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Review on methods for early detection of gastric cancer

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Abstract

Gastric cancer is a significant global health concern, contributing to high mortality rates worldwide. This article offers an in-depth overview of various detection methods for gastric cancer, covering aspects such as epidemiology, risk factors, pathogenesis, clinical presentation, diagnostic approaches, treatment modalities, and future research directions. Six distinct methodologies are examined: Pepsinogen, ABC, Spectroscopy, Endoscopic, Next Generation Sequencing (NGS), and Ultra-Performance Liquid Chromatography (UPLC). Each method presents unique advantages and limitations, from non-invasive techniques suitable for large-scale screenings to advanced, high-accuracy technologies. Pepsinogen and Spectroscopy methods are highlighted for their cost-effectiveness and suitability for initial screenings. The ABC method enhances sensitivity and specificity through combined evaluation but necessitates supplementary tests for confirmation. Despite being invasive and costly, the Endoscopic method remains the gold standard due to its direct visualization and biopsy capabilities. NGS and UPLC demonstrate promising advancements in early detection and non-invasive screening, with NGS offering high sensitivity and specificity through biomarkers like circulating tumour DNA (ctDNA) and microRNAs (miRNAs). However, these advanced methods require extensive validation and present ethical and privacy concerns. The article underscores the importance of economic methods for initial screenings but highlights that integrating advanced methodologies and optimizing their use based on patient risk profiles can significantly improve early detection and treatment of gastric cancer. Endoscopic and NGS methods are identified as the most frequently used and efficient for gastric cancer detection, with the application of NGS expected to grow as technology advances.

Keywords: Diagnostic Approaches; Pepsinogen; Endoscopic; Next Generation Sequencing; Ultra-Performance Liquid Chromatography

1. Introduction

Gastric cancer remains a critical global health issue, presenting significant challenges in diagnosis, treatment, and prevention. As one of the leading causes of cancer-related mortality worldwide, its impact on public health is profound [1]. This article seeks to provide a thorough overview of the methods for detecting gastric cancer, encompassing its epidemiology, risk factors, pathogenesis, clinical presentation, diagnostic approaches, treatment modalities, and future research and management strategies [2]. By exploring these elements, the goal is to enhance understanding of gastric cancer and improve patient outcomes through early detection, effective treatment strategies, and advancements in precision medicine [3].

Gastric cancer incidence and mortality rates vary significantly across the globe, with higher prevalence observed in East Asia, Eastern Europe, and parts of South America [4]. Factors such as diet, genetics, and infection with Helicobacter pylori contribute to these geographic disparities [5]. Identifying high-risk populations through epidemiological studies is crucial for targeted screening and early detection efforts [6]. Several risk factors are associated with the development

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of gastric cancer, including Helicobacter pylori infection, dietary habits, genetic predisposition, lifestyle choices, and certain medical conditions [7]. The pathogenesis of gastric cancer involves a multistep process, progressing from chronic gastritis to invasive carcinoma, driven by molecular changes in oncogenes, tumor suppressor genes, and signaling pathways. Clinically, gastric cancer often presents with non-specific symptoms, making early detection challenging and underscoring the need for effective screening methods [8].

Various diagnostic approaches, such as endoscopy, imaging techniques, biomarkers, and histopathology, are utilized to detect gastric cancer [9]. Treatment depends on the stage at diagnosis and includes surgery, chemotherapy, radiotherapy, and emerging therapies like targeted therapy and immunotherapy [10]. Future advancements in precision medicine, genomics, and artificial intelligence hold promise for improving gastric cancer management [11]. Key research areas include developing non-invasive biomarkers for early detection, personalizing treatment based on genetic and molecular tumor profiling, exploring novel immunotherapeutic agents, and enhancing minimally invasive surgical techniques [12]. By addressing these aspects, the article aims to enhance the understanding of gastric cancer and facilitate better patient outcomes through early detection, effective treatments, and advancements in precision medicine.

Despite the progress in understanding gastric cancer, challenges remain in improving early detection rates and patient survival. Current diagnostic methods vary in accuracy, invasiveness, and cost-effectiveness, with endoscopy being the gold standard due to its ability to directly visualize and biopsy suspicious lesions. However, its invasiveness and high cost limit its use in widespread screening programs. Non-invasive methods, such as blood-based biomarkers like pepsinogen, offer potential for large-scale screenings but require further validation to improve sensitivity and specificity [12].

The introduction of advanced technologies, such as next-generation sequencing (NGS) and ultra-performance liquid chromatography (UPLC), has opened new avenues for gastric cancer detection [13]. NGS allows for the identification of genetic mutations and molecular alterations in circulating tumor DNA (ctDNA) and microRNAs (miRNAs), offering high sensitivity and specificity [14]. UPLC provides a powerful tool for metabolomic profiling, aiding in the identification of unique biomarkers associated with gastric cancer. These technologies, while promising, necessitate extensive research and validation to overcome ethical, privacy, and logistical challenges before they can be integrated into routine clinical practice [15].

2. Pepsinogen method

2.1. Principle

ELISA operates on the principle that specific antibodies bind to target antigens, allowing for the detection and quantification of these antigens. To enhance the sensitivity and precision of the assay, it is essential to coat the plate with high-affinity antibodies [16].

2.2. Test

Pepsinogen detection is proposed as a non-invasive method to assess the gastric mucosa, primarily identifying atrophy rather than directly detecting gastric cancer (GC). Pepsinogen I (PgI) and Pepsinogen II (PgII) are crucial enzymes measured, each reflecting different regions of the stomach. Inflammation, often due to H. pylori infection, can raise the levels of both enzymes, complicating their interpretation. A lower PgI/PgII ratio indicates gastric atrophy, though cut-off values vary depending on the detection method. Meta-analyses reveal varying sensitivities (59% to 77.3%) and specificities (73% to 73.2%) for GC detection using pepsinogen levels, highlighting the need for standardized protocols.

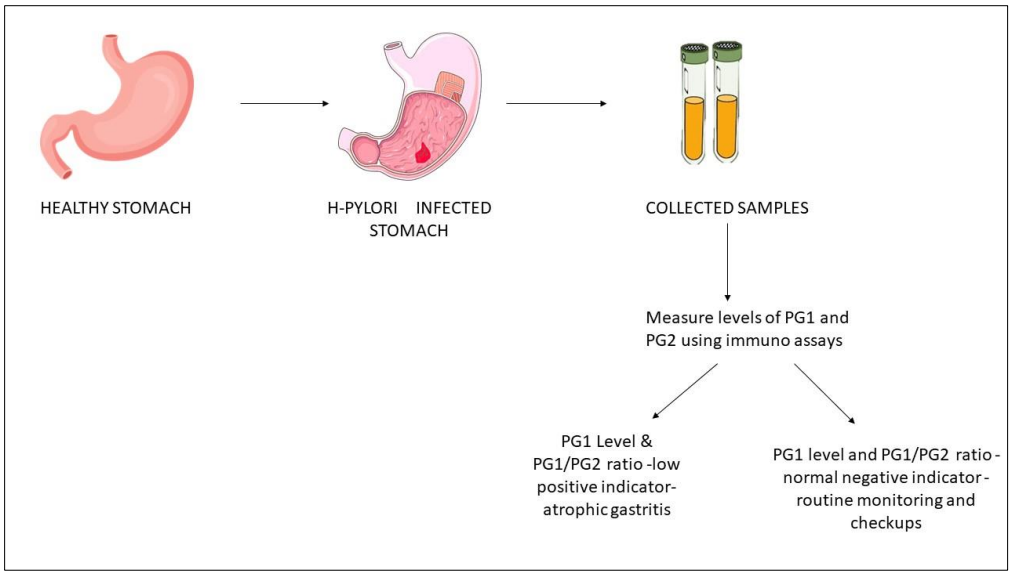

Figure 1 Gastric cancer detection by Pepsinogen method

2.2.1. Advantages

- Non-invasive: Requires only a blood sample.
- Screening Tool: Effective for detecting atrophic gastritis and gastric cancer.
- Early Detection: Identifies gastric mucosal atrophy early.
- Cost-effective: Less expensive than endoscopy.
- Convenience: Easy sample collection and lab processing.
- Risk Stratification: Identifies high-risk individuals for targeted surveillance.

2.2.2. Disadvantages

- False Results: Risk of false positives/negatives.
- Limited Scope: Primarily detects atrophic gastritis and related conditions.
- Variable Accuracy: Sensitivity and specificity can vary.
- Geographic Variability: Effectiveness varies by population.
- Supplementary Testing Needed: Positive results often need confirmation.
- H. pylori Influence: Infection can affect pepsinogen levels.

2.3. ABC method

The combined evaluation of pepsinogen levels and the presence of H. pylori for population-based testing, as suggested by Miki and colleagues in Japan, offers a refined approach [17]. The traditional method involves serological detection of antibodies to H. pylori, but this has limitations, such as false positives in patients with past infections and potential misclassification of patients who have undergone successful eradication therapy [18]. To address these issues, it is recommended to use additional methods, like the 13C-urea breath test, to confirm positive serology cases before employing the ABC method for clinical decision-making or treatment. This approach ensures more accurate assessments and reduces the risk of misclassifying patients into higher-risk groups [19].

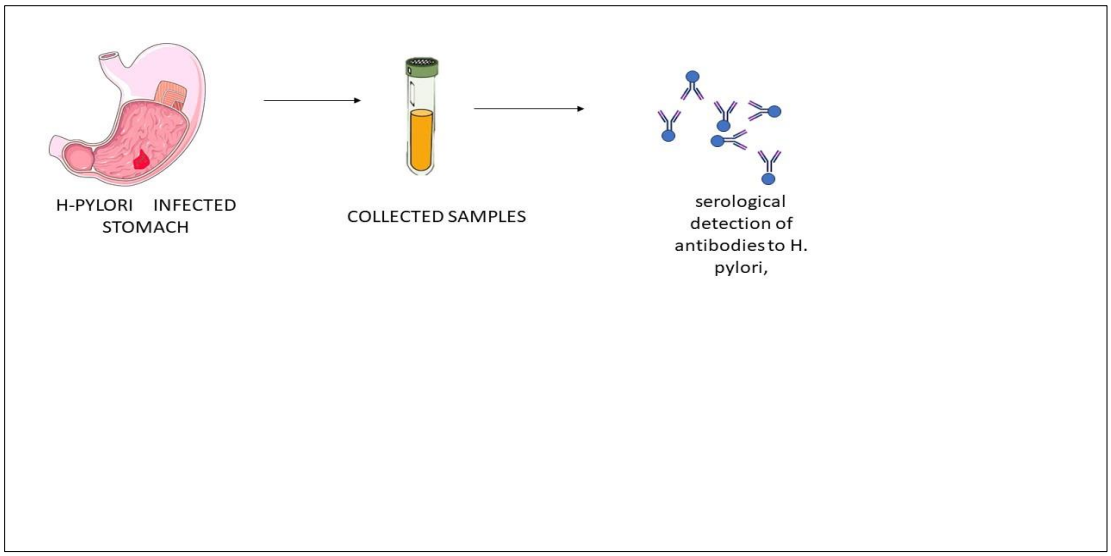

Figure 2 Gastric cancer detection by ABC method

2.3.1. Advantages

- Diverse options available, from traditional markers to advanced techniques.
- Targeted approaches for pre-cancerous lesions enable early intervention.
- Improved sensitivity and specificity, especially in newer methods.
- Non-invasive or minimally invasive methods are patient-friendly.
- Potential for use in large-scale screening programs.

2.3.2. Disadvantages

- Need for further validation and standardization.
- Cost and accessibility challenges, especially with advanced techniques.
- Complexity in interpretation and analysis for some methods.
- Risk of false positives, leading to unnecessary anxiety and testing.
- Influence of external factors like diet on specificity of certain methods.

3. Spectroscopy method

3.1. Principle

The Architect plus ci4000 is an automated clinical chemistry analyzer capable of processing multiple samples simultaneously [20]. It employs various analytical techniques, including photometry, turbidimetry, and immunoassays, to measure analytes in biological samples. Reagents interact with the target substances in the sample, generating signals such as changes in absorbance or fluorescence. The instrument uses known standards for calibration, performs quality control checks, and automatically analyzes data to deliver accurate test results for clinical interpretation [21].

3.2. Test

In this study, PGI and PGII levels in serum samples were measured using the Architect plus ci4000 analyzer [22]. Blood samples were collected from fasting patients using Vacuette tubes containing a clot activator [23]. After centrifugation, the serum samples were analyzed optically through latex agglutination, measuring changes in turbidity [24]. Calibration curves, constructed from known standards, were used to quantify PGI and PGII levels [25]. Specific PGI levels and ratios defined positive results. Patients with positive outcomes underwent endoscopy, and all participants were monitored for two years. Endoscopies were performed with standard equipment and anesthesia.

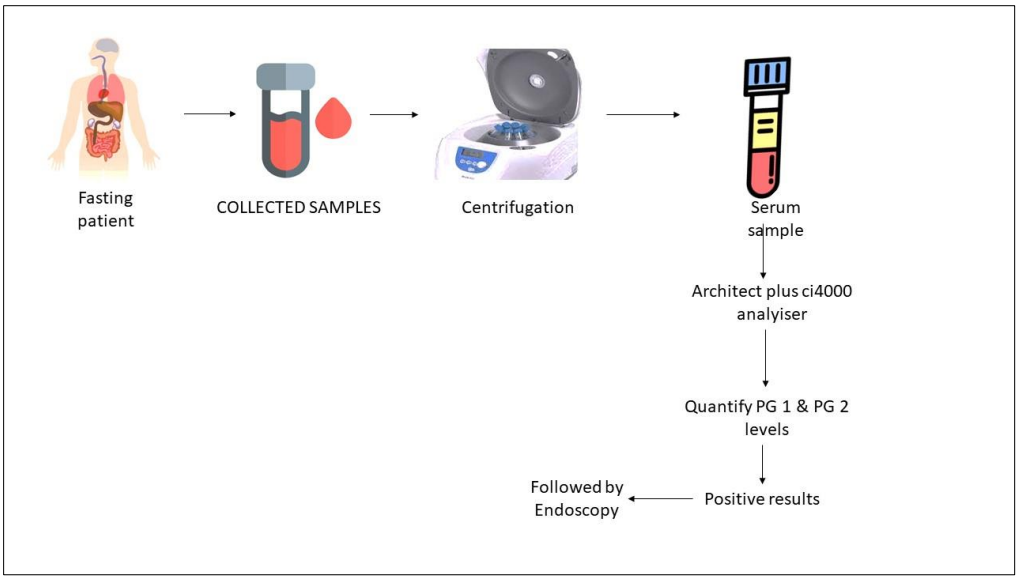

Figure 3 Gastric cancer detection by Spectroscopic method

3.2.1. Advantages

- Early Detection: Pepsinogen test aids early gastric cancer detection.
- Reliability: Shows good accuracy and predictive values.
- Non-invasive: Non-invasive nature makes it suitable for screening high-risk populations.
- Cost-Effective: Offers cost-effective screening compared to invasive methods.
- Routine Use: Can be integrated into routine lab assessments for high-risk patients.
- Statistical Analysis: Study uses robust statistical methods for evaluation.

3.2.2. Disadvantages

- Moderate Sensitivity: May miss some cases of gastric cancer (78.12% sensitivity).
- Specificity Concerns: Some false positives may occur (90.10% specificity).
- Limited Diagnostic Power: Moderate diagnostic power (AUC: 0.700) requires confirmation with other tests.
- Biopsy Confirmation: Relies on invasive biopsy for confirmation.
- Population Specificity: Effectiveness may vary in different populations.
- Long-Term Follow-up Needed: Short follow-up period (36 months) may limit long-term assessment.
- Lack of Specific Rates: No detailed data on false negatives and false positives.
- ENDOSCOPIC METHOD

3.2.3. Principle

The endoscope utilizes the principle of total internal reflection through optical Fibers to examine the interior of hollow organs or body cavities [26]. It consists of an optical system that delivers illumination to the area being observed. The NBI technique (Narrow Band Imaging) enhances the capabilities of video endoscopy by combining magnification and image processing [27]. It works by modifying the spectral characteristics of the light source, narrowing the bandwidth of the optical filter to improve visualization.

This randomized, open-label trial was conducted across 13 hospitals in Japan. High-risk gastric cancer patients were recruited and randomly assigned to either the WLI (White Light Imaging) group or the 2G-NBI (Second-Generation Narrow Band Imaging) group using a centralized randomization process [28]. Both groups utilized the EVIS LUCERA ELITE endoscopic system equipped with NBI capabilities [29]. Endoscopic criteria for diagnosing early gastric cancer (EGC) were established, and a systematic examination protocol was followed, which included non-magnifying observation and biopsy of target lesions. Pathological evaluation was conducted based on the revised Vienna classification.

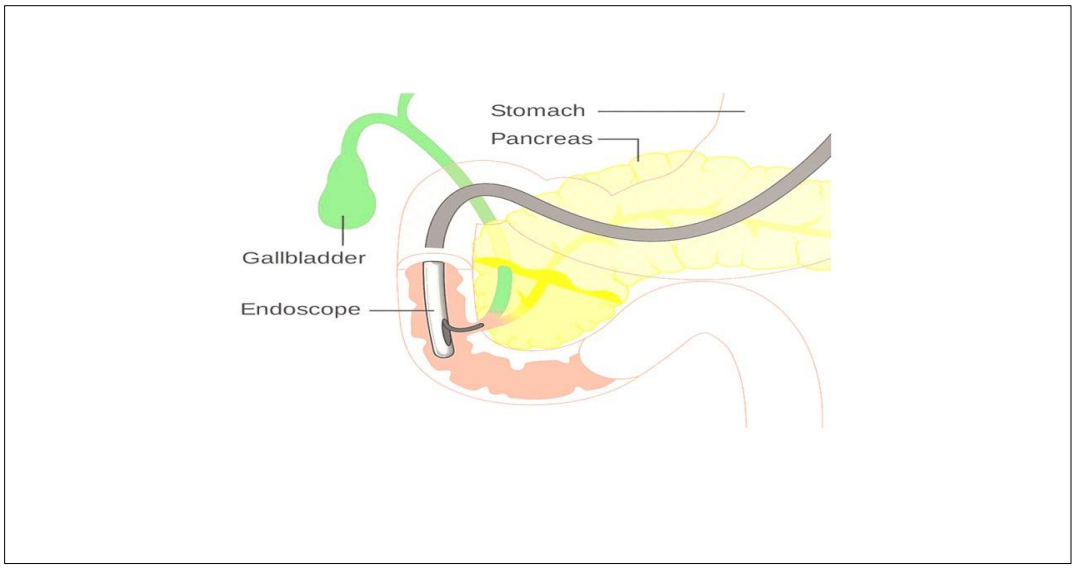

Figure 4 Gastric cancer detection by Endoscopic method

3.2.4. Advantages

- Randomised Controlled Trial: Provides rigorous scientific evidence by minimizing bias and allowing for a comparison between different imaging methods.
- Large Sample Size: Increases the reliability and generalizability of the findings.
- Standardised Protocol: Ensures consistency in the evaluation and diagnosis process.
- Disadvantages:
- Limited Detection Rate Improvement: 2G-NBI did not significantly increase the detection rate of early gastric cancer compared to conventional methods.
- Post Hoc Analysis: May introduce bias or limitations in interpreting results.
- Sensitivity Concerns: Highlights the need for improved sensitivity in primary endoscopy for early cancer detection.
- Need for Further Evaluation: The impact of the slightly better PPV of 2G-NBI requires additional assessment to understand its clinical significance fully.

4. Next generation sequencing method

Recent advancements in next-generation sequencing (NGS) have significantly enhanced our understanding of gastric cancer, leading to the identification of novel biomarkers for early diagnos

is [30]. Tumour cells release nucleic acids such as DNA and RNA into the bloodstream, allowing for non-invasive detection methods utilizing circulating tumour DNA (ctDNA), microRNAs (miRNAs), long noncoding RNAs (lncRNA), and circular RNA (circRNA). These biomarkers demonstrate superior sensitivity and specificity compared to traditional markers like CEA and CA 19-9.

Pilot studies have shown that ctDNA can differentiate gastric cancer patients from healthy individuals with high sensitivity and specificity [31]. Early-stage patients exhibit lower ctDNA levels, highlighting its potential for early diagnosis [32]. Specific miRNAs, such as miRNA-21 and miR-376c, are upregulated in early-stage patients, with positive predictive values reaching up to 90%. Additionally, lncRNA and circRNA are associated with tumour growth and metastasis, and their serum levels can detect early cancer and assess disease progression [33].

Larger studies are necessary to validate these biomarkers. In the meantime, advancements in AI and deep learning in endoscopy, exemplified by systems like ENDOANGEL-LD and AI-Scope, are showing promise in improving detection rates and estimating lesion invasion depth, providing a framework for more effective early cancer detection.

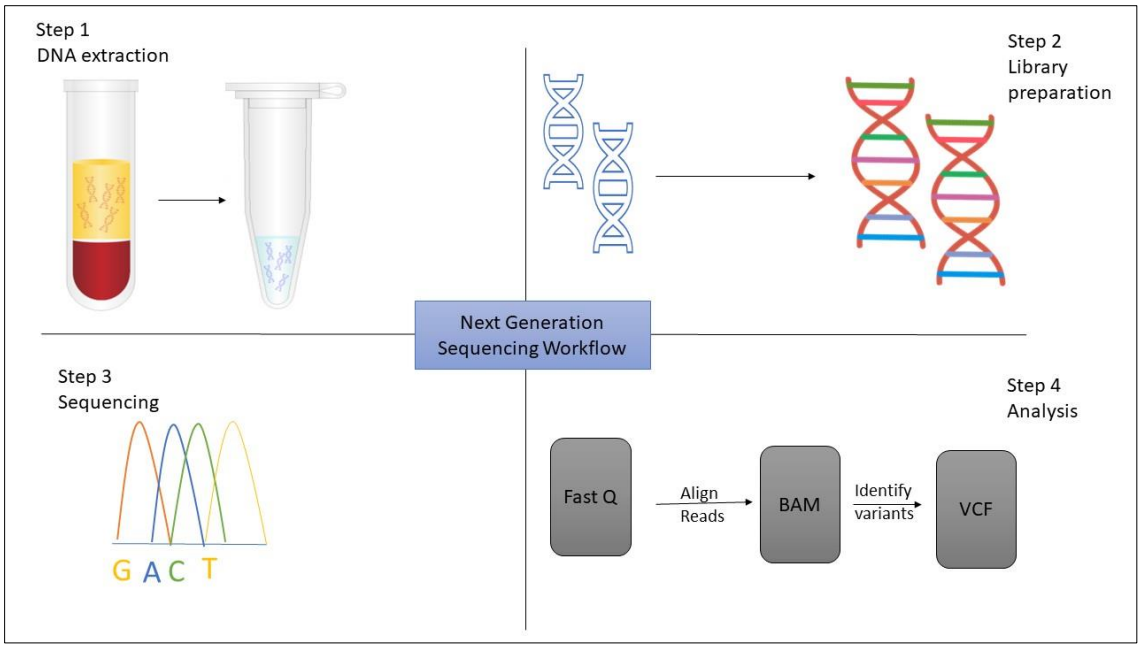

Figure 5 Gastric cancer detection by Next Generation Sequencing method

4.1.1. Advantages

- Enhanced Sensitivity and Specificity: Next-generation sequencing (NGS) biomarkers offer better accuracy compared to traditional markers.
- Non-invasive Detection: They can be detected from blood samples, avoiding invasive procedures.
- Early Detection and Monitoring: NGS biomarkers help detect early-stage cancer and monitor disease progression.
- Potential for Population Screening: Promising for cost-effective screening strategies in low-incidence areas.
- AI Advancements: AI in endoscopy improves detection rates, aiding early diagnosis.

4.1.2. Disadvantages

- Need for Validation: Larger studies needed to confirm reliability.
- Cost and Accessibility: Implementation may be costly and resource-intensive.
- Technical Expertise Required: Interpretation needs specialized skills.
- Ethical and Privacy Issues: Concerns around data privacy and algorithm biases.
- AI Model Limitations: Continuous refinement needed for accuracy and reliability.

4.2. UPLC method

4.2.1. Principle

UPLC-MS operates on the same principle as traditional LC-MS, integrating liquid chromatography for component separation with mass spectrometry for detection. However, UPLC-MS employs chromatography columns with smaller particles, allowing it to handle higher pressures [34].

4.2.2. Test

In this study, researchers investigated amino-containing compounds, which play crucial roles in various biological processes and are involved in metabolic pathways [35]. Their goal was to pinpoint specific biomarkers for diagnosing gastric cancer before surgery [36]. By using a novel derivatization reagent (3-DP-NHS) in conjunction with LC-MS, they analysed amino-containing metabolites in serum samples from both gastric cancer patients and healthy controls. This approach improved separation and sensitivity, requiring only 5 μL of serum to detect 202 metabolites [37]. Statistical analysis indicated significant changes in amino acid metabolism among cancer patients. UHPLC-MS/MS quantification revealed increased levels of tryptamine and decreased levels of arginine and tryptophan, with a higher tryptamine/tryptophan ratio suggesting its potential as a diagnostic biomarker [38]. The findings propose that serum amino acid biomarkers could support gastric cancer diagnosis and open up new treatment possibilities [39].

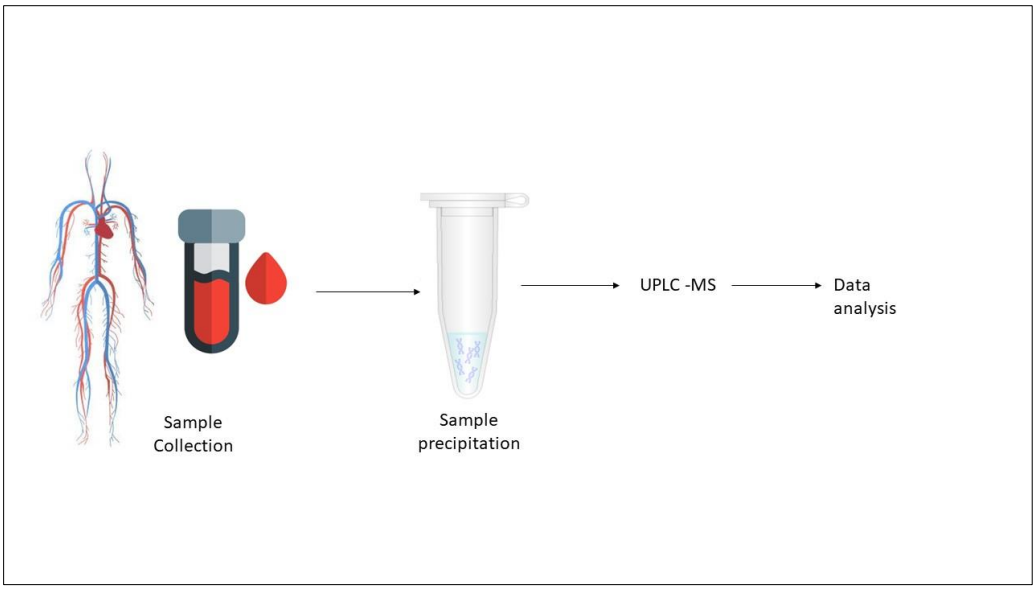

Figure 6 Gastric cancer detection by UPLC method

4.2.3. Advantages

- Comprehensive Profiling: Detects various amino-containing metabolites, offering a holistic view of metabolic changes.
- Enhanced Sensitivity: Improves detection of subtle metabolic alterations related to gastric cancer.
- Minimal Sample Requirement: Analyses with just 5 µL of serum, suitable for limited samples.
- Robust Performance: Shows good linearity, recovery, and precision, ensuring reliable results.
- Biomarker Identification: Pinpoints potential biomarkers like tryptamine/tryptophan ratio for gastric cancer diagnosis.

4.2.4. Disadvantages

- Technical Complexity: Requires specialized equipment and expertise.
- Cost: Involves expenses for reagents, equipment, and maintenance.
- Validation Needs: Requires further validation and standardization.
- Limited Clinical Application: Biomarker specificity and sensitivity may vary, needing more validation for routine clinical use.

5. Conclusion

In conclusion, various methods for gastric cancer detection offer distinct advantages and face specific challenges. The Pepsinogen and ABC methods are cost-effective and suitable for large-scale screenings, but they suffer from variability and require supplementary tests for confirmation. Spectroscopy provides reliable, non-invasive detection but necessitates biopsy confirmation for definitive diagnosis. The Endoscopic method remains the most frequently used and efficient technique due to its high accuracy and direct visualization capabilities, though it is invasive and costly. Next Generation Sequencing (NGS) shows promise for early detection with high sensitivity and specificity, but it requires further validation and raises ethical and privacy concerns. UPLC offers fast and sensitive detection with minimal sample requirements, but it demands specialized expertise and clinical validation. While economic methods like Pepsinogen and Spectroscopy are valuable for initial screening, advanced methods such as Endoscopy, NGS, and UPLC offer higher accuracy and potential for early detection. The future of gastric cancer detection lies in integrating these methodologies, optimizing their application based on patient risk profiles, and advancing research to enhance their clinical utility.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors do not have any conflict of interest.

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