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NEW BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF THERAPEUTIC APPROACHES TO GASTRIC CANCER: A LITERATURE REVIEW

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АННОТАЦИЯ

Relevance: *Gastric cancer is a heterogeneous disease whose development is associated with both genetic and acquired somatic mutations. Identifying optimal diagnostic markers for gastric cancer with high sensitivity and specificity can significantly improve patient survival rates and contribute to the advancement of personalized medicine. By integrating clinical data and comprehensive genomic analysis, the identification of biomarkers can dramatically enhance the accuracy of diagnosis, dis-ease progression prediction, recurrence risk assessment, and treatment response. This work discusses promising biological markers that may be used to diagnose gastric cancer early and predict the effec-tiveness of various treatment methods, potentially revolutionizing patient care.*

The study aimed to *analyze current scientific literature to identify new and recently developed bi-omarkers for diagnostic and prognostic value concerning malignant stomach tumors.*

Methods: *In this review, we comprehensively searched electronic medical literature in the PubMed and Google Scholar databases. The search utilized keywords: "biomarker," "gastric cancer," "early detection," "diagnosis," and "prognosis." We included full-text publications in English and Russian, which are available for open access. We focused on the role of biomarkers in early diagnosis and prognosis of gastric cancer, published in the last ten years. We excluded case reports, correspond-ence, letters, and studies not conducted on humans from the review, as these did not meet our criteria for inclusion.*

Results: *The analysis revealed an insufficient accuracy of existing biomarkers for gastric cancer di-agnosis and prognosis. Within the modern approach to disease classification framework, a new mo-lecular type was proposed: tumors infected with the Epstein-Barr virus, tumors with microsatellite instability, genomically stable tumors, and chromosomally unstable tumors.*

Conclusion: *Current research on gastric cancer focuses on identifying and validating new non-invasive biomarkers. Further studies are necessary to enhance sensitivity and broaden the application of these biomarkers for early diagnosis and predicting treatment efficacy.*

Keywords: *Biomarker, gastric cancer, early detection, diagnosis, prognosis.*

Introduction: Despite advances in medicine, food preservation techniques, and Helicobacter pylori treatment, gastric cancer remains the fifth most common cancer and the fourth leading cause of cancer deaths worldwide as of 2020 [1]. The prevalence of gastric cancer shows significant geographic variations, with men being twice as likely to be affected as women. According to recent data, the highest incidence rates are observed in East Asia and Central and Eastern Europe, where 87% of all new cases worldwide are concentrated. At the same time, Africa and North America have a significantly lower prevalence of gastric cancer [2].

One approach to reducing the burden of gastric cancer is early diagnosis. Although upper gastrointestinal endoscopy is recognized as the "gold standard" for screening, early tumor detection requires methods with higher accuracy, sensitivity, and specificity. Since many patients are asymptomatic at the initial stages of the disease and there are currently no effective screening methods for the early detection of gastric cancer, the diagnosis is often made at a late stage, which leads to a poor prognosis and low survival [3].

A more accessible and cost-effective method shall be developed to implement a large-scale screening program for gastric cancer in a healthy population.

In recent decades, serological tumor markers have traditionally been used to diagnose cancer in specific patient groups, as well as to monitor cancer progression.

Oncological biomarkers, also known as tumor markers, are specific molecules whose presence indicates the presence and development of malignant neoplasms. These biomarkers play a crucial role in cancer diagnostics, allowing physicians to detect the disease at an early stage and in planning personalized therapy, which increases the effectiveness of treatment [4]. In short, we are talking about objectively measurable characteristics used as indicators of normal body functioning, pathological processes, or response to therapy. Their use is steadily expanding due to genetic analysis and molecular therapy progress.

There are no biomarkers with sufficient accuracy and specificity for diagnosing gastric cancer in clinical practice. Such markers are relevant at all stages of the disease to optimize its course. This paper summarizes current achievements and approaches to developing gastric cancer biomarkers that can potentially be used for early diagnosis, accurate prediction of treatment effectiveness, and molecular classification of the tumor.

The study aimed to analyze current scientific literature to identify new and recently developed biomarkers for diagnostic and prognostic value concerning malignant stomach tumors.

Materials and Methods: In this review, we comprehensively searched electronic medical literature in the PubMed and Google Scholar databases. The search utilized keywords: "biomarker," "gastric cancer," "early detection," "diagnosis," and "prognosis." We included full-text publications in English and Russian, which are available for open access. We focused on the role of biomarkers in early diagnosis and prognosis of gastric cancer, published in the last ten years. We excluded case reports, correspondence, letters, and studies not conducted on humans from the review, as these did not meet our criteria for inclusion.

Results: Modern medicine increasingly relies on non-invasive biomarkers to diagnose malignant neoplasms promptly and monitor their progression. In clinical practice, tumor markers are commonly employed for the early detection of gastric cancer. The most widely used markers include carcinoembryonic antigen (CEA), carbohydrate antigens such as CA19-9, CA72-4, CA125, CA24-2, and CA50, along with pepsinogen and α-fetoprotein (AFP) [5]. However, these serological biomarkers often exhibit low specificity and sensitivity, and none serve as a specific or personalized marker for gastric cancer diagnosis [6]. This issue will be revisited later.

T. Li highlights the potential of 'liquid biopsy' as an innovative diagnostic approach for gastric cancer. This method involves detecting circulating tumor cells, tumor DNA or RNA fragments, exosomes, and atypical platelets in biological fluids like blood and urine, enabling early disease detection [7]. Despite its promise, the American Society of Clinical Oncology (ASCO), in a recent review, concluded that current evidence is insufficient to establish its clinical relevance and efficacy for gastric cancer diagnosis [8]. Similarly, guidelines from the European Society for Medical Oncology (ESMO) and the US National Comprehensive Cancer Network (NCCN) recommend liquid biopsy only when tumor tissue sampling is unfeasible or the available material is inadequate for analysis [9].

Advancements in high-throughput technologies have significantly improved the understanding of the molecular mechanisms underlying gastric adenocarcinoma. This progress has resulted in a molecular classification system that distinguishes four subtypes based on distinct genomic characteristics.

The Cancer Genome Atlas (TCGA) project has refined this classification, stratifying gastric cancer based on genetic and epigenetic alterations. This molecular stratification enhances understanding of the disease progression mechanisms and is a foundation for developing targeted therapies [10].

– **Epstein-Barr virus-infected tumors:** These tumors are characterized by the presence of a viral agent, the Epstein-Barr virus, in the tumor cells, which may affect the immune response and disease progression.

– **Tumors with microsatellite instability (MSI):** These tumors show a high frequency of mutations in short repetitive DNA sequences called microsatellites. Microsatellite instability is associated with certain cancers and may serve as a marker for immunotherapy.

– **Genomically stable (GS) tumors:** This group includes tumors with no microsatellite instability (MSI) or chromosomal instability (CIN). The diverse molecular characteristics of these tumors make their classification particularly challenging.

– **Chromosomally unstable (CIN)** tumors are characterized by instability in the number and structure of chromosomes, resulting in aneuploidy and other genetic abnormalities. CIN may be associated with an aggressive disease course and poor survival rates.

The Asian Cancer Research Group (ACRG) classifies gastric cancer based on MSI (microsatellite instability) and MSS (microsatellite stable) markers. Tumors exhibiting microsatellite mutations are categorized as MSI, while MSS tumors are further divided into three subtypes:

* MSS/EMT: Tumours demonstrating epithelial-mesenchymal transition.

* MSS/TP53+: Tumours with an active TP53 gene mutation.

* MSS/TP53-: Tumours with absence of TP53 gene activity [11, 12].

This new classification has provided the foundation for several clinical trials to identify effective therapeutic strategies that combine immune checkpoint inhibitors with molecularly targeted therapies. Early results from these studies are highly promising [13]. Nevertheless, early disease detection remains critical, underscoring the importance of ongoing research to discover novel biological markers or genetic signatures associated with the pathology.

According to a systematic review by H.Shimada, although some circulating tumor antigens have long been used in routine clinical practice, their efficacy in the early diagnosis of gastric cancer remains questionable due to the high frequency of false-positive and false-negative results [14, 15]. CEA, CA19-9, and CA72-4 are widely used as

standard markers in diagnostics, disease prognosis determination, treatment efficacy monitoring, and gastric cancer recurrence detection [16]. In cancer diagnostics, both CEA and CA 19-9 levels can serve as valuable prognostic markers to assess the extent of the tumor process and the presence of distant metastases [17]. Despite particular possibilities, these methods do not have sufficient accuracy and selectivity for screening programs for the early detection of gastric cancer [18].

According to T. Matsuoka and M. Yashiro, the CA72-4 indicator has greater sensitivity and accuracy than CEA. However, the number of studies evaluating its effectiveness in screening tests for gastric cancer is limited [4].

F. Feng et al. have found that tumor markers such as AFP and CA125 have low sensitivity in the early diagnosis of gastric cancer [19]. In addition, CA50 has limited diagnostic value [20].

In their search for ways to enhance the accuracy of gastric cancer diagnosis through the combined analysis of several serological tumor markers, S. Ning et al. demonstrated that simultaneous detection of CEA, CA19-9, and CA72-4 along with thymidine kinase 1 (TK1) –a biomarker of cell proliferation – markedly improves the sensitivity and specificity of gastric cancer detection compared to the utilization of individual biomarkers [21].

A recent study by Li J. proposed a diagnostic model for early detection of gastric cancer. The model is based on the levels of CEA, CA72-4, and three inflammatory cytokines: tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-8. In a validation study, the model demonstrated high performance in differentiating between healthy subjects, individuals with atypical gastric mucosal hyperplasia, patients with early-stage GC, and patients with advanced-stage GC [22].

In a study of gastric cancer in 2015, M. Kanda and Y. Kodera discovered an elevated expression of several genes, including xpg, interferon-induced transmembrane protein 1 (iftim1), matrix metalloproteinase-9 (mmp-9), pituitary tumor transforming gene-1 (pttg1), and stc1. These genes show potential as biomarkers for early disease detection [23].

This review also emphasizes promising directions for searching gastric cancer biomarkers based on different molecular genetic characteristics (Table 1). These biomarkers have been classified depending on their roles in early disease diagnosis, recurrence prediction, and chemotherapy efficacy assessment.

Kazakhstani scientists have also studied DNA double-strand breaks with repair activity, such as γ-H2AX and 53BP1, as biomarkers in gastric cancer [46]. These markers have clinical significance and can be used as diagnostic tools in personalized medicine.

Gastric cancer biomarkers play an important role in personalized treatment, allowing for a more accurate therapy selection and prediction of outcomes. However, many of them are in the clinical trial stage. In the future, biomarkers may be integrated into clinical practice, helping doctors improve treatment outcomes and choose the most effective therapies while minimizing side effects.

Biomarker-based prognosis will help identify patients at high risk of recurrence and tailor individualized therapeutic efficacy, which is of great importance in determining survival and quality of life for patients with gastric cancer. A study by D. Wu et al. found increased serum levels of IFNGR1, TNFRSF19L, GHR, SLAMF8, FR-beta, and integrin alpha 5 proteins in patients with gastric cancer. This discovery indicates the prospect of using these proteins as novel biomarkers for early detection and prediction of the disease course of gastric cancer [47].

According to W. Hou et al., the level of CD44 protein expression can serve as an independent prognostic marker for gastric cancer. This protein correlates with immune infiltration in tumor tissue and shows increased activity in patients with this disease [48].

Prof X. Zhou et al. found that the presence of piR-1245 in gastric juice could serve as a promising biological marker for diagnosing and prognosis of gastric cancer [49].

A study by J. Ji et al. demonstrated increased expression of KK-LC-1 in gastric cancer patient tissues compared to normal tissues. In addition, a correlation between higher KK-LC-1 expression and more prolonged survival of gastric cancer patients was established. These results indicate the potential value of KK-LC-1 as a biomarker to predict favorable outcomes in patients with gastric cancer [50].

CircERBB2 concentrations in preoperative plasma samples can be considered a non-invasive prognostic biomarker for gastric cancer. In addition, monitoring postoperative circERBB2 plasma concentrations may help detect gastric cancer recurrence [51].

Recent studies in China have shown a strong correlation between high levels of COMMD10 gene expression and unfavorable prognosis for gastrointestinal cancer patients. The functional activity of COMMD10 is associated with the modification of N6-methylamino adenosine (m6A) mRNA and plays a vital role in gastric cancer's immune tumor infiltration processes [52].

The study by W. Gu et al. found a correlation between the level of ITGB1 gene expression and the activity of the Wnt/β-catenin signaling pathway in gastric cancer. Data analysis from TCGA-STAD/ACRG/GSE15459 cohorts showed a positive association between ITGB1 expression and factors inhibiting the immune response and a negative association with factors activating the immune response. Thus, ITGB1 affects the prognosis of patients with gastric cancer and plays a crucial role in suppressing the immune response [53].

Table 1 – Topical issues of molecular markers application in diagnostics, prognosis of the course, and response to therapy of gastric cancer (adapted from the article [4])

Biological marker	Change	Clinical goal	Detection method	Reference
Genes associated with metastasis				
Growth factors				
HER2 - Gene encoding a receptor associated with cell growth.	Overexpression	Diagnostic / prognostic	Tissue	[24]
FGFR – Fibroblast growth factor involved in cell proliferation and differentiation.				[25]
PI3K/Akt/mTOR (PIK3CA) - Gene encoding a subunit involved in a signal transduction pathway that promotes cell growth.				[26]
MET - Gene encoding a receptor associated with growth and metastasis.				[27]
VEGF (VEGF-2) - Vasoendothelial growth factor involved in angiogenesis.				[28]
VEGF-D) - Vasoendothelial growth factor involved in angiogenesis.				[29]
Cell cycle regulation				
TP53 - Gene encoding a protein involved in cell cycle control.	Mutation	Diagnostic	Tissue	[30]
Adhesion molecule				
E-cadherin (CDH1) - Adhesion molecule involved in intercellular communication.	Mutation/epigenetic alteration	Diagnostic / prognostic	Tissue/Blood	[31]
Immune checkpoint				
PD-L1 - An immune checkpoint that regulates the immune response.	Mutation	Prognostic / therapeutic	Tissue	[32]
Epigenetic alterations				
CDH1, CHFR, DAPK, GSTP1, p15, p16, RARβ, RASSF1A, RUNX3, TFPI2 - Groups of gene methylation changes associated with cancer.	Hypermethylation	Diagnostics	Tissue	[33]
Genetic polymorphism				
IL1-β, IL-1RN, CD44	SNP	Prognostic	Tissue	[34]
TP53, SYNE1, CSMD3, LRP1B, CDH1, PIK3CA, ARID1A, PKHD, KRAS, JAK2, CD274, PDCD1LG2 - Variations in DNA affecting disease susceptibility.	Copy number variations/ mutations	Diagnostic/prognostic/ therapeutic	Tissue	[35]
Circulating tumor cells				
CD44, N-cadherin, vimentin - Cells released into the blood from the tumor.	Overexpression	Diagnostic/therapeutic	Blood	[36]
pan-CK, E-cadherin	Reduced expression	EMT process	Blood	[37]
EE2 - Estrogen, which can influence tumor growth.	Overexpression	Therapeutic	Blood	[38]
Gastrin specific biomarker				
ADAM23, GDNF, MINT25, MLF1, PRDM5, RORA - Genes associated with gastric cancer.	Hypermethylation	Diagnostic	Gastric lavage	[39]
BARHL2 - Genes associated with gastric cancer.	Hypermethylation	Diagnostic/therapeutic	Gastric lavage/juice	[40]
PVT1	Regulated	Diagnostic / prognostic	Gastric juice	[41]
miR-421, miR-21, miR-106a, miR-129 - MicroRNAs involved in gene regulation.	Regulated	Diagnostic	Gastric juice	[42]
KagA	Regulated	Diagnostic	Tissue	[43]
VAK	Regulated	Diagnostic	Tissue	[44]
Gastrokin 1 - Protein associated with the regulation of digestive processes.	Deactivation	Prognostic	Tissue	[45]

Discussion: The current review discusses the most commonly used cancer markers, including CEA and CA, such as CA19-9, CA72-4, CA125, CA24-2, CA50, pepsinogen, and AFP. According to ASCO, ESMO, and NCCN guidelines, liquid biopsy is acceptable only when tumor tissue sampling is impossible, or the obtained sample is insufficient for analysis.

It should be noted that modern scientific literature offers a classification of gastric cancer based on the TCGA project, which is based on the analysis of genetic and epigenetic alterations.

Although several researchers have confirmed the effectiveness of standard serological methods of oncomarker diagnosis in detecting and assessing the risk of gastric cancer recurrence, the limited specificity and sensitivity of these molecular markers do not allow their use for early diagnosis of the disease.

This review article presents promising research directions for gastric cancer biomarkers based on different molecular genetic characteristics. A classification of these biomarkers according to their function in early diagnosis of the disease, prediction of recur-

rence, and evaluation of chemotherapy efficacy is performed.

Biomarkers of gastric cancer play an essential role in diagnostics, predicting the outcome of the disease, monitoring its course, and developing more effective treatment methods. Due to the often asymptomatic course of gastric cancer in its early stages, its diagnostics are a significant challenge. Biomarkers offer new opportunities to improve the accuracy of diagnostics and timely detection of this disease.

In the future, new molecular markers may significantly change the approach to treating and monitoring gastric cancer, providing more personalized treatment strategies.

Conclusion: Gastric cancer remains one of the leading causes of mortality from malignant neoplasms worldwide, primarily due to late diagnosis when therapeutic options are limited. Current biomarkers used for diagnosis and prognosis exhibit inadequate sensitivity and specificity. Diagnosis often relies solely on invasive procedures like upper gastrointestinal endoscopy. Consequently, ongoing research in gastric cancer is directed toward identifying and validating non-invasive biomarkers secreted by tumor tissues into body fluids. However, many of these biomarkers are detected only in advanced stages of the disease, rendering them unsuitable for early diagnosis. Further studies are necessary to enhance sensitivity and broaden the application of these biomarkers for early diagnosis and predicting treatment efficacy.

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АҢДАТПА

АСҚАЗАН ОБЫРЫНА ТЕРАПЕВТІК ТӘСІЛДЕРДІ ЕРТЕ АНЫҚТАУ МЕН БОЛЖАУҒА АРНАЛҒАН ЖАҢА БИОМАРКЕРЛЕР: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Асқазан обыры гетерогенді ауру болып табылады, оның дамуы генетикалық және жүре пайда болған соматикалық мутациялардың әсерімен байланысты.*

Асқазан обырына арналған жоғары сезімталдығы мен ерекшелігі бар оңтайлы диагностикалық маркерлерді бөлу пациенттердің өмір сүру көрсеткіштерін арттыруға мүмкіндік береді және дербес медицинаның дамуына ықпал ететін болады. Клиникалық деректерді біріктіру және геномды кешенді талдау негізінде биомаркерлерді сәйкестендіру диагностиканың нақтылығын, аурудың ағымын болжауды, қайталану қаупін және терапияға реакцияны айтарлықтай жақсартуы мүмкін. Бұл жұмыста асқазан обырын ерте диагностикалау және әртүрлі емдеу әдістерінің тиімділігін болжау үшін пайдаланылуы мүмкін перспективалық биологиялық маркерлер қарастырылады.

Зерттеудің мақсаты *– асқазанның қатерлі ісіктеріне қатысты диагностикалық және болжамдық құндылығы бар жаңа және таяуда әзірленген биомаркерлерді анықтау мақсатында қазіргі заманғы ғылыми әдебиетке талдау жүргізу.*

Әдістері: *Осы шолуда PubMed және Google Scholar дерекқорларын пайдалана отырып, медициналық әдебиетте электрондық іздеу пайдаланылды. Іздестіру «биомаркер», «асқазан обыры», «ерте анықтау», «диагностика», «болжам» деген негізгі сөздер бойынша жүргізілді. Шолуға ағылшын және орыс тіліндегі ашық қолжетімді, асқазан обыры ағымын ерте диагностикалау мен болжауда биомаркерлердің рөлін зерттеуге арналған толық мәтінді жарияланымдар енгізілді. Олар соңғы он жылда жарияланды. Адамдарда жүргізілмеген жеке бақылаулар, хат алмасу, хаттар мен зерттеулер туралы есептер шолуға енгізілмеген.*

Нәтижелері: *Жүргізілген зерттеулер барысында асқазан обыры ағымын диагностикалау және болжау үшін қолда бар биомаркерлердің жеткіліксіз дәлдігі бар екені анықталды. Ауруды жіктеудің қазіргі заманғы тәсілі шеңберінде жаңа молекулалық түр ұсынылды: Эпштейн-Барр (EBV) вирусын жұқтырған ісіктер, микрожүйе тұрақсыздығы бар ісіктер (MSI), геномдық тұрақты ісіктер (GS) және хромосомдық тұрақсыз ісіктер (CIN).*

Қорытынды: *Асқазан обырын зерттеу жаңа инвазивті емес биомаркерлерді іздеуге және тексеруге бағытталған. Сезімталдықты арттыру және биомаркерлерді қолдану саласын кеңейту үшін ерте диагностикалау және емдеу тиімділігін болжау мақсатында қосымша зерттеулер қажет.*

Түйінді сөздер: *биомаркер, асқазан обыры, ерте анықтау, диагностика, болжам.*

АННОТАЦИЯ

НОВЫЕ БИОМАРКЕРЫ ДЛЯ РАННЕГО ВЫЯВЛЕНИЯ И ПРОГНОЗИРОВАНИЯ ТЕРАПЕВТИЧЕСКИХ ПОДХОДОВ К РАКУ ЖЕЛУДКА: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Рак желудка представляет собой гетерогенное заболевание, развитие которого связано с воздействием как генетических, так и приобретенных соматических мутаций.*

Выделение оптимальных диагностических маркеров для рака желудка с высокой чувствительностью и специфичностью позволит повысить показатели выживаемости пациентов и будет способствовать развитию персонализированной медицины. Идентификация биомаркеров на основе интеграции клинических данных и комплексного анализа генома может существенно улучшить точность диагностики, прогнозирования течения заболевания, риска рецидива и реакции на терапию. В данной работе рассматриваются перспективные биологические маркеры, которые могут быть использованы для ранней диагностики рака желудка и предсказания эффективности различных методов лечения.

Цель исследования *– провести анализ современной научной литературы с целью выявления новых и недавно разработанных биомаркеров, обладающих диагностической и прогностической ценностью в отношении злокачественных новообразований желудка.*

Методы: *В настоящем обзоре был использован электронный поиск в медицинской литературе с использованием баз данных PubMed и Google Scholar. Поиск осуществлялся по ключевым словам: «биомаркер», «рак желудка», «раннее выявление», «диагностика», «прогноз». В обзор были включены полнотекстовые публикации на английском и русском языках, доступные в открытом доступе, посвященные исследованию роли биомаркеров в ранней диагностике и прогнозировании течения рака желудка. Опубликованы они были за последние десять лет. Отчеты о единичных наблюдениях, переписка, письма и исследования, не проводившиеся на людях, в обзор не включались.*

Результаты: *В ходе проведенных исследований было выявлено, что существующие биомаркеры для диагностики и прогнозирования течения рака желудка обладают недостаточной точностью. В рамках современного подхода к классификации заболевания был предложен новый молекулярный тип: опухоли, инфицированные вирусом Эпштейна-Барра, опухоли с нестабильностью микроспутников, геномно-стабильные опухоли и хромосомно-нестабильные опухоли.*

Заключение: *Современные исследования рака желудка направлены на поиск и проверку новых неинвазивных биомаркеров. Для повышения чувствительности и расширения области применения биомаркеров в целях ранней диагностики и прогнозирования эффективности лечения необходимы дополнительные исследования.*

Ключевые слова: *биомаркер, рак желудка, раннее выявление, диагностика, прогноз.*

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