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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 საქურაღებოლ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დაიცვათ 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, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრაფიების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შედეგის 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.

E. Didebulidze, L. Nadareishvili, S. Sturua, G. Berishvili, S. Tsertsvadze, N. Janelidze, N. Geliashvili, M. Kutateladze, P.M. Lydyard, M. Tediashvili. EARLY HUMORAL IMMUNE RESPONSES TO BACTERIOPHAGES AND SHORT-COURSE PHAGE THERAPY OUTCOMES IN PATIENTS WITH URINARY TRACT INFECTIONS.....	6-17
Iryna Yevchenko, Andrii Masliuk, Serhii Myronets, Inna Lapchenko, Nataliia Ortikova. CORRELATION OF EMOTIONAL EMPATHY WITH MENTAL HEALTH INDICATORS IN ADULTS TO DETECT PSYCHOLOGICAL WELL-BEINGMARKERS.....	18-26
Maksat Seiitkhan, Altyn Saparbek, Aibergen Tleubergenov, Kurmanay Soltanbayeva, Sayazhan Stanova. ENDOSCOPIC ENDONASAL TREATMENT OF PRIMARY INVERTED PAPILLOMA OF THE SPHENOID SINUS: A CLINICAL CASE.....	27-34
Dae-Hwan Lee, Bong-Sik Woo, Jung-Ho Lee. RETROSPECTIVE EVALUATION OF A COMMUNITY-BASED ELASTIC BAND EXERCISE PROGRAM USING A BALANCE PAD IN RURAL OLDER WOMEN.....	35-42
Mohamed Abdelhadi, Muna HM Alhendi, Khalil AlShowaiker, Ahmad Almaimooni, Khaled Aljenae, Sulaiman Hajji, Ramadan Eldamarawy, Neveen Shalaby. A RARE PRESENTATION OF DIFFUSE LARGE B-CELL LYMPHOMA AS SEVERE ACUTE HEPATITIS AND SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN A YOUNG ADULT: A CASE REPORT.....	43-46
Lian-Ping He, Ling-Ling Zhou, Jing-Jin Yang, Ying-Rui Huang, Guang Chen. ARTIFICIAL INTELLIGENCE-ASSISTED TEACHING MODEL AS A STRATEGY TO ENHANCE CORE COMPETENCIES OF CLINICAL MEDICINE UNDERGRADUATES: A SCIENTIFIC HYPOTHESIS.....	47-51
Diana Sargsyan, Arevhat Badalyan, Sona Harutyunyan, Siranush Hovhannisyan. THE STUDY OF CORRELATIONS OF PSYCHOLOGICAL FACTORS ENSURING THE FAMILY MENTAL HEALTH.....	52-60
Gani Uakkazy, Chingiz Shashkin, Natalya Slivkina, Viktor Tkachev, Mirbanu Aikhozhayeva, Gulbana Khussainova, Raushan Baigenzheyeva, Zilola Mavlyanova, Raikhan Burumbayeva, Mereke Alaidarova, Joseph Almazan, Amangali Akanov. CONTEXTUAL ANALYSIS OF ADAPTED BOXING AND KICK-/KNEE-STRIKE EXERCISE MODULES IN MULTIDISCIPLINARY NEUROREHABILITATION AND NURSING CARE: SECONDARY ANALYSIS OF TWO PROSPECTIVE STUDIES.....	61-70
Turkiyah Mohsin Elias, Anmar B. AL-Dewachi. DETERMINANTS OF DIABETIC FOOT AMONG PATIENTS WITH TYPE 2 DIABETES: A CASE-CONTROL STUDY.....	71-77
Khatuna Kudava. CLINICAL CHARACTERISTICS OF INFECTION-ASSOCIATED PALMOPLANTAR DERMATOSIS IN PREPUBERTAL CHILDREN: AN OBSERVATIONAL STUDY.....	78-81
Renta Sanxhaku, Ditila Doracaj, Delina Xhafaj, Stela Sanxhaku, Andi Gjini, Alban Xhafaj, Edi Grabocka. HOMOCYSTEINE TESTING IN PREVENTIVE HEALTHCARE: COMPARATIVE INSIGHTS AND POLICY IMPLICATIONS FOR ALBANIA.....	82-87
Sara Ali, Marwan Ismail, Praveen kumar, Salma Elnour Mohamed, Weam Alyoubi, Hiba Mohamed, Raghad Alamri, Fatima Mohamed Osman Yasin, Safa Mohamed Abdelrahman, Huda F. Alshaibi, Einas Awad Osman, Akhtamova Shahzoda Fozilovna, Matlyuba Badritdnova, Rihab Akasha, Mohamed Alfaki. PAN-CANCER ANALYSIS OF CHEMOKINE (C-C MOTIF) LIGAND 26 (Ccl26) AS A PROMISING PROGNOSTIC BIOMARKER AND IMMUNOMODULATORY MEDIATOR.....	88-115
Altin Sallahu, Ferat Sallahu. PROGNOSTIC AND PREDICTIVE VALUE OF TUMOR BUDDING, LYMPHOVASCULAR INVASION, AND PERINEURAL INVASION IN COLORECTAL CARCINOMA.....	116-119
Ghukasyan Norayr, Gharibyan Edita, Geokchyan Haykuhi, Vardanyan Ara, Gekchyan Gor, Sahakyan Lusine. SUCCESSFUL PREGNANCY AND TERM DELIVERY AFTER RADICAL SURGERY FOR COLON CANCER: A CASE REPORT.....	120-124
G.N.K. Ganesh, Clara Shertaeva, Galiya Umurzakhova, Malik Sapakbay, Sabina Seidaliyeva. DIGITALISATION OF THE PHARMACEUTICAL INDUSTRY IN KAZAKHSTAN: HOW IS THE SECTOR ADAPTING TO NEW REALITIES?	125-130
Klara Kaldygozova, Aigul Sergazina, Gulmira Datkayeva, Sulugaisha Kalen, Maya Maksut. METABOLIC DISORDERS IN CHILDREN SUFFERING FROM ACUTE RESPIRATORY VIRAL INFECTIONS (ARVI): COMPLICATIONS AND PREVENTIVE MEASURES.....	131-140
Anas Alhur, Sarah Ibrahim Al-Atif, Afrah Alhur, Fahad Saud Alshammari, Hozan Muslat Nasser Al-Taweel, Reeuof Abdullah Zarbah, Remas Abdullah Mohammed Al-Shahrani, Shaimaa Ahmed Yahya Al-Abdullah, Jana Jameel Salamah Allah, Dhay Hammad Al-Amer, Alhanouf Sulaiman Alharbi, Ali Ahmed Alzahrani, Sultan Saad Ali Alowaydi, Reema Al Shahrani, Abdulrahman A. Alsaqabi. GENERATIVE AI-ASSISTED DRUG-DRUG INTERACTION CASE SUPPORT AND PHARMACY STUDENTS' COMPETENCE: A MIXED-METHODSSTUDY.....	141-151

Sara Abdelmehmoud Omer, Alaa Hanafi Makki Elkhalfifa, Abdelkarim Abobakr Abdrabo, Einas A Osman. ASSOCIATION BETWEEN THYROID HORMONE LEVELS AND ADVANCED LIVER FIBROSIS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND NON-ALCOHOLIC FATTY LIVER DISEASE.....	152-157
Lingzhi Bao, Jie Ma. NAVIGATING AI IN MEDICAL EDUCATION: A NARRATIVE REVIEW OF APPLICATIONS, CHALLENGES, AND FUTURE STRATEGIES.....	158-166
Mukasheva Gulbarshyn, Seitmaganbetova Indira, Kurmangali Zhanar K. SOCIODEMOGRAPHIC DETERMINANTS OF PRENATAL CARE ACCESS AMONG PREGNANT WOMEN IN THE MANGYSTAU REGION: A CROSS-SECTIONAL STUDY.....	167-173
Sultan M. Siham, Ali L. Jasim, Amar K. Almajidy. INVESTIGATING THE PERSPECTIVES OF RESPIRATORY PHYSICIANS ON HOW SOCIAL DETERMINANTS OF HEALTH AND HEALTH LITERACY INFLUENCE ASTHMA OUTCOMES: A QUALITATIVE STUDY.....	174-178
Datumyan G.S, Sargsyan M.V, Shaboyan K.R, Hovhannisyan M.E, Sahakyan K.M, Muradyan A.A, Hakobyan A.I, Hovhannisyan H.V. SEVERE UPPER EXTREMITY CRUSH SYNDROME IN A NON-DISASTER SETTING: A CASE REPORT OF SUCCESSFUL MULTIMODAL MANAGEMENT WITH COMPLETE RENAL RECOVERY.....	179-184
Tea Chitadze. TEMPORAL DYNAMICS OF GLOBAL LONGITUDINAL STRAIN AND NT-PROBNP IN THE EARLY DETECTION OF ANTHRACYCLINE-INDUCED CARDIOTOXICITY: A 24-MONTH PROSPECTIVE STUDY IN POSTMENOPAUSAL WOMEN WITH BREASTCANCER.....	185-197
Bodnar-Petrovska O.B, Verenkiotova O.V, Petrovskiy A.V, Krykun V.V, Batryn O.V, Ivakhnenko O.A. COMPARATIVE ANALYSIS OF MATERNAL AND CHILD HEALTH CARE IN THE MEMBER STATES OF THE EUROPEAN UNI ON.....	198-208
Gulbarshyn Mukasheva, Tolkyun Bulegenov, Indira Seitmaganbetova, Aigul Tugelbayeva, Meruyert Malik. QUALITY OF LIFE AMONG YOUNG ADULT PATIENTS WITH CARDIOVASCULAR DISEASE.....	209-215
Marina Zhorobekova, Salima Nayzabekova, Dinara Alieva, Saikal Melisova. MEDICAL AND SOCIAL REHABILITATION OF ELDERLY PATIENTS WITH POST-COVID SYNDROME AND COPD: THE EXPERIENCE OF KYRGYZSTAN.....	216-224
Davit Chakvetadze, Otar Darjanian. PREVALENCE, RISK FACTORS, AND STRUCTURAL CHARACTERISTICS OF DENTOALVEOLAR ANOMALIES IN THE SCHOOL- AGED POPULATION OF KUTAISI.....	225-232
Kurmangaliyeva Klara, Shlymova Raikhan, Askarova Karashash, Darybayeva Aisha, Kazangapova Assem, Sagyndykova Gulnur, Yeshmagambetova Zhanna, Akhmedyarova Elmira. EFFECTIVENESS OF PLASMA EXCHANGE IN THE THERAPY OF DRUG-INDUCED HEPATITIS IN PATIENTS WITH PULMONARY TUBERCULOSIS AND CHRONIC VIRAL HEPATITIS B AND C.....	233-242
Matitaishvili T, Domianidze T, Burjanadze G, Shengelia M, Menteshashvili N. EFFECTS OF LONG-TERM SOCIAL ISOLATION ON MEMORY AND DEPRESSIVE-LIKE BEHAVIOR IN RATS OF DIFFERENT SOCIAL STATUS.....	243-248
Svetlana Trofimova, Aruzhan Mendybayeva, Irina Izbassarova, Aida Bokayeva, Aliya Aituganova. DIFFERENTIAL DIAGNOSIS CHALLENGES OF PULMONARY SARCOIDOSIS IN PRIMARY CARE PRACTICE: THE ROLE OF MULTIDISCIPLINARY AND PERSONALIZED APPROACHES.....	249-254
Farman K. Rafeeq, Zeina A. Al-Thanoon. THE POTENTIAL HEPATOPROTECTIVE EFFECT OF PALMITOLEIC ACID AGAINST KETAMINE-INDUCED LIVER INJURY IN RATS: OXIDATIVE, INFLAMMATORY, AND HISTOPATHOLOGICAL EVALUATION.....	255-261
Zakharov Oleg B, Vasileva Anastasiya A, Idiatullin Ravil M, Maslov Vladimir G, Malashikhina Alyona V, Solomonov Sergei A, Falicheva Anastasiia O, Ruchkina Kseniia A, Popov Vasilii V, Litiuk Daria V, Oshchipok Damir D, Tarusina Viktoriia M, Kulbyakova Maria L, Saryeva Albina R, Torba Danil G, Korotkova Sofia E, Sakharova Viktoriya S, Mamutova Zeyneb M, Yaksun Vasilisa S, Suvorova Sofia M. BEYOND CONTRACTILITY: PHENOTYPIC SWITCHING OF VASCULAR SMOOTH MUSCLE CELLS IN ATHEROSCLEROSIS.....	262-269
A.V. Podobed, V.P. Kurchyn, I. Kobidze. VIDEO-ASSISTED THORACOSCOPIC RESECTION OF THE LEFT BRACHIOCEPHALIC AND SUPERIOR VENA CAVA FOR PRIMARY AND RECURRENT THYMIC TUMORS.....	270-275
Fadia Thamir Ahmed. ASSESSMENT OF MELATONIN USE PATTERNS, SAFETY, AND ATTITUDES TOWARD ITS USE IN ADULT POPULATION.....	276-281
Daniel Godoy-Monzon, Patricio Telesca, Jose Manuel Pascual Espinosa. MID-TERM CLINICAL AND RADIOLOGICAL OUTCOMES OF SHORT-STEM VERSUS CONVENTIONAL-STEM TOTAL HIP ARTHROPLASTY IN PATIENTS WITH OSTEONECROSIS OF THE FEMORAL HEAD: A PROSPECTIVE CASE-CONTROL STU DY.....	282-287

PROGNOSTIC AND PREDICTIVE VALUE OF TUMOR BUDDING, LYMPHOVASCULAR INVASION, AND PERINEURAL INVASION IN COLORECTAL CARCINOMA

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Abstract.

Background: Colorectal carcinoma (CRC) remains one of the most common malignancies worldwide and a leading cause of cancer-related mortality. Accurate prediction of recurrence is essential for risk stratification and individualized postoperative management. This study aimed to evaluate the prognostic and predictive significance of tumor budding (TB), lymphovascular invasion (LVI), and perineural invasion (PNI) in colorectal carcinoma.

Methods: A retrospective cohort study was conducted including patients treated at the Clinic of Abdominal Surgery and the Department of Pathology, University Clinical Center of Kosovo (UCCK), between January 2020 and June 2025. Follow-up data collection continued until December 2025, and only patients with a minimum follow-up duration of 6 months were included in the final analysis. Clinical, surgical, and histopathological data were collected, including TB, LVI, and PNI status. Statistical analysis included descriptive methods, chi-square test, binary logistic regression, receiver operating characteristic (ROC) curve analysis with area under the curve (AUC), and Kaplan–Meier disease-free survival (DFS) analysis with the log-rank test.

Results: High tumor budding (BD3) was identified in 29.2% of patients, LVI in 34.1%, and PNI in 26.7%. At least one invasive histopathological factor was present in 48.6% of the cohort. All three markers were significantly associated with disease recurrence ($p < 0.001$). Multivariate logistic regression demonstrated that independent predictors of recurrence were LVI (OR 4.72; 95% CI 2.46–9.03), PNI (OR 3.91; 95% CI 1.98–7.72), and TB (OR 3.24; 95% CI 1.67–6.29). LVI showed the highest predictive accuracy in ROC analysis (AUC = 0.781). Kaplan–Meier survival analysis demonstrated significantly shorter median disease-free survival (DFS) in patients with one or more positive invasive histopathological factors compared with patients without such factors. Median DFS was 22.4 months (95% CI: 18.7–26.1) versus 35.1 months (95% CI: 31.4–38.8), respectively (log-rank $p < 0.001$).

Conclusions: Tumor budding, lymphovascular invasion, and perineural invasion are independent prognostic markers in colorectal carcinoma. Among them, LVI demonstrated the strongest predictive value for recurrence. Routine incorporation of these parameters into pathological reports may improve prognostic assessment and support therapeutic decision-making.

Key words. Colorectal carcinoma, tumor budding, lymphovascular invasion, perineural invasion, recurrence, disease-free survival.

Introduction.

Colorectal carcinoma (CRC) is one of the most frequently diagnosed malignancies worldwide and remains a leading cause of cancer-related mortality [1-3]. According to recent global

estimates, more than 1.9 million new cases and over 900,000 deaths are reported annually, making CRC a major public health challenge [1,2]. The burden of disease continues to rise in many developing and transitional countries, where changes in lifestyle, dietary habits, and population aging contribute to increasing incidence rates [1,3].

Despite substantial advances in surgical techniques, systemic chemotherapy, radiotherapy, and multidisciplinary oncologic care, recurrence and long-term survival remain strongly influenced by the biological behavior of the primary tumor [4-17]. Therefore, accurate identification of prognostic histopathological markers is essential for individualized treatment planning, postoperative surveillance, and risk stratification [4,16]. Among the most important invasive histopathological parameters are tumor budding (TB), lymphovascular invasion (LVI), and perineural invasion (PNI) [5-7].

Tumor budding is defined as the presence of isolated single tumor cells or small clusters of up to four cells at the invasive front and is considered a morphological manifestation of epithelial–mesenchymal transition and early metastatic potential [5,18,19]. Lymphovascular invasion indicates the presence of malignant cells within lymphatic or blood vessels and represents a major pathway for tumor dissemination [6,13]. Perineural invasion refers to tumor infiltration in, around, or through nerve structures and has been associated with aggressive disease, local recurrence, and reduced survival [7,20]. Although the TNM staging system remains the cornerstone of prognostic assessment in CRC, it does not fully capture the biological heterogeneity of tumors with similar anatomical stage [8,21]. For this reason, additional pathological markers may improve the prediction of oncologic outcomes [14,22]. Modern statistical approaches, including multivariate logistic regression, receiver operating characteristic (ROC) curve analysis, and survival models, enable objective evaluation of prognostic factors and may support the development of integrated clinicopathological models for recurrence risk and disease-free survival (DFS) [14,22,23].

The aim of this study was to evaluate the prognostic and predictive significance of three invasive histopathological features—tumor budding (TB), lymphovascular invasion (LVI), and perineural invasion (PNI)—in patients surgically treated for colorectal carcinoma at the University Clinical Center of Kosovo (UCCK). Specifically, the study aimed to determine the association of these parameters with tumor stage (TNM classification), disease recurrence, and disease-free survival (DFS), and to identify which factors independently predict oncologic outcomes.

Materials and Methods.

A retrospective cohort study was conducted including patients treated at the Clinic of Abdominal Surgery and the

Department of Pathology, University Clinical Center of Kosovo (UCCK), between January 2020 and June 2025. Follow-up data collection continued until December 2025, and only patients with a minimum follow-up duration of 6 months were included in the final analysis. Eligible patients had histologically confirmed adenocarcinoma of the colon or rectum and complete clinicopathological documentation available for analysis. Among patients with rectal cancer, selected individuals with locally advanced disease received neoadjuvant chemoradiotherapy according to institutional multidisciplinary treatment protocols. Histopathological evaluation in these cases was based on postoperative pathological staging (ypTNM). Because of the retrospective design and incomplete treatment stratification, neoadjuvant therapy was not included as an adjustment variable in the multivariate analysis.

The variables collected included age, sex, tumor localization, type of surgical procedure, histological grade, TNM stage, and the presence of tumor budding (TB), lymphovascular invasion (LVI), and perineural invasion (PNI). Tumor budding was assessed according to the recommendations of the International Tumor Budding Consensus Conference (ITBCC, 2016) [5,18]. Assessment of tumor budding was performed on routine hematoxylin and eosin (H&E)-stained histological sections. Immunohistochemical staining with cytokeratin markers was not routinely utilized for tumor budding evaluation. Pathological reporting followed the criteria of the 8th edition of the College of American Pathologists (CAP) [21]. Statistical analysis was performed using IBM SPSS Statistics version 26.0. Descriptive statistics were used to summarize baseline characteristics. Comparative analyses included the chi-square test, Student's t-test, and Mann-Whitney U test, as appropriate. Binary logistic regression analysis was applied to identify independent predictors of disease recurrence. Receiver operating characteristic (ROC) curve analysis was used to evaluate the discriminatory performance of TB, LVI, and PNI by calculating the area under the curve (AUC). Disease-free survival (DFS) was analyzed using Kaplan-Meier survival curves, and differences between groups were assessed with the log-rank test.

Results.

The study cohort consisted of 243 patients, including 138 males (56.8%) and 105 females (43.2%), with a mean age of 63.4 years. Tumor localization was the rectum in 96 patients

(39.5%), the left colon in 87 patients (35.8%), and the right colon in 60 patients (24.7%). The most frequently performed surgical procedures were low anterior resection in 32.1% of cases, left hemicolectomy in 29.6%, right hemicolectomy in 24.3%, and abdominoperineal resection in 14.0%.

Histopathological evaluation demonstrated high tumor budding (BD3) in 71 patients (29.2%), lymphovascular invasion (LVI) in 83 patients (34.1%), and perineural invasion (PNI) in 65 patients (26.7%). Overall, 118 patients (48.6%) presented with at least one positive invasive histopathological factor (TB, LVI, or PNI). Regarding tumor differentiation, histological grade was G1 in 22 patients (9.1%), G2 in 156 patients (64.2%), and G3 in 65 patients (26.7%).

According to TNM staging, 48 patients (19.8%) were classified as stage I, 174 patients (71.6%) as stage II-III, and 21 patients (8.6%) as stage IV disease. During a mean follow-up period of 30.4 months (range: 6-48 months), 64 patients (26.3%) developed local or distant recurrence. The prevalence of lymphovascular invasion, perineural invasion, and high tumor budding was significantly higher among patients with recurrence compared with those without recurrence ($p < 0.001$ for all three variables). Kaplan-Meier survival analysis demonstrated significantly shorter median DFS in patients presenting with one or more positive invasive histopathological factors compared with patients without positive invasive factors. Median DFS was 22.4 months (95% CI: 18.7-26.1) versus 35.1 months (95% CI: 31.4-38.8), respectively (log-rank $p < 0.001$). Kaplan-Meier survival curves demonstrated significantly shorter DFS in patients with one or more positive invasive histopathological factors (Figure 1).

Discussion.

The present study, conducted at the University Clinical Center of Kosovo (UCCK) between 2020 and 2025, confirms the important prognostic role of tumor budding (TB), lymphovascular invasion (LVI), and perineural invasion (PNI) in patients undergoing surgical treatment for colorectal carcinoma. Nearly half of the cohort (48.6%) demonstrated at least one positive invasive histopathological factor, indicating that aggressive biological behavior is present in a substantial proportion of colorectal tumors. The database cutoff date for follow-up analysis was December 31, 2025.

Our findings showed that LVI, PNI, and high tumor budding (BD3) were all significantly associated with disease recurrence.

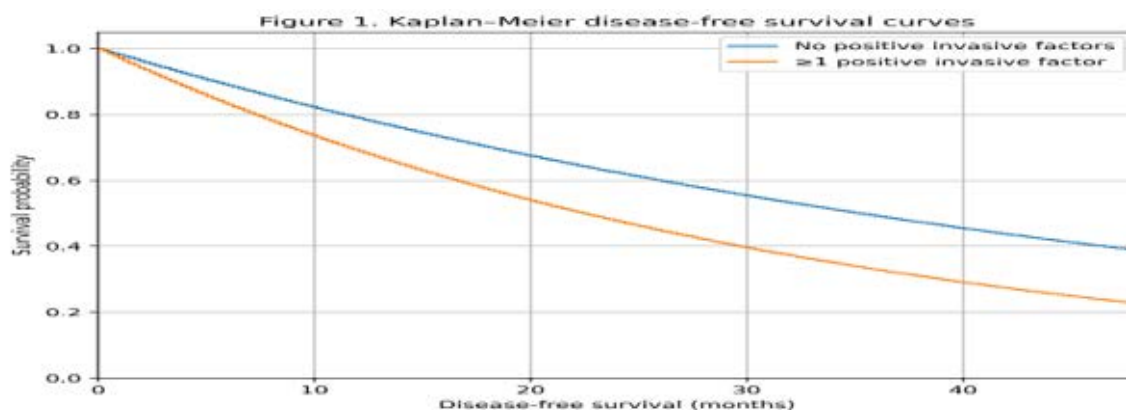


Figure 1. Kaplan-Meier disease-free survival curves according to invasive histopathological factors.

Table 1. Association between histopathological factors and disease recurrence.

Histopathological factors	Recurrence (+) n=64	Recurrence (-) n=179	p-value
LVI positive	47 (73.4%)	36 (20.1%)	<0.001
PNI positive	39 (60.9%)	26 (14.5%)	<0.001
High tumor budding (BD3)	41 (64.1%)	30 (16.8%)	<0.001

Abbreviations: LVI: lymphovascular invasion; PNI: perineural invasion.

Table 2. Binary logistic regression analysis of predictors of disease recurrence.

Prognostic factors	OR	95% CI	p-value
LVI (positive vs negative [reference])	4.72	2.46–9.03	<0.001
PNI (positive vs negative [reference])	3.91	1.98–7.72	<0.001
Tumor budding (BD3 vs BD1–2 [reference])	3.24	1.67–6.29	0.002
TNM stage (III–IV vs I–II [reference])	2.31	1.19–4.47	0.016

Abbreviations: OR: odds ratio; CI: confidence interval.

Table 3. Kaplan–Meier disease-free survival analysis according to invasive histopathological factors.

Group	Median DFS (months)	95% CI	Log-rank p-value
No positive invasive factors	35.1	31.4–38.8	
≥1 positive invasive factor	22.4	18.7–26.1	<0.001

In multivariate logistic regression analysis, each marker remained an independent predictor of recurrence, with LVI demonstrating the strongest effect (OR 4.72; 95% CI 2.46–9.03). These results are consistent with previous studies reporting vascular and perineural invasion as major pathways of tumor dissemination and relapse [5,6,11,13,19]. Several authors, including Lugli et al. and Betge et al., have similarly identified LVI as a marker of systemic spread and unfavorable oncologic prognosis [5,6].

The prognostic superiority of LVI was further supported by ROC curve analysis, in which LVI achieved the highest predictive accuracy (AUC = 0.781), compared with PNI (AUC = 0.752) and tumor budding (AUC = 0.735). This suggests that vascular invasion may serve as a practical surrogate marker of tumor aggressiveness and micrometastatic potential, supporting its use in postoperative risk stratification and treatment planning [14,22].

Survival analysis also demonstrated a clinically meaningful impact of these markers. Patients without positive invasive factors had significantly longer median disease-free survival (DFS) compared with those presenting at least one positive invasive factor (35.1 months; 95% CI: 31.4–38.8 vs. 22.4 months; 95% CI: 18.7–26.1, log-rank $p < 0.001$). This finding indicates that even a single invasive histopathological feature may adversely affect oncologic outcomes and should prompt closer surveillance and consideration of adjuvant therapy in selected patients [9,10,23].

From a biological perspective, these markers reflect complementary mechanisms of tumor progression. Tumor budding is considered a morphological correlate of epithelial–mesenchymal transition and early metastatic activation. Lymphovascular invasion represents dissemination through vascular and lymphatic channels, whereas perineural invasion reflects neurotropic spread and is often associated with locoregional recurrence and more advanced disease. Together, these factors identify an aggressive tumor phenotype that may not be fully captured by conventional TNM staging alone [5–7,18–20].

The strengths of this study include a relatively homogeneous histopathological evaluation and the application of objective

statistical methods, including logistic regression, ROC analysis, and Kaplan–Meier survival models. However, several limitations should be acknowledged. The study was retrospective, performed in a single institution, and based on a moderate sample size. In addition, molecular biomarkers such as KRAS, NRAS, BRAF, or microsatellite instability (MSI) status were not available for correlation, which may further refine prognostic modeling [22,23].

Another limitation of this study is that the impact of neoadjuvant chemoradiotherapy in patients with rectal cancer was not separately analyzed. Since preoperative treatment may influence histopathological features such as tumor budding, lymphovascular invasion, perineural invasion, and pathological staging, this factor may represent a potential confounding variable. Selection bias inherent to the retrospective study design should also be considered when interpreting the study findings. The relatively limited follow-up duration for a subset of recently enrolled patients may have influenced long-term survival estimation.

Overall, our results support the routine assessment of tumor budding, lymphovascular invasion, and perineural invasion as valuable histopathological predictors of recurrence and survival in colorectal carcinoma. Their systematic incorporation into pathology reports and multidisciplinary decision-making may improve individualized patient management.

Conclusion.

This retrospective cohort study of 243 patients with colorectal carcinoma treated at the University Clinical Center of Kosovo (UCCCK) confirms the prognostic importance of invasive histopathological markers, namely lymphovascular invasion (LVI), perineural invasion (PNI), and tumor budding (TB). Each of these factors was independently associated with disease recurrence, while LVI demonstrated the highest predictive accuracy (AUC = 0.781) [5,6,14].

Patients with one or more positive invasive features had significantly reduced median disease-free survival (DFS) compared with those without such findings (22.4 months; 95% CI: 18.7–26.1 vs. 35.1 months; 95% CI: 31.4–38.8; log-rank $p < 0.001$).

These results emphasize the value of comprehensive histopathological assessment as an important complement to conventional TNM staging [8,21]. Incorporation of these markers into routine pathology reporting may improve oncologic risk stratification, guide postoperative management, and support long-term follow-up strategies in colorectal carcinoma [14,22,23].

Recommendations.

Routine assessment of tumor budding, lymphovascular invasion (LVI), and perineural invasion (PNI) should be systematically incorporated into all histopathological reports of colorectal carcinoma [5-7,14]. Patients demonstrating one or more of these adverse features should be considered a high-risk subgroup and may benefit from intensified clinical, radiological, and oncologic follow-up [15-17,25].

Future prognostic models should integrate clinicopathological parameters with molecular biomarkers in order to improve the accuracy of recurrence and survival prediction [22,23]. In addition, these findings should be validated through prospective, multicenter studies to better define their therapeutic implications and support broader implementation at national and regional levels [14,22,23].

Conflict of Interest.

The authors declare no conflict of interest.

Ethical Approval.

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of the University Clinical Center of Kosovo (UCCK). Due to the retrospective nature of the study, the requirement for informed consent was waived.

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