERD

Diagnostic Approach	Description	Advantages	Limitations	Citations
1. Clinical Evaluation	- Patient history and symptom assessment (heartburn, acid regurgitation, chest pain, dysphagia). - Identifying risk factors and comorbidities (obesity, smoking, asthma, etc.). - Differentiating GERD from other diseases.	- Useful for initial diagnosis and differentiating from other conditions. - Symptom questionnaires (e.g., GERD-Q, Gerd-HRQL) guide treatment. - Helps guide treatment decisions.	Symptoms may overlap with other conditions like cardiovascular disease or functional dyspepsia.	(62; 63)
2. Monitoring-Based Diagnostic Approaches				
2.1 Endoscopy	- Visualizes esophagus for detecting erosive esophagitis, ulcerations, and complications like Barrett's esophagus.	- Direct visualization of esophagus. Detects complications and rules out other conditions.	- Does not detect non-erosive GERD (NERD).	(64; 65)
2.2 pH Monitoring	- Measures acid exposure in esophagus using 24-hour pH monitoring or wireless BRAVO	- Provides detailed data on acid reflux severity and symptom correlation.	- Traditional pH monitoring is invasive; wireless systems may not detect non-acid reflux.	(66; 67)

capsule systems.

2.3 Manometry	- Assesses esophageal motility and LES function by measuring pressure and peristalsis.	- Useful for atypical GERD symptoms or patients undergoing surgery.	- Limited availability; mainly used for surgical evaluation.	(68)
2.4 Impedance Monitoring	- Detects both acid and non-acid reflux by measuring movement of liquids, gas, and mixed contents in esophagus.	- Can detect non-acid reflux, important for NERD and atypical GERD symptoms.	- Requires specialized equipment and expertise.	(69; 70)
3. Noninvasive Diagnostic Approaches				
3.1 Salivary Biomarkers (Pepsin)	- Detects pepsin in saliva after acid reflux episodes.	- Noninvasive; promising for diagnosing NERD and atypical GERD symptoms.	- Still under research, limited clinical validation.	(71; 72; 73; 74; 75)
3.2 miRNA Biomarkers	- miRNAs (e.g., miR-205, miR-4668) are differentially expressed in GERD patients and stable in saliva.	- Noninvasive; could be useful for diagnosing NERD and atypical GERD.	- Not widely validated for clinical use.	(76; 77; 78; 79; 80)
3.3 Hormonal Markers (Gastrin, Ghrelin)	- Gastrin and ghrelin are being studied for GERD diagnosis.	- May provide insights into LES function and acid production.	- In early research phases; not yet widely used in routine clinical practice.	(81; 82; 83; 84; 85; 86)
4. Emerging Diagnostic Methods				

4.1 Artificial Intelligence (AI)	- AI analyzes endoscopic images and patient data for improved diagnostic accuracy, especially for complications.	- Assists in early detection and data-driven treatment decisions.	- Requires large datasets and validation before widespread use.	(87; 88; 89; 90; 91)
4.2 Advanced Imaging (Ultrasound, MRI)	- High-resolution ultrasound and MRI provide detailed images of reflux events and esophageal motility.	- Non-invasive; offers more detailed images compared to traditional methods.	- High cost and limited availability.	(92; 93; 94; 95)
4.3 Genetic and Biomarker Testing	- Genetic markers associated with GERD and its complications are being studied.	- Potential for earlier intervention and improved diagnostic accuracy.	- In early stages of research; not yet widely adopted in clinical practice.	(96; 97; 98; 99; 100)

CHALLENGES IN DIAGNOSIS

NON-SPECIFIC SYMPTOMS OF GERD

One of the primary challenges in diagnosing lies in its non-specific symptoms, which often overlap with other conditions. While heartburn and acid regurgitation are the hallmark symptoms, they are not exclusive. Chronic cough, hoarseness, globus sensation (the feeling of a lump in the throat), and chest pain are common among patients, but these symptoms are also frequently seen in other conditions such as asthma, upper respiratory infections, cardiovascular diseases, and esophageal motility disorders. This overlap makes it difficult to differentiate GERD from other diseases based solely on clinical presentation.

Atypical symptoms, such as laryngopharyngeal reflux (LPR), further complicate diagnosis. LPR refers to the backflow of stomach contents into the larynx or pharynx and can lead to symptoms like hoarseness, chronic throat clearing, and sore throat. These symptoms are often mistakenly attributed to viral infections or allergies, delaying proper diagnosis. The difficulty in linking these non-specific symptoms with GERD means that many patients remain undiagnosed or are misdiagnosed, especially those who do not exhibit the classic heartburn symptoms.

Moreover, atypical symptoms can occur in the absence of esophageal damage, making it even harder to detect the disease with traditional diagnostic methods like endoscopy. Patients with non-erosive reflux disease (NERD) present with GERD symptoms, but their esophageal lining appears normal during endoscopy, leading to misdiagnosis or under-

treatment. As a result, accurate diagnosis relies on symptom correlation through advanced diagnostic tests, such as pH monitoring and impedance monitoring, which still face limitations in terms of accessibility, patient compliance, and cost (101).

LIMITATIONS OF CURRENT METHODS

While current diagnostic methods for GERD, including endoscopy, pH monitoring, manometry, and impedance monitoring, are essential in diagnosing and assessing the severity of the disease, they all have their limitations. Endoscopy, though invaluable in detecting erosive esophagitis and Barrett's esophagus, is invasive, expensive, and may not identify non-erosive reflux disease. In fact, studies show that non-erosive constitutes more than half of cases, yet these patients often do not display visible esophageal damage, limiting the utility of endoscopy in these cases. Similarly, pH monitoring, the gold standard for assessing acid reflux, can only detect acidic reflux and does not account for non-acid reflux, which may still contribute to symptoms. As a result, this test may miss significant reflux events that are not acidic but still harmful to the esophagus. Furthermore, 24-hour ambulatory pH monitoring can be uncomfortable for patients and is often labor-intensive, limiting its widespread use. Wireless alternatives, such as the BRAVO system, are more comfortable, but they are still relatively cost-prohibitive for some healthcare settings. Manometry, which assesses LES function and esophageal motility, provides valuable information, but it is invasive and is primarily used in patients undergoing surgical interventions or those with atypical symptoms. Impedance monitoring is a valuable adjunct to pH monitoring, as it can detect both acidic and non-acid reflux and has the advantage of assessing non-acid reflux that contributes to GERD. However, impedance monitoring is less commonly available and may not always correlate with symptom severity. Furthermore, all these tests require patient cooperation and expert interpretation, which adds to the complexity and cost of diagnosis (68).

The limitations of these methods underscore the need for more accessible, non-invasive, and cost-effective diagnostic tools to accurately diagnose GERD, particularly in cases with atypical symptoms or NERD, which often remain undiagnosed with current practices.

NEED FOR STANDARDIZED GUIDELINES

Despite advances in diagnostics, there remains a lack of standardized guidelines for the diagnosis and management of GERD, especially in cases with atypical symptoms or NERD. The variability in diagnostic practices, test accessibility, and interpretation across different healthcare settings can lead to misdiagnosis or under diagnosis. Establishing clear, evidence-based guidelines for when and how to use different diagnostic tests would improve diagnostic accuracy, treatment efficacy, and patient outcomes. Standardized approaches would help clinicians better navigate the complexities of diagnosing, particularly in light of its diverse clinical presentations and non-specific symptoms (102).

DISCUSSION

This review explored the range of diagnostic techniques available for GERD, focusing on both traditional and emerging methods. Clinical evaluation, the first step in diagnosing, remains foundational in identifying typical symptoms like heartburn and acid regurgitation. However, atypical symptoms, such as chronic cough and laryngopharyngeal reflux (LPR), pose significant challenges in clinical diagnosis. These non-specific symptoms often overlap with conditions like asthma, cardiovascular disease, and upper respiratory infections, leading to potential misdiagnoses. The difficulty in diagnosing the disease in the absence of classic symptoms reinforces the need for advanced diagnostic methods.

Endoscopy, the gold standard for assessing erosive esophagitis and Barrett's esophagus, provides invaluable insight into esophageal damage caused by chronic acid reflux. However, its inability to detect non-erosive, a condition that affects up to 60% of GERD patients, limits its diagnostic capabilities. pH monitoring, though effective in confirming acid reflux, only measures acidic reflux and is unable to detect non-acid reflux, which can also contribute to the condition symptoms. This highlights the importance of impedance monitoring, which can detect both acid and non-acid reflux, offering a broader view of reflux events that might trigger symptoms, particularly in atypical cases. The combination of impedance-pH monitoring provides a more comprehensive understanding of reflux episodes and their relationship to symptoms.

Moreover, non-invasive diagnostic approaches like salivary biomarkers, miRNAs, and hormonal markers represent promising advancements in diagnosis. Salivary pepsin and miRNAs offer a relatively easy, non-invasive method for diagnosing NERD and laryngopharyngeal reflux, which are often missed by traditional methods. Hormonal markers such as gastrin and ghrelin are being explored for their role in LES function and acid reflux, but further validation is required. These emerging non-invasive methods hold the potential to significantly improve the diagnostic accuracy of GERD and reduce patient discomfort associated with invasive tests like endoscopy and pH monitoring.

When comparing the current monitoring-based diagnostic approaches with emerging methods, several strengths and limitations become apparent. Endoscopy is invaluable for detecting erosive esophagitis, Barrett's esophagus, and other structural complications, making it crucial for patients presenting with severe or complicated symptoms. However, endoscopy is invasive and costly, and it fails to detect non-erosive type and extra-esophageal symptoms. Furthermore, patient discomfort and the need for sedation during the procedure make it less ideal for routine screening or follow-up assessments, particularly for milder cases.

pH monitoring and impedance monitoring complement endoscopy by providing a quantitative assessment of acid reflux. However, pH monitoring only measures acidic reflux, which means it may miss important non-acid reflux events. This gap is addressed by

impedance monitoring, which can detect a broader range of gastric contents and provide a more comprehensive view of reflux in non-erosive. Yet, these methods can be inconvenient for patients and require expert interpretation, which limits their accessibility in some clinical settings.

On the other hand, non-invasive approaches, such as salivary biomarkers and miRNA testing, offer significant promise for diagnosing GERD without the need for invasive procedures. Salivary pepsin, in particular, has been found to correlate with reflux events, offering a relatively simple, patient-friendly, and cost-effective diagnostic tool. Similarly, miRNA testing is emerging as a valuable tool for detecting non-erosive and Barrett's esophagus. However, these non-invasive tests still require further validation in larger clinical trials to confirm their diagnostic accuracy and clinical utility.

Emerging technologies, such as AI-based analysis of endoscopic images and advanced imaging techniques like MRI and high-resolution ultrasound, are opening new frontiers in GERD diagnosis. These innovations offer more detailed imaging and the potential for real-time diagnosis, but they are still in the experimental phase and not yet widely available in clinical practice. The integration of advanced diagnostic methods, particularly non-invasive approaches, is likely to have a profound impact on patient care and clinical outcomes. Accurate diagnosis of disease is crucial for effective management and prevention of complications. Early detection of erosive esophagitis, Barrett's esophagus, and esophageal adenocarcinoma can significantly reduce morbidity and mortality associated with GERD-related cancers. Non-invasive diagnostics like salivary pepsin and miRNA testing could play a key role in identifying non-erosive type of disease and atypical cases that often go undiagnosed with traditional methods. The combination of monitoring-based diagnostics (e.g., pH monitoring, manometry) and emerging non-invasive tests could provide a personalized approach to h disease management, allowing healthcare providers to tailor treatments based on individual patient profiles. This would improve patient outcomes by ensuring that the most effective therapies are selected for each patient. The integration of AI and machine learning into diagnostic workflows further enhances decision-making by assisting clinicians in interpreting complex data from multiple diagnostic tests, ultimately improving diagnostic accuracy and treatment efficacy. However, for these advancements to be fully realized in clinical practice, significant work is needed to overcome accessibility and cost barriers. As these technologies become more affordable and widely available, they will likely become integral to routine diagnosis and management.

The findings from this review suggest several key implications for clinical practice. First, clinicians should integrate a combination of clinical evaluation and advanced diagnostic tools to ensure accurate diagnosis. Given the wide variability in symptoms, a personalized approach using monitoring-based diagnostic techniques like pH monitoring, impedance monitoring, and salivary biomarkers will

improve diagnostic accuracy. For patients with atypical symptoms or non-erosive GERD, non-invasive methods such as miRNA testing and salivary pepsin could provide a simple and cost-effective diagnostic solution. Emerging technologies, including AI-driven diagnostics and advanced imaging techniques, should be considered for patients with complex or severe presentations, as these methods can provide real-time data and assist in personalized treatment planning.

Finally, standardized diagnostic guidelines should be established to incorporate these new technologies into routine practice. Such guidelines would streamline the diagnostic process, improve treatment outcomes, and ensure that GERD patients receive the most appropriate care.

CONCLUSION

The diagnosis of GERD continues to evolve with advancements in non-invasive diagnostics and emerging technologies. While endoscopy and pH monitoring remain foundational, new methods like salivary biomarkers, miRNA testing, and AI-based diagnostics promise to enhance diagnostic accuracy and patient comfort. The integration of these technologies into clinical practice could improve personalized care, leading to better patient outcomes and reduced complications. However, further validation and standardized guidelines are needed to incorporate these innovations into routine clinical workflows and ensure their widespread implementation.

REFERENCES

1. Maret-Ouda J, Markar SR, Lagergren J. Gastroesophageal reflux disease: a review. Jama. 2020 Dec 22;324(24):2536-47.
2. Li N, Yang WL, Cai MH, Chen X, Zhao R, Li MT, Yan XL, Xue LW, Hong L, Tang MY. Burden of gastroesophageal reflux disease in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of disease study 2019. BMC Public Health. 2023 Mar 29;23(1):582.
3. Jung HK. Epidemiology of gastroesophageal reflux disease in Asia: a systematic review. Journal of neurogastroenterology and motility. 2011 Jan 26;17(1):14.
4. Maresova P, Rezny L, Hruska J, Klimova B, Swanstrom LL, Kuca K. Diagnosis and treatment of patients with gastroesophageal reflux disease–a systematic review of cost-effectiveness and economic burden. BMC Health Services Research. 2024 Nov 6;24(1):1351.
5. Manabe N, Joh T, Higuchi K, Iwakiri K, Kamiya T, Haruma K, Nakada K. Clinical significance of gastroesophageal reflux disease with minimal change: a multicenter prospective observational study. Scientific Reports. 2022 Sep 3;12(1):15036.
6. Fuchs KH, Musial F, Eypasch E, Meining A. Gastrointestinal quality of life in gastroesophageal reflux disease: a systematic review. Digestion. 2022 Jul 1;103(4):253-60.
7. Asreah RH, Abdullhameed A. Risk factors of erosive esophagitis and barrett's esophagus in patients with reflux

symptoms. Medical Journal of the Islamic Republic of Iran. 2021 Jun 12;35:75.

8. Sonnenberg A. Time trends of US hospitalization for esophageal disease. Journal of Clinical Gastroenterology. 2014 Sep 1;48(8):e71-5.
9. Sharma P, Falk GW, Bhor M, Ozbay AB, Latremouille-Viau D, Guerin A, Shi S, Elvekrog MM, Limburg P. Healthcare resource utilization and costs among patients with gastroesophageal reflux disease, Barrett's esophagus, and Barrett's esophagus-related neoplasia in the United States. Journal of Health Economics and Outcomes Research. 2023 Mar 3;10(1):51.
10. Gerson LB, McLaughlin T, Balu S, Jackson J, Lunacsek O. Variation of health-care resource utilization according to GERD-associated complications. Diseases of the Esophagus. 2012 Dec 1;25(8):694-701.
11. Nirwan JS, Hasan SS, Babar ZU, Conway BR, Ghori MU. Global prevalence and risk factors of gastro-oesophageal reflux disease (GORD): systematic review with meta-analysis. Scientific reports. 2020 Apr 2;10(1):5814.
12. Hunt R, Armstrong D, Katelaris P, Afihene M, Bane A, Bhatia S, Chen MH, Choi MG, Melo AC, Fock KM, Ford A. World gastroenterology organisation global guidelines: GERD global perspective on gastroesophageal reflux disease. Journal of clinical gastroenterology. 2017 Jul 1;51(6):467-78.
13. Jung HK. Epidemiology of gastroesophageal reflux disease in Asia: a systematic review. Journal of neurogastroenterology and motility. 2011 Jan 26;17(1):14.
14. Wickramasinghe N, Devanarayana NM. Insight into global burden of gastroesophageal reflux disease: Understanding its reach and impact. World Journal of Gastrointestinal Pharmacology and Therapeutics. 2025 Mar 5;16(1):97918.
15. Sarici IS, Eriksson SE, Chaudhry N, Zheng P, Chalikonda S, Bartlett DL, Ayazi S. Socioeconomic Disparities in the Progression of GERD and Barrett's Esophagus to Esophageal Adenocarcinoma. Annals of surgery. 2025 Feb 25:10-97.
16. Wickramasinghe N, Devanarayana NM. Insight into global burden of gastroesophageal reflux disease: Understanding its reach and impact. World Journal of Gastrointestinal Pharmacology and Therapeutics. 2025 Mar 5;16(1):97918.
17. Alrezuk AM, Ismail MH, Alsulaiman RM, Alamri TA, Alhafid IA, Alzahrani IM, Alotaibi AD, Alqahtani SY, Alam AH, Alelyani JM, Aljidhr ZH. Prevalence and Risk Factors of Gastroesophageal Reflux Disease in Patients with Dyspeptic and Reflux Symptoms: An Endoscopy-Based Prospective Study from Al Khobar, Saudi Arabia. Journal of Epidemiology and Global Health. 2025 Apr 10;15(1):58.
18. Bunt V, Visser J, AlRefaee F, Seckel S, Jiang M, Chen J, Zakharova I, Geppe N, Dupont C, Szajewska H, Goossens D. Prevalence and possible causes of crying and mild gastrointestinal and skin

symptoms in infants reported by healthcare professionals-worldwide data. European Journal of Pediatrics. 2025 May 14;184(6):341.

19. Wei Y, Liu E, Peng J, Liu Y, Sun X, Yao X. Global burden of esophageal diseases: a comprehensive analysis of disease trends and risk factors from 1990 to 2021. BMC gastroenterology. 2025 Jul 21;25(1):528.
20. Farooq Q, Hassan S. Relationship Between Dietary Patterns and Symptom Severity in Gastroesophageal Reflux Disease (GERD): A Patient-Centered Survey. Journal of Health and Rehabilitation Research. 2025 Jan 31;5(1):1-9.
21. Alatawi HS, Alshaikh AA, Behairi MM, Alsudairy NM, Alshaikh JA. Prevalence and Lifestyle Factors Associated With Gastroesophageal Reflux Disease Symptoms Among Adults in Saudi Arabia: A Cross-Sectional Study. Cureus. 2025 Apr 25;17(4).
22. Chowdhury SD, George G, Ramakrishna K, Ramadass B, Pugazhendhi S, Mechenro J, Jeyaseelan L, Ramakrishna BS. Prevalence and factors associated with gastroesophageal reflux disease in southern India: a community-based study. Indian Journal of Gastroenterology. 2019 Feb 14;38(1):77-82.
23. Zhang D, Liu S, Li Z, Wang R. Global, regional and national burden of gastroesophageal reflux disease, 1990–2019: update from the GBD 2019 study. Annals of medicine. 2022 Dec 31;54(1):1372-84.
24. Rasool MF, Sarwar R, Arshad MS, Imran I, Saeed H, Majeed A, Akbar M, Chaudhry MO, Rehman AU, Ashraf W, Ahmad T. Assessing the frequency and risk factors associated with gastroesophageal reflux disease (GERD) in Southern Punjab, Pakistan. Risk Management and Healthcare Policy. 2021 Nov 12:4619-25.
25. Sadeghi A, Boustani P, Mehrpour A, Asgari AA, Sharafkhah M, Yazdanbod A, Somi MH, Nejatizadeh A, Moradpour F, Rezaeian M, Mansour-Ghanaei F. Prevalence and risk factors of gastroesophageal reflux disease in Iran: A cross-sectional analysis from the PERSIAN cohort. Plos one. 2024 Jul 11;19(7):e0306223.
26. Saeedy SA, Faiz AF, Rahimi A, Shayan NA. Assessment of gastroesophageal reflux disease signs, symptoms, and food behaviors concerning mental health in Herat, Afghanistan: A descriptive study. Health Science Reports. 2024 Aug;7(8):e2301.
27. Imanbayeva A, Zhakiev B, Yelemessov A, Adaibayev K, Tussupkaliyeva K, Turebayev D, Urazova S, Mamesheva L, Afshar A. Assessing academic impact through a bibliometrics analysis: Gastroesophageal reflux disease in the context of obesity treatment and bariatric surgery. SAGE Open Medicine. 2025 May;13:20503121251336304.
28. Nwokediuko SC, Adekanle O, Akere A, Olokoba A, Anyanechi C, Umar SM, Maiyaki A, Ijoma U, Obienu O, Uhunmwangho A, Ndububa D. Gastroesophageal reflux disease in a typical African population: a symptom-based

multicenter study. BMC gastroenterology. 2020 Apr 15;20(1):107.

29. Alrezuk AM, Ismail MH, Alsulaiman RM, Alamri TA, Alhafid IA, Alzahrani IM, Alotaibi AD, Alqahtani SY, Alam AH, Alelyani JM, Aljidhr ZH. Prevalence and Risk Factors of Gastroesophageal Reflux Disease in Patients with Dyspeptic and Reflux Symptoms: An Endoscopy-Based Prospective Study from Al Khobar, Saudi Arabia. Journal of Epidemiology and Global Health. 2025 Apr 10;15(1):58.
30. Kpossou AR, Vignon RK, Gnahoui SA, Sokpon CN, Ahouada C, Azandjèmè C, Séhonou J. Typical gastroesophageal reflux disease in the general adult population in cotonou: Prevalence and associated socio-demographic factors. Open Journal of Gastroenterology. 2021 Feb 9;11(2):29-38.
31. Bains K, Iqbal H, Attri A, Dhiman M, Singh I, Kohli I, Chaudhry H, Dukovic D, Sohal A, Yang J. Impact of Gender on Gastroesophageal Reflux Disease Complications: Analysis of 27 Million Hospitalizations. Journal of Gastrointestinal & Liver Diseases. 2024 Mar 1;33(1).
32. Xie M, Deng L, Fass R, Song G. Obesity is associated with higher prevalence of gastroesophageal reflux disease and reflux related complications: a global healthcare database study. Neurogastroenterology & Motility. 2024 Apr;36(4):e14750.
33. Pan J, Cen L, Chen W, Yu C, Li Y, Shen Z. Alcohol consumption and the risk of gastroesophageal reflux disease: a systematic review and meta-analysis. Alcohol and Alcoholism. 2019 Jan 1;54(1):62-9.
34. Sadafi S, Azizi A, Pasdar Y, Shakiba E, Darbandi M. Risk factors for gastroesophageal reflux disease: a population-based study. BMC gastroenterology. 2024 Feb 5;24(1):64.
35. El-Serag HB, Thrift AP. Obesity and gastroesophageal reflux disease. The Esophagus. 2021 Jul 9:624-32.
36. Fox M, Gyawali CP. Dietary factors involved in GERD management. Best practice & research Clinical gastroenterology. 2023 Feb 1;62:101826.
37. Newberry C, Lynch K. The role of diet in the development and management of gastroesophageal reflux disease: why we feel the burn. Journal of thoracic disease. 2019 Aug;11(Suppl 12):S1594.
38. Ness-Jensen E, Lagergren J. Tobacco smoking, alcohol consumption and gastro-oesophageal reflux disease. Best practice & research Clinical gastroenterology. 2017 Oct 1;31(5):501-8.
39. Taraszewska A. Risk factors for gastroesophageal reflux disease symptoms related to lifestyle and diet. Roczniki Państwowego Zakładu Higieny. 2021;72(1):21-8.
40. Yu C, Wang T, Gao Y, Jiao Y, Jiang H, Bian Y, Wang W, Lin H, Xin L, Wang L. Association between physical activity and risk of gastroesophageal reflux disease: A systematic review and meta-analysis. Journal of sport and health science. 2024 Sep 1;13(5):687-98.

41. Alsahafi MA, Alajhar NA, Almahyawi AO, Alsulami HH, Alghamdi WA, Alharbi LA, Alsulami AS, Aljehani JT, Alkhowaiter SS, Mosli MH. The prevalence and risk factors for hiatal hernia among patients undergoing endoscopy: a retrospective analysis. Saudi Medical Journal. 2023 May;44(5):509.
42. Le YT, Luu MN, Mai LH, Hoang AT, Nguyen TT, Quach DT. Prevalence and characteristics of gastroesophageal reflux disease in pregnant women. Revista de Gastroenterología de México (English Edition). 2023 Oct 1;88(4):341-6.
43. Caballero-Mateos AM, López-Hidalgo JL, Torres-Parejo Ú, Hernández-González JM, Quintero-Fuentes MD, Caballero-Plasencia AM, Redondo-Cerezo E. Risk factors for functional dyspepsia, erosive and non-erosive gastroesophageal reflux disease: A cross-sectional study. Gastroenterologia y hepatologia. 2023 Aug 1;46(7):542-52.
44. Argyrou A, Legaki E, Koutserimpas C, Gazouli M, Papaconstantinou I, Gkiokas G, Karamanolis G. Risk factors for gastroesophageal reflux disease and analysis of genetic contributors. World journal of clinical cases. 2018 Aug 16;6(8):176.
45. Gharahkhani P, Tung J, Hinds D, Mishra A, Barrett's and Esophageal Adenocarcinoma Consortium (BEACON), Vaughan TL, Whiteman DC, MacGregor S. Chronic gastroesophageal reflux disease shares genetic background with esophageal adenocarcinoma and Barrett's esophagus. Human molecular genetics. 2016 Feb 15;25(4):828-35.
46. Picos A, Vulturar R, Picos A, Chis A, Chiorean I, Piciu A, Petrachescu N, Dumitrascu DL. Interleukin-1A and interleukin-1B gene polymorphisms in gastroesophageal reflux disease. Experimental and therapeutic medicine. 2020 Oct;20(4):3394-8.
47. Ong JS, Gharahkhani P, Vaughan TL, Whiteman D, Kendall BJ, MacGregor S. Assessing the genetic relationship between gastro-esophageal reflux disease and risk of COVID-19 infection. Human Molecular Genetics. 2022 Feb 1;31(3):471-80.
48. Yang C, Ge F, Peng M, Cheng L, Wang K, Liu W. Exploring the genetic link between gastroesophageal reflux disease and pancreatic cancer: insights from Mendelian randomization. BMC cancer. 2025 Apr 18;25(1):729.
49. Cheng X, Shi J, Zhang D, Li C, Xu H, He J, Liang W. Assessing the genetic relationship between gastroesophageal reflux disease and chronic respiratory diseases: a mendelian randomization study. BMC pulmonary medicine. 2023 Jul 4;23(1):243.
50. Cheng Y, Kou F, Liu J, Dai Y, Li X, Li J. Systematic assessment of environmental factors for gastroesophageal reflux disease: an umbrella review of systematic reviews and meta-analyses. Digestive and Liver Disease. 2021 May 1;53(5):566-73.
51. Argyrou A, Legaki E, Koutserimpas C, Gazouli M, Papaconstantinou I, Gkiokas G, Karamanolis G. Risk factors for gastroesophageal reflux disease and analysis of genetic contributors. World journal of clinical cases. 2018 Aug 16;6(8):176.

52. Seo HS, Hong J, Jung J. Relationship of meteorological factors and air pollutants with medical care utilization for gastroesophageal reflux disease in urban area. World journal of gastroenterology. 2020 Oct 21;26(39):6074.
53. Cao R, Jiang H, Zhang Y, Guo Y, Zhang W. Causal relationship between air pollution, lung function, gastroesophageal reflux disease, and non-alcoholic fatty liver disease: univariate and multivariate Mendelian randomization study. Frontiers in Public Health. 2024 Apr 29;12:1368483.
54. Li J, He C, Ying J, Hua B, Yang Y, Chen W, Liu W, Ye D, Sun X, Mao Y, Chen K. Air pollutants, genetic susceptibility, and the risk of incident gastrointestinal diseases: A large prospective cohort study. Environmental Research. 2024 Apr 15;247:118182.
55. Mungan Z, Pınarbaşı Şimşek B. Which drugs are risk factors for the development of gastroesophageal reflux disease?. Turkish Journal of Gastroenterology. 2017.
56. Ismoilova M, Mirzajonova S. CALCIUM CHANNEL BLOCKERS AS A ETHIOLOGICAL FACTOR FOR GASTROESOPHAGEAL REFLUX DISEASE. International journal of medical sciences. 2025 May 9;1(3):165-8.
57. Maruyama T, Fukata M, Akashi K. Association of atrial fibrillation and gastroesophageal reflux disease: Natural and therapeutic linkage of the two common diseases. Journal of arrhythmia. 2019 Feb;35(1):43-51.
58. Jalalyazdi M, Gharaee AM. The Effects of Pantoprazole on the Treatment of Palpitation in Patients with Gastro esophageal Reflux Disease (GERD): A Case Series. J Cardiothorac Med. 2015 May 1;3(2):309-12.
59. Mungan Z, Pınarbaşı Şimşek B. Which drugs are risk factors for the development of gastroesophageal reflux disease?. Turkish Journal of Gastroenterology. 2017.
60. Schneider JL, Zhao WK, Corley DA. Aspirin and nonsteroidal anti-inflammatory drug use and the risk of Barrett's esophagus. Digestive diseases and sciences. 2015 Feb;60(2):436-43.
61. Tai FW, McAlindon ME. Non-steroidal anti-inflammatory drugs and the gastrointestinal tract. Clinical Medicine. 2021 Mar 1;21(2):131-4.
62. Savarino E, Bredenoord AJ, Fox M, Pandolfino JE, Roman S, Gyawali CP. Advances in the physiological assessment and diagnosis of GERD. Nature reviews Gastroenterology & hepatology. 2017 Nov;14(11):665-76.
63. Yadlapati R, Gyawali CP, Pandolfino JE, Chang K, Kahrilas PJ, Katz PO, Katzka D, Komanduri S, Lipham J, Menard-Katcher P, Muthusamy VR. AGA clinical practice update on the personalized approach to the evaluation and management of GERD: expert review. Clinical Gastroenterology and Hepatology. 2022 May 1;20(5):984-94.
64. Simadibrata DM, Lesmana E, Fass R. Role of endoscopy in gastroesophageal reflux disease. Clinical endoscopy. 2023 Nov 1;56(6):681-92.

65. Kuribayashi S, Hosaka H, Nakamura F, Nakata K, Sato K, Itoi Y, Hashimoto Y, Kasuga K, Tanaka H, Uraoka T. The role of endoscopy in the management of gastroesophageal reflux disease. DEN open. 2022 Apr;2(1):e86.
66. Frazzoni M, De Bortoli N, Frazzoni L, Tolone S, Savarino V, Savarino E. Impedance-pH monitoring for diagnosis of reflux disease: new perspectives. Digestive diseases and sciences. 2017 Aug;62(8):1881-9.
67. Penagini R, Sweis R, Mauro A, Domingues G, Vales A, Sifrim D. Inconsistency in the diagnosis of functional heartburn: usefulness of prolonged wireless pH monitoring in patients with proton pump inhibitor refractory gastroesophageal reflux disease. Journal of neurogastroenterology and motility. 2015 Apr;21(2):265.
68. Jandee S, Keeratichananont S, Tack J, Vanuytsel T. Concise review: applicability of high-resolution manometry in gastroesophageal reflux disease. Journal of Neurogastroenterology and Motility. 2022 Oct 30;28(4):531.
69. Marabotto E, Savarino V, Ghisa M, Frazzoni M, Ribolsi M, Barberio B, Savarino E. Advancements in the use of 24-hour impedance-pH monitoring for GERD diagnosis. Current Opinion in Pharmacology. 2022 Aug 1;65:102264.
70. Forootan M, Zojaji H, Ehsani MJ, Darvishi M. Advances in the diagnosis of GERD using the esophageal pH monitoring, gastro-esophageal impedance-pH monitoring, and pitfalls. Open access Macedonian journal of medical sciences. 2018 Oct 24;6(10):1934.
71. Alberto B, Chiara M, Alessandra V, Ginevra C, Antonio N, Mario C, Gioacchino L, Tiziana M, Gian LD, Francesco DM. A non-invasive method for the diagnosis of upper GI diseases. Acta Bio Medica: Atenei Parmensis. 2018;89(Suppl 8):44.
72. Mohamed HI, Khodeer SA, Shaheen WA. Study of pepsin level in saliva as a noninvasive marker for diagnosis of gastroesophageal reflux disease. Menoufia Medical Journal. 2020;33(1):94-100.
73. Dongiovanni P, Meroni M, Casati S, Goldoni R, Thomaz DV, Kehr NS, Galimberti D, Del Fabbro M, Tartaglia GM. Salivary biomarkers: novel noninvasive tools to diagnose chronic inflammation. International journal of oral science. 2023 Jun 29;15(1):27.
74. Farooqi MS, Podury S, Crowley G, Javed U, Li Y, Liu M, Kwon S, Grunig G, Khan AR, Francois F, Nolan A. Noninvasive, MultiOmic, and multicompartmental biomarkers of reflux disease: a systematic review. Gastro hep advances. 2023 Jan 1;2(4):608-20.
75. Du X, Wang F, Hu Z, Wu J, Wang Z, Yan C, Zhang C, Tang J. The diagnostic value of pepsin detection in saliva for gastro-esophageal reflux disease: a preliminary study from China. BMC gastroenterology. 2017 Oct 17;17(1):107.
76. Mallick R, Patnaik SK, Wani S, Bansal A. A systematic review of esophageal microRNA markers for diagnosis and

monitoring of Barrett's esophagus. Digestive diseases and sciences. 2016 Apr;61(4):1039-50.

77. Votto M, De Filippo M, Castagnoli R, Delle Cave F, Giffoni F, Santi V, Vergani M, Caffarelli C, De Amici M, Marseglia GL, Licari A. Non-invasive biomarkers of eosinophilic esophagitis. Acta Bio Medica: Atenei Parmensis. 2021 Nov 29;92(Suppl 7):e2021530.
78. Chen YH, Wang H. The association between depression and gastroesophageal reflux based on phylogenetic analysis of miRNA biomarkers. Current Medicinal Chemistry. 2020 Nov 1;27(38):6536-47.
79. Craig MP, Rajakaruna S, Paliy O, Sajjad M, Madhavan S, Reddy N, Zhang J, Bottomley M, Agrawal S, Kadakia MP. Differential microRNA signatures in the pathogenesis of Barrett's esophagus. Clinical and Translational Gastroenterology. 2020 Jan 1;11(1):e00125.
80. Yan X, Zhu S, Zhang H. miR-203 Expression in Exfoliated Cells of Tongue Coating Represents a Sensitive and Specific Biomarker of Gastroesophageal Reflux Disease. Gastroenterology research and practice. 2016;2016(1):2349453.
81. Tseng PH, Yang WS, Liou JM, Lee YC, Wang HP, Lin JT, Wu MS. Associations of circulating gut hormone and adipocytokine levels with the spectrum of gastroesophageal reflux disease. PLoS One. 2015 Oct 27;10(10):e0141410.
82. Syrjänen K. Serological biomarker panel (GastroPanel®): A test for non-invasive diagnosis of dyspeptic symptoms and for comprehensive detection of. Helicobacter pylori. 2017:1-0.
83. He J, Li J, Hu Z, Wang Y, Ma G, Wu H, Zhang J, Dong Y. Clinical effect of acupuncture for gastroesophageal reflux disease based on the" heart-stomach connection" theory and its effects on serum gastrointestinal hormones. Zhongguo Zhen jiu= Chinese Acupuncture & Moxibustion. 2024 Jun 1;44(6):625-30.
84. Di Mario F, Crafa P, Franceschi M, Rodriguez-Castro K, Baldassarre G, Ferronato A, Antico A, Panozzo MP, Franzoni L, Barchi A, Russo M. Low levels of gastrin 17 are Related with endoscopic findings of esophagitis and typical symptoms of GERD. Journal of Gastrointestinal and Liver Diseases. 2021;30(1):25-9.
85. Pardak P, Filip R, Woliński J, Krzaczek M. Associations of obstructive sleep apnea, obestatin, leptin, and ghrelin with gastroesophageal reflux. Journal of Clinical Medicine. 2021 Nov 7;10(21):5195.
86. Romash I, Mischuk V, Romash I, Krasilych I, Romash N, Vus V, Kolinko Y. Manifestations of excessive daytime sleepiness and ghrelin level in case of gastroesophageal reflux disease in patients with undifferentiated connective tissue disease. Wiadomości Lekarskie. 2022;2(75):344-50.
87. Wong MW, Rogers BD, Liu MX, Lei WY, Liu TT, Yi CH, Hung JS, Liang SW, Tseng CW, Wang JH, Wu PA. Application of artificial intelligence in measuring novel pH-impedance metrics for optimal

diagnosis of GERD. Diagnostics. 2023 Mar 3;13(5):960.

88. Ge Z, Wang B, Chang J, Yu Z, Zhou Z, Zhang J, Duan Z. Using deep learning and explainable artificial intelligence to assess the severity of gastroesophageal reflux disease according to the Los Angeles Classification System. Scandinavian Journal of Gastroenterology. 2023 Jun 3;58(6):596-604.
89. Visaggi P, De Bortoli N, Barberio B, Savarino V, Oleas R, Rosi EM, Marchi S, Ribolsi M, Savarino E. Artificial intelligence in the diagnosis of upper gastrointestinal diseases. Journal of Clinical Gastroenterology. 2022 Jan 1;56(1):23-35.
90. Alhithlool AW, Almutlaq AS, Almulla SA, Alhamdan AB, Alotaibi ZB, AlHithlool AW, Kamal AH, Daoud MY, Zakaria OM. How do medical students perceive the role of artificial intelligence in management of gastroesophageal reflux disease?. Medical Teacher. 2025 Jun 3;47(6):1022-8.
91. Maity R, Sankari VR, Salvador AL. Explainable AI based automated segmentation and multi-stage classification of gastroesophageal reflux using machine learning techniques. Biomedical Physics & Engineering Express. 2024 Jun 28;10(4):045058.
92. Manning MA, Shafa S, Mehrotra AK, Grenier RE, Levy AD. Role of multimodality imaging in gastroesophageal reflux disease and its complications, with clinical and pathologic correlation. Radiographics. 2020 Jan;40(1):44-71.
93. East JE, Vleugels JL, Roelandt P, Bhandari P, Bisschops R, Dekker E, Hassan C, Horgan G, Kiesslich R, Longcroft-Wheaton G, Wilson A. Advanced endoscopic imaging: European Society of Gastrointestinal Endoscopy (ESGE) technology review. Endoscopy. 2016 Nov;48(11):1029-45.
94. Simadibrata DM, Lesmana E, Fass R. Role of endoscopy in gastroesophageal reflux disease. Clinical endoscopy. 2023 Nov 1;56(6):681-92.
95. Zhang S, Joseph AA, Gross L, Ghadimi M, Frahm J, Beham AW. Diagnosis of gastroesophageal reflux disease using real-time magnetic resonance imaging. Scientific reports. 2015 Jul 15;5(1):12112.
96. Reding-Bernal A, Sánchez-Pedraza V, Moreno-Macías H, Sobrino-Cossio S, Tejero-Barrera ME, Burguete-García AI, León-Hernández M, Serratos-Canales MF, Duggirala R, López-Alvarenga JC. Heritability and genetic correlation between GERD symptoms severity, metabolic syndrome, and inflammation markers in families living in Mexico City. PloS one. 2017 Jun 5;12(6):e0178815.
97. Gong T, Kuja-Halkola R, Harder A, Lundholm C, Smew AI, Lehto K, Andreasson A, Lu Y, Talley NJ, Pasman JA, Almqvist C. Shared genetic architecture between gastro-esophageal reflux disease, asthma, and allergic diseases. Communications Biology. 2024 Sep 2;7(1):1077.
98. Kia L, Hirano I. Distinguishing GERD from eosinophilic oesophagitis: concepts

and controversies. Nature Reviews Gastroenterology & Hepatology. 2015 Jul;12(7):379-86.

99. Shoda T, Wen T, Caldwell JM, Collins MH, Besse JA, Osswald GA, Abonia JP, Arva NC, Atkins D, Capocelli KE, Dellon ES. Molecular, endoscopic, histologic, and circulating biomarker-based diagnosis of eosinophilic gastritis: Multi-site study. Journal of Allergy and Clinical Immunology. 2020 Jan 1;145(1):255-69.
100. Rothenberg ME. Molecular, genetic, and cellular bases for treating eosinophilic esophagitis. Gastroenterology. 2015 May 1;148(6):1143-57.
101. Kahrilas P, Yadlapati R, Roman S. Emerging dilemmas in the diagnosis and management of gastroesophageal reflux disease. F1000Research. 2017 Sep 25;6:1748.
102. Katz PO, Dunbar KB, Schnoll-Sussman FH, Greer KB, Yadlapati R, Spechler SJ. ACG clinical guideline for the diagnosis and management of gastroesophageal reflux disease. Official journal of the American College of Gastroenterology| ACG. 2022 Jan 1;117(1):27-56.
103. Kahrilas PJ. Cigarette smoking and gastroesophageal reflux disease. Digestive Diseases. 1992 Nov 4;10(2):61-71.
104. Pan J, Cen L, Chen W, Yu C, Li Y, Shen Z. Alcohol consumption and the risk of gastroesophageal reflux disease: a systematic review and meta-analysis. Alcohol and Alcoholism. 2019 Jan 1;54(1):62-9.
105. Sfara A, Dumitrascu DL. The management of hiatal hernia: an update on diagnosis and treatment. Medicine and pharmacy reports. 2019 Oct 25;92(4):321.
106. Manzo CA, Asti E, Bonavina L. Hiatal hernia, lower esophageal sphincter and their combined effect on the natural history of gastroesophageal reflux disease: implications for surgical therapy. Annals of Laparoscopic and Endoscopic Surgery. 2021 Oct 20;6.
107. VĂRȘA R, CIOBANU A, CIMPOCARAPTIS B, GICĂ C, BOTEZATU R, GICĂ N, PANAITESCU A. Gastroesophageal reflux disease in pregnancy. Romanian JouRnal of medical Practice. 2021;16(3):78.