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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии
საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებშიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman (Кириллица)**, для текста на грузинском языке следует использовать **AcadNusx**. Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи.** Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - <http://www.spinesurgery.ru/files/publish.pdf> и http://www.nlm.nih.gov/bsd/uniform_requirements.html. В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректур авторам не высылаются, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or computer-printed on a single side of standard typing paper, with the left margin of 3 centimeters width, and 1.5 spacing between the lines, typeface - **Times New Roman (Cyrillic)**, print size - 12 (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf

In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

**Articles that Fail to Meet the Aforementioned
Requirements are not Assigned to be Reviewed.**

ავტორთა საყურადღებო!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე, დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx**. შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემავსებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრაფიის ფოტოსურათები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შედეგების ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფხიხლებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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CORRELATION OF HER2 STATUS WITH LYMPH NODE METASTASIS IN KAZAKH PATIENTS WITH GASTRIC

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Abstract.

Objective: To investigate the correlation between HER2 expression and lymph node metastasis in Kazakh gastric cancer patients, assess the clinicopathological characteristics of HER2-negative and HER2-positive patients, and evaluate the association of HER2 expression with advanced lymph node involvement, while assessing its impact on overall survival to enhance clinical understanding and treatment strategies. In this study, "prognostic marker" refers to markers that predict clinical outcomes such as overall survival; markers associated only with pathological features (e.g., nodal stage) are described as "associated with" or "linked to" those features.

Methods: A cross-sectional study was conducted on 159 gastric cancer patients at NJSC West Kazakhstan Marat Ospanov Medical University. Histopathological and immunohistochemical assessments were performed, including HER2 evaluation using IHC. Statistical analysis with SPSS version 26 was used to identify predictors of lymph node metastasis.

Result: This study investigates the correlation between HER2 expression and lymph node metastasis in Kazakh gastric cancer patients. The mean age of participants was 58.87 ± 9.14 years, with a predominance of males (70.4%). Most patients were diagnosed with locally advanced GC (56%), with tumors predominantly located in the body of the stomach (40.3%). HER2-negative patients had a higher incidence of localized GC (45.5%) and lower lymph node involvement compared to HER2-positive patients, who exhibited more extensive lymph node metastasis (36.0%), especially in the N3 stage ($p = 0.027$). Statistical analysis revealed a significant association between HER2 status and pathological lymph node stage ($p = 0.027$). Survival analysis showed no significant difference in overall survival between HER2-negative and HER2-positive groups ($p = 0.58$), suggesting HER2 status does not significantly impact survival.

Conclusion: This study identifies a significant association between HER2 overexpression and lymph node metastasis in gastric cancer, suggesting HER2 expression is associated with more advanced lymph node involvement in this cohort; no significant association with overall survival was observed (log-rank $p = 0.58$), though its impact on survival remains inconclusive.

Key words. HER2 protein, gastric neoplasms, lymphatic metastasis, immunohistochemistry, Kazakhstan.

Introduction.

Gastric cancer (GC) remains a significant global health burden and is one of the leading causes of cancer-related mortality worldwide. The rising incidence and mortality rates are largely attributed to population growth and an aging global population [1,2]. Gastric cancer is notably more prevalent in certain regions and ethnic groups, with Eastern Asia exhibiting the highest cumulative risk at 2.64%, compared to 0.42% in Southern Africa [3]. While some high-income countries have observed decreases in both incidence and mortality, GC remains a major health challenge. The burden of gastric cancer varies due to differences in dietary habits, socioeconomic status, and the widespread presence of *Helicobacter pylori* infection, which is a key risk factor for the disease [4,5].

Kazakhstan carries a significant gastric cancer burden, particularly among the indigenous Kazakh population, where the prevalence remains high, often diagnosed at late stages, leading to poor outcomes. According to GLOBOCAN, Kazakhstan ranks tenth globally in gastric cancer prevalence. Over the past decade, more than 19,672 gastric cancer-related deaths have been recorded, with an average annual age-standardized mortality rate of 13.2 per 100,000 and a five-year survival rate of less than 20%. In this study, "prognostic marker" refers to markers that predict clinical outcomes such as overall survival; markers associated only with pathological features (e.g., nodal stage) will be described as "associated with" those features [6]. These figures underscore the pressing need for improved diagnostic and prognostic tools tailored to the region's biological and ethnic context.

HER2, a member of the ERBB receptor tyrosine kinase family, is a key biomarker and therapeutic target in various cancers, including gastric cancer. HER2 regulates cell proliferation and survival, and its overexpression or amplification is associated with aggressive tumor behavior and poor clinical outcomes. In gastric cancer, HER2 status not only informs prognosis but also directs targeted treatment strategies, such as trastuzumab therapy [7,8]. Despite its global relevance, the specific biological implications of HER2 status in gastric cancer remain underexplored in certain ethnic cohorts, including the Kazakh population.

Lymph node metastasis (LNM) is a crucial prognostic factor in gastric cancer, as it plays a pivotal role in disease staging, treatment decisions, and survival. In the absence of distant metastasis, disease stage is determined primarily by tumor invasion depth (T category) and the extent of nodal involvement (N category) [9]. The TNM staging system classifies LNM into N1 (1-2 nodes), N2 (3-6 nodes), and N3 (≥ 7 nodes), which directly correlates with advancing disease stages and poorer prognosis [10]. Even in early gastric cancer (T1), LNM is observed in approximately 10% of cases, underscoring the importance of comprehensive nodal evaluation during diagnosis and treatment planning [11].

The correlation between HER2 expression and lymph node involvement is pivotal for improving clinical decision-making and developing personalized treatment strategies. However, comprehensive data on this correlation within the Kazakh demographic is limited [12,13]. Despite advances in AI-enhanced diagnostics and artifact-free MRI imaging, there is a notable gap in data specific to Kazakh patients, impeding the development of ethnicity-specific prognostic models and therapeutic approaches. This lack of knowledge restricts the creation of effective treatment strategies for gastric cancer in Kazakhstan's unique epidemiological context [14].

The aim of this study is to investigate the correlation between HER2 expression and lymph node metastasis (LNM) in Kazakh patients diagnosed with gastric cancer. The study will evaluate the prognostic value of HER2 status within this specific population. By examining the relationship between HER2 expression and LNM, the research seeks to determine whether a significant correlation exists that can inform clinical decision-making and enhance the understanding of HER2's role in the prognosis and treatment of gastric cancer in Kazakh patients.

Literature review.

A study evaluating HER2 status in 172 gastric cancer (GC) patients from Kazakhstan found 15.1% overexpression of HER2, predominantly in older males with poorly differentiated tumors located in the stomach body or gastroesophageal junction. HER2 detection was performed using immunohistochemistry, confirmed via FISH/SISH. Patients with HER2-positive tumors exhibited significantly better overall survival, highlighting HER2 expression as a crucial factor in tumor location, type, and grade. These findings underscore the prognostic value of HER2 and its potential role in guiding targeted, personalized therapies [15].

In another study, a scientometric analysis of 536 publications from 1993 to 2024, focusing on biomarkers in diagnosing and predicting outcomes of GC in young patients, revealed a steady annual growth of 7.71% in related research. China, the USA, and Japan emerged as the top contributors, with leading institutions such as Sungkyunkwan, Sun Yat-sen, and Fudan Universities. Despite high national research output, international collaboration remained low at 19.4%. The study identified rising interest in diagnostics, immunohistochemistry, personalized treatment, and prognosis. This reflects a global shift towards precision medicine approaches for managing GC in younger populations and indicates evolving scientific priorities in oncology research [16].

A review examining treatment strategies for locally advanced gastric cancer (LAGC) emphasizes that standard care involves surgery combined with neoadjuvant and adjuvant chemotherapy. Some patients may benefit from targeted therapies and intraperitoneal chemotherapy (IPC) methods like HIPEC and PIPAC. While targeted therapies focusing on HER2 and VEGF pathways show promise, the use and effectiveness of IPC require further investigation. HIPEC results are mixed, and the preventive role of PIPAC lacks sufficient clinical validation. The review highlights the need for additional research to define optimal treatment combinations, timing, and integration, which could significantly improve survival and quality of life for patients with LAGC [17].

A 2023 study analyzed 119 patients treated with perioperative FLOT chemotherapy and surgery to identify predictors of tumor pathomorphosis. The study found that patients with stage I disease responded better to FLOT than those with advanced stages. A strong association was observed between lower lymph node involvement and better tumor regression (TRG I-II). Tumor differentiation and histological subtype did not significantly affect treatment response. Although adjuvant chemotherapy did not show statistically significant effects in survival models, trends suggested it may lower risks, warranting further investigation with larger cohorts and longer observation periods [18].

An analysis of intertumoral heterogeneity of HER2, dMMR, and PD-L1 in 44 patients with locally advanced gastric adenocarcinoma revealed HER2 overexpression in 11.4% of cases, all showing heterogeneity. dMMR was present in 4.5%, with one case showing discordance between primary tumors and lymph node metastases. PD-L1 expression was mostly consistent, although 11.4% exhibited variation. These findings highlight the frequent heterogeneity of HER2 expression, supporting multi-block testing, and underscore the clinical relevance of dMMR and PD-L1 variability in guiding targeted therapy and improving diagnostic precision [19].

A study by the Uzbekistan Korea Oncology Consortium reviewed the challenges of managing gastric and colorectal cancers in Uzbekistan. With rising life expectancy and cancer burden, the authors emphasized the need for enhanced prevention, early detection, and treatment infrastructure. Gastrointestinal cancer screening, particularly through endoscopy, was identified as a cost-effective strategy. The study also called for public education on lifestyle and dietary habits, which contribute to cancer risk. Drawing from South Korea's two decades of nationwide screening experience, the report recommended adopting proven Korean strategies and improving diagnostic services and research on local cancer risk factors to tailor cancer prevention strategies [20].

A clinical case report on the use of neoadjuvant immunotherapy in a patient with MSI-H locally advanced gastric cancer (GC) showed promising results. Traditionally, neoadjuvant chemotherapy rarely achieves pathological complete response in GC, but the patient, given the MSI-H tumor's known sensitivity to PD-1 inhibitors, received preoperative nivolumab, resulting in significant tumor shrinkage. Post-surgical histology confirmed the complete absence of malignant cells. This case

demonstrates the potential of incorporating immunotherapy into neoadjuvant regimens for MSI-H GC and supports including MSI-H testing in diagnostic workflows and considering immunotherapy in treatment planning. The authors recommend further trials evaluating immune-based therapies for gastric cancer [21]. Recent studies highlight the growing importance of HER2 as a prognostic marker and therapeutic target in gastric cancer (GC). Research shows HER2 overexpression correlates with better survival outcomes and is linked to tumor location and type. Additionally, advances in precision medicine, such as targeted therapies and immunotherapy, are gaining traction, with significant studies on biomarkers like HER2, dMMR, and PD-L1 in GC. The rising global focus on personalized treatments reflects a shift toward more tailored management strategies, though further validation, especially in regions like Kazakhstan, is needed to address regional variations and improve diagnostic and therapeutic approaches.

Materials and Methods.

Study design:

A cross-sectional study with random sampling.

Study Setting:

The study was conducted at the Medical Centre of the NJSC West Kazakhstan Marat Ospanov Medical University and included clinical data from 159 patients diagnosed with gastric cancer (GC). All patients were residents of the Aktobe region and underwent surgical treatment between 01.01.2018 and 01.06.2021.

Sample Size:

A total of 159 patients aged between 18 and 78 years (age range - 59 years [95% CI: 57.43–60.29]) were included.

Inclusion criteria:

(1) pathomorphologically confirmed diagnosis of GC, (2) stages I, IIa, IIb, IIIa, IIIb, IIIc according to the TNM classification (8th edition), (3) presence of tumours in any gastric location (cardia, body, or antrum), (4) resectable disease, and (5) histological type according to Lauren's classification (intestinal and diffuse types).

Exclusion criteria:

Patients with multiple metachronous or synchronous cancers and newly diagnosed GC, those who received preoperative chemotherapy or radiotherapy, pregnant women with GC, patients after exploratory laparotomy or bypass gastroenteroanastomosis, and patients with neuroendocrine tumours, sarcomas, or lymphomas of the stomach.

Surgical Intervention:

After a preoperative diagnosis, all patients underwent planned laparotomy. The surgical extent was determined by individual tumour spread and included standard gastrectomy with D2 lymphadenectomy (LD) or combined gastrectomy with D2 LD.

Histopathological and Immunohistochemical Assessment:

Postoperative gastric tissue was sent to the pathomorphological laboratory for histological and immunohistochemical (IHC) evaluation. Haematoxylin and eosin staining was performed using standard methodology. IHC slides were assessed under

400x magnification using a Leica 10x10 microscope by two independent pathomorphologists (double-blind method) unaware of clinical details. HER2 expression was evaluated using rabbit monoclonal antibody (clone 4B5, DAKO, Arizona, USA). Tissue sections were cut at 4 µm, air-dried for 12 hours, deparaffinised in xylene, and processed in alcohol series. Epitope retrieval was done in a water bath at 95–99°C for 40 minutes, followed by peroxidase blocking, incubation with HER2 antibody (1:100), and visualization with DAB solution (EnVision, DAKO A/S, USA). Counterstaining was done using haematoxylin.

Preparation Protocol:

Tissue samples were fixed in 10% neutral-buffered formalin for 18–24 hours at a fixative: tissue volume ratio of 20:1. Sections were prepared using a rotary microtome (Accu-Cut SRM 200) at 4 µm thickness, placed on Superfrost+ slides, floated on preheated water (≤45°C), and dried in a thermostat (TC-80) at 56–60°C for 60 minutes. Staining was performed on an automated BenchMark XT stainer (VENTANA, Tucson, AZ). Slides were scanned using KF-PRO-120 telepathology system (Ningbo Konfoong Bionformation Tech Co., Ltd, China).

HER2 Scoring:

HER2 expression was classified per National Comprehensive Cancer Network (NCCN) criteria:

- “-” = no reactivity or membranous reactivity in <10% of cancer cells
- “+” = weak/barely perceptible membranous reactivity in ≥10%
- “++” = complete basolateral/lateral reactivity (weak to moderate) in ≥10%
- “+++” = strong complete basolateral/lateral reactivity in ≥10%

Scores of “-” or “+” were considered negative; “+++” was positive. “++” cases were confirmed by in situ hybridization (ISH), with HER2 copy number ≥6.0 per cell deemed positive. The absence of fluorescence in situ hybridization (FISH) confirmation for the 2+ cases is considered a limitation of this study.

Statistical Analysis:

Data analysis was performed using SPSS version 26. Descriptive statistics summarized the demographic and clinicopathological characteristics. The Pearson Chi-square test assessed associations between categorical variables and HER2 status. Kaplan-Meier survival curves were used to compare overall survival between HER2-negative and HER2-positive patients. Log-rank tests evaluated survival differences, with a p-value of <0.05 considered statistically significant.

Clarification of Prognostic Terminology:

In this study, the term “prognostic marker” referred to markers that predicted clinical outcomes such as overall survival. Markers that were associated only with pathological features (e.g., nodal stage) were described as “associated with” or “linked to” those features.

Results.

Table 1 presents the clinical and morphological characteristics of the study participants. The mean age of participants was

58.87 ± 9.14 years, with a majority (74.2%) aged under 65 years, while 25.8% were over 65 years. The study population was predominantly male (70.4%), with women constituting 29.6%. In terms of disease stage, 44% of patients had localized gastric cancer (GC), classified as stages I, IIa, or IIb, while 56% had locally advanced GC (stages IIIa, IIIb, and IIIc). Tumor localization predominantly involved the body of the stomach (40.3%), followed by the cardia and fundus (34%), and the antral and pyloric section (21.4%). Disease staging revealed that 68.6% of patients were diagnosed with stage III GC, 28.3% with stage II, and 3.1% with stage I. These demographic and clinical features provide essential context for exploring the correlation between HER2 status and lymph node metastasis in the study population.

Table 1. Clinical and Morphological Characteristics of Study Participants.

Variables	Subgroup	Frequency (%)
Age in years (Mean ± SD)	58.87 ± 9.14	
Age groups	<65	118 (74,2%)
	>65	41 (25,8%)
Gender	Women	47 (29,6%)
	Men	112 (70,4%)
pTNM stage	Localized GC (I, IIa, IIb)	70 (44%)
	Locally advanced GC (IIIa, IIIb, IIIc)	89 (56%)
Localization of the tumor	Cardio and Fundus	54 (34%)
	Body	64 (40,3%)
	Antral and Pyloric Section	41 (21,4%)
Stage	Stage I	5 (3,1%)
	Stage II	45 (28,3%)
	Stage III	109 (68,6%)

Table 2 details the clinicopathological characteristics of patients according to their HER2 status, focusing on the distribution of various variables between HER2-negative and HER2-positive groups. ISH was used for 2+ cases, and FISH was not employed.

Table 2. Clinicopathological characteristics according to HER2 status (with ISH).

Variable	HER2 Negative n (%)	HER2 Positive n (%)	Df	Pearson's Chi-square test p-value
Stage (pTNM*)			1	0.378
Localised GC (Stages I, IIa, IIb)	61 (45.5%)	9 (36.0%)		
Locally advanced GC (Stages IIIa, IIIb, IIIc)	73 (54.5%)	16 (64.0%)		
Tumour localisation			2	0.271
Cardia and Fundus	42 (31.3%)	12 (48.0%)		
Body	56 (41.8%)	8 (32.0%)		
Antrum and Pyloric region	36 (26.9%)	5 (20.0%)		
Stage			2	0.859
Stage I	4 (3.0%)	1 (4.0%)		

Stage II	37 (27.6%)	8 (32.0%)		
Stage III	93 (69.4%)	16 (64.0%)		
Histological type (Lauren's classification)			1	0.245
Diffuse-type GC	80 (59.7%)	18 (72.0%)		
Intestinal-type GC	54 (40.3%)	7 (28.0%)		
Tumour emboli in vessels			1	0.575
No	106 (79.1%)	21 (84.0%)		
Yes	28 (20.9%)	4 (16.0%)		
pN stage**			3	0.027
N0	49 (36.57%)	9 (36.0%)		
N1	28 (20.90%)	1 (4.0%)		
N2	38 (28.36%)	6 (24.0%)		
N3	19 (14.18%)	9 (36.0%)		
Tumour differentiation			3	0.441
Well-differentiated	3 (2.2%)	2 (8.0%)		
Moderately differentiated	22 (16.4%)	3 (12.0%)		
Poorly differentiated	88 (65.7%)	17 (68.0%)		
Undifferentiated	21 (15.7%)	3 (12.0%)		

In terms of disease stage (pTNM classification), 45.5% of HER2-negative patients had localized gastric cancer (GC), whereas 36.0% of HER2-positive patients were in this category. 54.5% of HER2-negative patients had locally advanced GC (Stages IIIa, IIIb, and IIIc), compared to 64.0% of HER2-positive patients. This difference, however, lacked statistical significance ($p=0.378$). Tumor localization showed that 31.3% of HER2-negative patients had tumors in the cardia and fundus, whereas 48.0% of HER2-positive patients did. However, no statistically significant difference was found ($p=0.271$). Regarding histological type (according to Lauren's classification), 59.7% of HER2-negative patients had diffuse-type GC, while only 72.0% of HER2-positive patients had this form. Statistical testing also showed no significant association ($p=0.245$). A statistically significant association was found in pN stage (pathological lymph node stage), where 36.0% of HER2-positive patients were classified as N3 compared to 14.2% of HER2-negative patients. This represents a marked increase in lymph node metastasis (LNM) in the HER2-positive cohort ($p=0.027$). However, no significant differences were noted in other stages (N0, N1, and N2).

Figure 1 illustrates the Kaplan-Meier survival curves for gastric cancer patients stratified by HER2 status, comparing overall survival rates between HER2-negative (red) and HER2-positive (blue) groups over a period of 50 months.

The survival curves show that both groups follow similar trajectories, with no significant divergence between them. The p-value of 0.58 indicates that the difference in overall survival between HER2-negative and HER2-positive patients is not statistically significant, suggesting that HER2 expression is

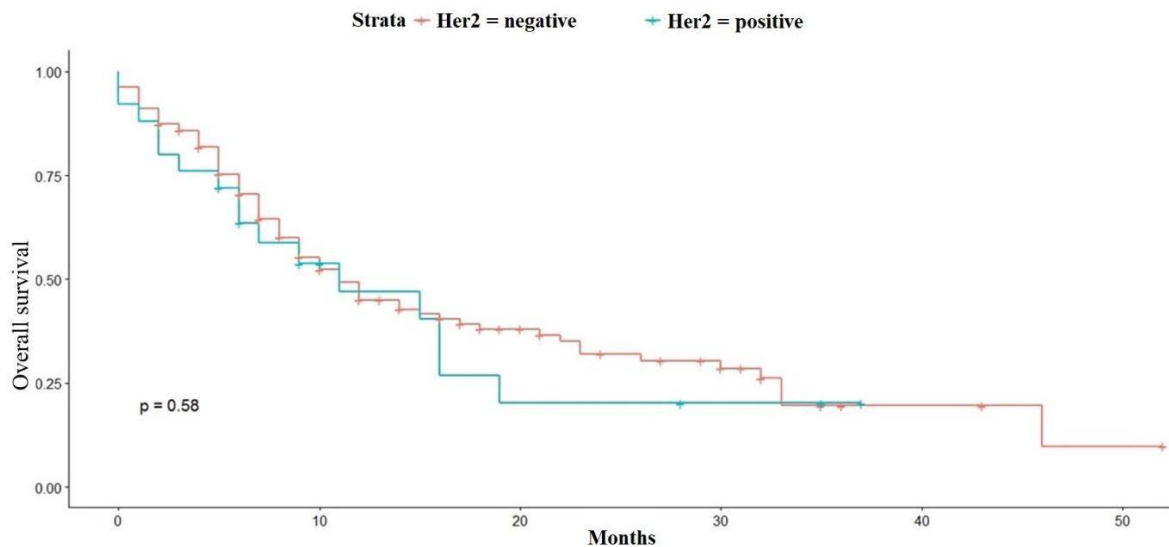


Figure 1. Survival According to HER2 Status.

associated with more advanced lymph node involvement in this cohort; no significant association with overall survival was observed.

Discussion.

The findings of this study, which examined the correlation between HER2 status and lymph node metastasis (LNM) in Kazakh patients with gastric cancer (GC), align with several previous studies that highlight the significance of HER2 overexpression as a prognostic biomarker in GC. In this study, “prognostic marker” was referred to markers that predicted clinical outcomes such as overall survival, while markers associated only with pathological features (e.g., nodal stage) was described as “associated with” or “linked to” those features. Similar to our study, a descriptive cross-sectional study found a male predominance in gastric cancer patients, with a male-to-female ratio of 1.9:1 and a mean age of 58 years, consistent with our study’s demographic characteristics [22,23]. This suggests common epidemiological patterns across South and Central Asia, despite geographical differences. In terms of histological subtype, our findings are in contrast with a study conducted in Western countries, where diffuse-type gastric adenocarcinoma is more common. In our study, a significant proportion of patients had intestinal-type GC, which reflects regional variations in the prevalence of gastric adenocarcinoma [24,25].

Furthermore, the late-stage presentation of gastric cancer remains a major issue in regions such as Central Asia, contributing to poor prognosis and high metastasis rates, as reported in a 2020 study by Kim et al. [26]. Our study, which showed that a large proportion of patients presented with locally advanced GC (56%), corroborates this observation. The high burden of advanced-stage disease in countries with lower socio-demographic indices (SDI), such as Kazakhstan, underscores the importance of early detection and timely intervention [27,28].

In line with other studies, our data also support the association between HER2 overexpression and aggressive tumor behavior. A study at King Abdulaziz University Hospital, which analyzed 122 GC cases, found that HER2 overexpression occurred in

13.5% of tumors, but no significant correlation was observed between HER2 status and clinicopathological parameters [29]. However, other studies have shown a significant association between HER2 positivity and increased LNM in gastric cancer. For instance, patients with HER2-positive GC were more likely to have distant lymphatic recurrence and para-aortic lymph node metastasis, highlighting the role of HER2 in promoting lymphatic spread [30].

Additionally, meta-analyses and radiomic studies have further supported the relationship between HER2 overexpression and poor prognosis in gastric cancer. For example, HER2 overexpression correlates with tumor aggressiveness and microenvironment alterations, and HER2 status has been shown to be a significant predictor of LNM in undifferentiated early gastric cancer [31,32]. This is consistent with our study’s findings, where HER2-positive patients had a higher incidence of lymph node involvement, particularly in advanced disease stages.

The findings from our survival analysis are consistent with recent studies that have reported mixed results regarding the impact of HER2 overexpression on survival. HER2 expression is associated with more advanced lymph node involvement in this cohort; however, no significant association with overall survival was observed ($p = 0.58$). This lack of significant survival difference could be attributed to several factors, including the heterogeneity of gastric cancer, the relatively small sample size, and the lack of FISH confirmation for 2+ cases. The small cohort of HER2-positive patients ($n = 25$), particularly, may have affected the statistical power of this investigation. It is possible that the absence of a notable survival difference stems from inadequate power to detect a true difference (Type II error), rather than an actual lack of difference between the groups. These limitations may contribute to classification bias and affect the generalizability of the results.

The biological mechanism underlying the association between HER2 positivity and metastasis is likely related to HER2’s role in activating signaling pathways such as PI3K/Akt and MAPK, which are known to enhance tumor cell proliferation, survival,

angiogenesis, and invasion. HER2 overexpression may promote epithelial-mesenchymal transition (EMT), facilitating cancer cell detachment, migration, and the establishment of secondary sites like lymph nodes. This molecular insight supports HER2 as not only a therapeutic target but also a biologically plausible marker of metastatic potential [33,34]. Several studies have also demonstrated that HER2 overexpression in gastric cancer is linked to increased tumor angiogenesis, which could further explain the poor prognosis and high metastasis rates in HER2-positive patients [35].

In this study, the significant correlation between HER2 status and lymph node metastasis underscores the potential role of HER2 as a prognostic biomarker in gastric cancer. However, the survival analysis results suggest that HER2 alone may not be sufficient to predict patient outcomes. This highlights the need for a more comprehensive approach that integrates HER2 status with other clinicopathological factors, such as tumor size, differentiation, and lymphovascular invasion, to better predict patient prognosis.

These findings are consistent with the increasing recognition of HER2 as an essential biomarker in gastric cancer. HER2-targeted therapies, such as trastuzumab, have shown promising results in improving survival in metastatic cases [36,37]. Given the association between HER2 overexpression and LNM, HER2 testing is crucial for guiding treatment decisions, particularly for patients with metastatic gastric cancer. The potential for HER2 to serve as both a prognostic and therapeutic marker emphasizes the importance of incorporating HER2 assessment into routine clinical practice.

While this study provides valuable insights, it is important to note its limitations. The modest sample size and single-center design may limit the generalizability of the findings. Additionally, the use of IHC alone for HER2 status assessment, without confirmation by FISH in borderline cases, may introduce classification bias. Future multicenter studies with larger sample sizes and more comprehensive HER2 testing, including FISH, are needed to validate these findings and establish HER2 as a reliable predictor of LNM and treatment response in gastric cancer.

Conclusion.

This study highlights the significant association between HER2 overexpression and lymph node metastasis (LNM) in patients with gastric cancer. While HER2 positivity was correlated with more advanced disease stages and increased lymph node involvement, the overall survival analysis did not demonstrate a significant survival benefit for HER2-positive patients. These findings suggest that HER2 expression is associated with more advanced lymph node involvement in this cohort; no significant association with overall survival was observed. The observed heterogeneity in HER2 expression and its association with tumor aggressiveness underline the importance of personalized treatment approaches, especially in regions with high incidence rates of gastric cancer, such as Kazakhstan. Furthermore, the study underscores the need for comprehensive HER2 testing in gastric cancer, including the use of advanced techniques like fluorescence in situ hybridization (FISH) for more accurate

classification. In this study, “prognostic marker” was referred to markers that predicted clinical outcomes such as overall survival, while markers associated only with pathological features (e.g., nodal stage) was described as “associated with” or “linked to” those features. Although HER2 overexpression is linked to poorer prognostic factors such as increased metastasis, further research with larger sample sizes and multi-center collaborations is essential to validate these results and establish standardized protocols for HER2 assessment in clinical practice. This would ultimately enhance personalized treatment strategies, particularly in the context of HER2-targeted therapies, which could improve patient outcomes, especially in metastatic cases.

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