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Prognostic Value of *BAP1* Protein Expression in Uveal Melanoma

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ABSTRACT

BACKGROUND: Uveal melanoma is the most common malignant ocular tumor in adults. It carries a high risk of metastatic spread and death. Typical clinical and morphological signs fail to provide accurate disease prognosis. Thus, investigations of molecular markers such as BAP1 expression are warranted to improve survival prediction and optimize treatment strategies.

AIM: The work aimed to determine the prognostic value of the histological type of uveal melanoma and BAP1 expression for survival of patients.

METHODS: We performed a retrospective analysis of the data of 68 patients with uveal melanoma who received curative treatment. A standard procedure was used for the morphological examination of enucleated eyes. BAP1 protein expression was evaluated using immunohistochemistry. Survival was analyzed using Kaplan–Meyer methods and a Cox proportional hazard model.

RESULTS: Median survival in patients with homo- or heterogeneous (focal, mosaic) loss of BAP1 expression was 48 months, whereas patients with homogeneous BAP1 expression of variable degree (mild to severe) did not achieve the median by the end of follow-up. The log-rank test showed statistically significant differences between these groups (χ^2=4.344; p=0.037). Mortality risk for patients with homo- or heterogeneous loss of BAP1 expression was 2.6 times higher (HR=2.602, 95% confidence interval: 0.573–0.96). However, mortality risk for patients with epithelioid cell and mixed tumor types was only 1.27 times higher than for patients with spindle cell cancer (HR=1.265, 95% confidence interval: 1.062–2.846).

CONCLUSION: The study highlights the importance of using molecular genetic methods, including immunohistochemistry of BAP1, to predict disease outcomes more accurately.

Keywords: uveal melanoma; BAP1; histologic type; survival.

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Прогностическая значимость экспрессии белка BAP1 при увеальной меланоме

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АННОТАЦИЯ

Обоснование. Увеальная меланома — наиболее распространённая злокачественная опухоль глаза у взрослых, характеризующаяся высоким риском метастазирования и летального исхода. Традиционные клинические и морфологические признаки не позволяют точно спрогнозировать течение заболевания. В связи с этим актуально изучение молекулярных маркеров, таких как экспрессия белка BAP1, для уточнения прогноза выживаемости и выбора оптимальной тактики ведения пациентов.

Цель — определить прогностическое значение гистологического типа увеальной меланомы и экспрессии белка BAP1 в оценке выживаемости пациентов.

Материалы и методы. Проведён ретроспективный анализ данных 68 пациентов с увеальной меланомой, перенёсших ликвидационное лечение. Для морфологического исследования энуклеированных глаз применяли стандартную методику. Экспрессию белка BAP1 оценивали с использованием иммуногистохимического исследования. Выживаемость анализировали с помощью методов Каплана–Мейера и модели пропорциональных рисков Кокса.

Результаты. Медиана выживаемости пациентов с равномерно или гетерогенно (очагово, мозаично) отсутствующей экспрессией BAP1 составила 48 мес., тогда как для пациентов с равномерно положительной экспрессией BAP1 разной интенсивности (от слабой до выраженной) медиана не достигнута к концу наблюдения. Логарифмический ранговый критерий показал статистически значимые различия между данными группами (χ^2=4,344; p=0,037). Риск летального исхода с равномерно или гетерогенно отсутствующей экспрессией BAP1 был в 2,6 раза выше (HR=2,602, 95% доверительный интервал 0,573–0,96). При этом риск летального исхода для пациентов с эпителиоидноклеточным и смешанным типами опухоли всего в 1,27 раза выше, чем для пациентов с веретеновидноклеточным типом (HR=1,265, 95% доверительный интервал 1,062–2,846).

Заключение. Исследование подчеркивает важность использования молекулярно-генетических методов, включая иммуногистохимический анализ BAP1, для более точного прогнозирования исхода заболевания.

Ключевые слова: увеальная меланома; BAP1; гистологический тип; выживаемость.

Как цитировать

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BACKGROUND

Uveal melanoma (UM) is the most common primary intraocular malignant tumor [1]. The UM incidence in Western countries is about 5 cases per 1 million people per year. In Moscow, the incidence of UM is 9 per 1 million adults. [2]. At diagnosis, 2%–4% of patients already have distant metastases [3]. A total of 30% of patients with UM develop metastases within 5 years after the curative treatment of the primary tumor. Median survival after detection of distant liver metastases is 4–15 months [4]. There are many prognostic factors of a risk of metastasis. They include various clinical, morphological, and genetic factors [5].

One of the significant histological parameters is the tumor type—epithelioid-, spindle-, or mixed-cell [6]. Epithelioid-cell UM is associated with worse prognosis compared with spindle-cell UM, which is of more favorable prognosis.

Recent studies of UM genome have identified molecular subsets indicative of an individual risk of metastasis [7]. This molecular genetic classification of UM is based on chromosomal aberrations, mutations in key genes, and mRNA expression of specific genes in tumor cells. The most significant prognostic factor is the tumor suppressor gene *BRCA* (*BReast CAncer*) associated protein1 (*BAP1*) [7–9].

The *BAP1* gene is located on chromosome 3p21.1, which is often completely deleted in UM. Monosomy 3 is considered a relatively early event in the UM pathogenesis, and several studies have shown that this aberration significantly correlates with patient survival [10, 11]. BAP1 is a deubiquitinating enzyme (DUB) with tumor suppressive activity, and its loss is associated with a higher risk of tumor growth and metastasis. Published data suggest that immunohistochemistry significantly correlates with Sanger sequencing in predicting the UM metastatic potential [12, 13].

The study aimed to determine the prognostic value of the UM histological type and BAP1 expression for patient survival.

METHODS

We performed a retrospective analysis of the medical records and enucleated material of 68 patients (68 eyes) with stage IIIA–IIIC UM after curative surgical treatment (enucleation or exenteration) in the ophthalmological department of the Moscow Regional Research and Clinical Institute named after M. F. Vladimirskiy from 2014 to 2023. UM was staged using the UICC TNM (8th revision, 2017).

Patients were predominantly male (1.3:1). The mean age of patients was 64.9 years (median: 65.8 years). All enrolled patients were followed up. The mean follow-up period was 42 months (11–105 months), and the median follow-up period was 31 months. A total of 27 (39.7%) of patients were followed up until death, and the data were censored because of ongoing follow-up at the time of the study in 41 (60.3%) patients.

Homogeneous distribution of age, sex, tumor size, and ciliary body involvement minimized the influence of clinically significant prognostic factors on the UM prognosis worsening. For this purpose, patients with extraocular tumor growth were excluded from the study.

A standard procedure was used for the morphological examination of enucleated eyes. The material was fixed in 10% buffered formalin and paraffin embedded using a standard procedure. Serial 3 μm paraffin sections were de-waxed per a standard procedure and stained with hematoxylin and eosin. To assess BAP1 expression, immunohistochemistry of serial 2 μm paraffin sections was performed using a standard procedure. The intensity of marker expression was evaluated semi-quantitatively based on antigen concentration and location: (–) = negative reaction; (+) = weak focal reaction; (++) = moderate reaction; (+++) = strong cytoplasmic reaction.

The UM histological type was assessed using the criteria of The International Histological Classification of Tumors 8th edition (2018) (G1, G2, G3), which stated that spindle-cell melanoma is a tumor with over 90% of spindle cells, mixed-cell melanoma is a tumor with 11%–89% of epithelioid cells, and epithelioid-cell melanoma is a tumor with over 90% of epithelioid cells.

IBM SPSS Statistics version 27 (IBM Corp., Armonk, New York, USA) and Microsoft Office Excel 2016 (Microsoft, USA) were used for statistical data processing. Survival during the entire follow-up was analyzed using the Kaplan–Meier method; the significance of differences was assessed using the log-rank test. The Cox proportional hazards model was used to assess the effect of the tested factors on survival.

RESULTS

The study revealed choroidal melanoma in 66.2% (45/68) of eyes. The tumor was located in the choroid and ciliary body in 27.9% (19/68) of cases and in the choroid and iris in only 5.9% (4/68) of cases. The mean tumor diameter and thickness were 15.5 (12.7–17.2) and 9.5 (7.8–13.5) mm, respectively.

The histological examination found a spindle-cell tumor in 23/68 (33.8%) cases. Epithelioid-cell and mixed-type tumors were observed in 33/68 (48.5%) and 12/68 (17.6%) cases, respectively. We did not find statistically significant correlation between the tumor location and histological type ($p = 0.278$). Necrosis and hemorrhages were detected in 14.5% (9/68) and 16.4%

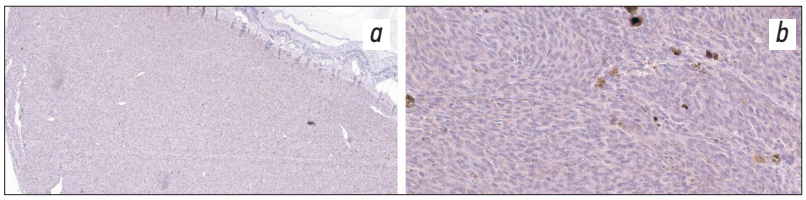

Fig. 1. Immunohistochemistry of BAP1: *a*, negative BAP1 expression, ×50; *b*, false positive reaction in pigment, ×400.

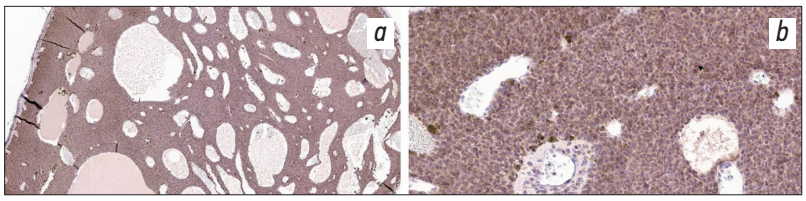

Fig. 2. Immunohistochemistry BAP1: *a*, homogeneous diffuse cytoplasmic expression of BAP1, ×50; *b*, granular expression of BAP1 over the entire tumor area, ×400.

(10/68) of eyes, respectively. Scleral infiltration was detected in 48.5% (33/68) of eyes. The resection margins were negative in 98.5% (67/68) of cases and positive in only one (1.5%) case. UM is usually pigmented, and the non-pigmented form was found only in 11.8% (8/68) of eyes. The pigmentation severity varied from 5% to 100% of tumor volume.

Analysis of BAP1 expression revealed a positive and negative reaction in 63.2% (43/68) and 36.8% (25/68) of cases, respectively (see Figs. 1, 2).

The intensity of BAP1 expression was the following: weak reaction (1 point) in 41.9% (18/43) of cases; moderate reaction (2 points) in 41.9% (18/43); strong reaction (3 points) in 16.3% (7/43). Notably, the analysis of heavily pigmented tumors was most challenging because of a false positive reaction. Pigmentation was considered heavy when over 50% of the total tumor volume was pigmented. These tumors were found in 4 (4/68; 5.9%) cases. However, 44.1% (19/43) of cases showed a true heterogeneous, mosaic reaction pattern. In 16/19 cases, the reaction was heterogeneous, with no reaction either at the tumor apex or base periphery in 7/16 and 9/16 samples, respectively. The reaction demonstrated a mosaic pattern in 3/19 cases. Comparison of the histological type with the intensity of IHC staining revealed that epithelioid-cell or mixed-cell tumors were observed in 72% of eyes in the group with a completely negative reaction (no BAP1 expression). Notably, not even single BAP1-negative tumor cells were observed in all 7/43 cases with a strong IHC BAP1 reaction, and the staining was homogeneously intensive, which indicates complete expression of native BAP1 in the entire tumor.

Kaplan–Meier survival analysis was performed in two histological groups (epithelioid-cell/mixed-cell vs. spindle-cell tumors). Due to insufficient number of patients, groups with mixed-cell and epithelioid-cell tumors were pooled. Mean survival was 62.2 months in these patients and 72.9 months in patients with a spindle-cell tumor. Overall mean survival was 65.8 months.

Median survival was 63 months in patients with an epithelioid-cell/mixed-type tumor and was not determined in patients with a spindle-cell tumor, as a significant proportion of their data was censored. However, the endpoint in this group was not achieved by the end of follow-up.

The Mantel–Cox log-rank test was used to assess differences in survival between the groups with different histological tumor types. The analysis showed non-significant differences between the groups ($\chi^2 = 1.161$; $p = 0.281$) (see Fig. 3).

To assess overall survival depending on BAP1 expression using the Kaplan–Meier method, patients were divided into 2 groups based on 4 criteria:

- Criterion 1: loss of BAP1 expression compared with any BAP1 expression level (weak to strong) (see Fig. 4, *a*).
- Criterion 2: lost or weak BAP1 expression compared with moderate or strong BAP1 expression (see Fig. 4, *b*).
- Criterion 3: lost, weak, or moderate BAP1 expression compared with strong BAP1 expression (see Fig. 4, *c*).
- Criterion 4: homo- or heterogeneous (focal, mosaic) loss of BAP1 expression compared with homogeneous weak, moderate, or strong BAP1 expression in the tumor. The results are illustrated in Fig. 5.

The first three sampling criteria missed intratumor heterogeneity (focal or mosaic). The results showed that the between-group differences were not statistically significant: $\chi^2 = 0.62$ and $p = 0.431$ for criterion 1; $\chi^2 = 0.933$ and $p = 0.334$ for criterion 2; $\chi^2 = 0.007$ and $p = 0.932$ for criterion 3. Comparison of overall survival in the group with homo- or heterogeneous (focal, mosaic)

loss of BAP1 expression vs. the group with homogeneous BAP1 expression of variable IHC reaction intensity demonstrated that mean survival was 56.4 and 75.4 months, respectively. Median survival was 48 months in patients with homo- or heterogeneous (focal, mosaic) loss of BAP1 expression, but was not determined in patients with homogeneous BAP1 expression as the endpoint was not achieved in a significant proportion of patients by the end of follow-up. The Mantel–Cox log-rank test demonstrated that the differences between the groups can be considered statistically significant ($\chi^2 = 4.344$ $p = 0.037$).

Data of this sample were also analyzed using the Cox proportional hazards model. The results showed that mortality risk for patients with homo- or heterogeneous (focal, mosaic) loss of BAP1 expression was 2.6 times higher (*HR* = 2.602; 95% confidence interval: 0.573–0.96) than for patients with homogeneous *BAP1* expression of variable degree (weak to strong). However, mortality risk for patients with epithelioid-cell and mixed tumor types was only 1.27 times higher than for patients with spindle-cell cancer (*HR* = 1.265; 95% confidence interval: 1.062–2.846).

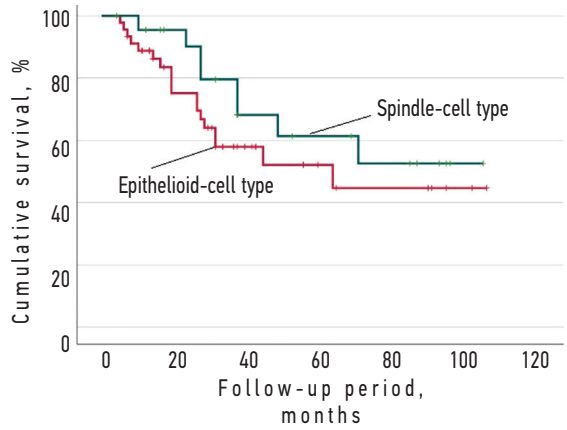

Fig. 3. Kaplan–Meier survival curves for patients with uveal melanoma. Log-rank test: $\chi^2 = 1.161$; $p = 0.281$.

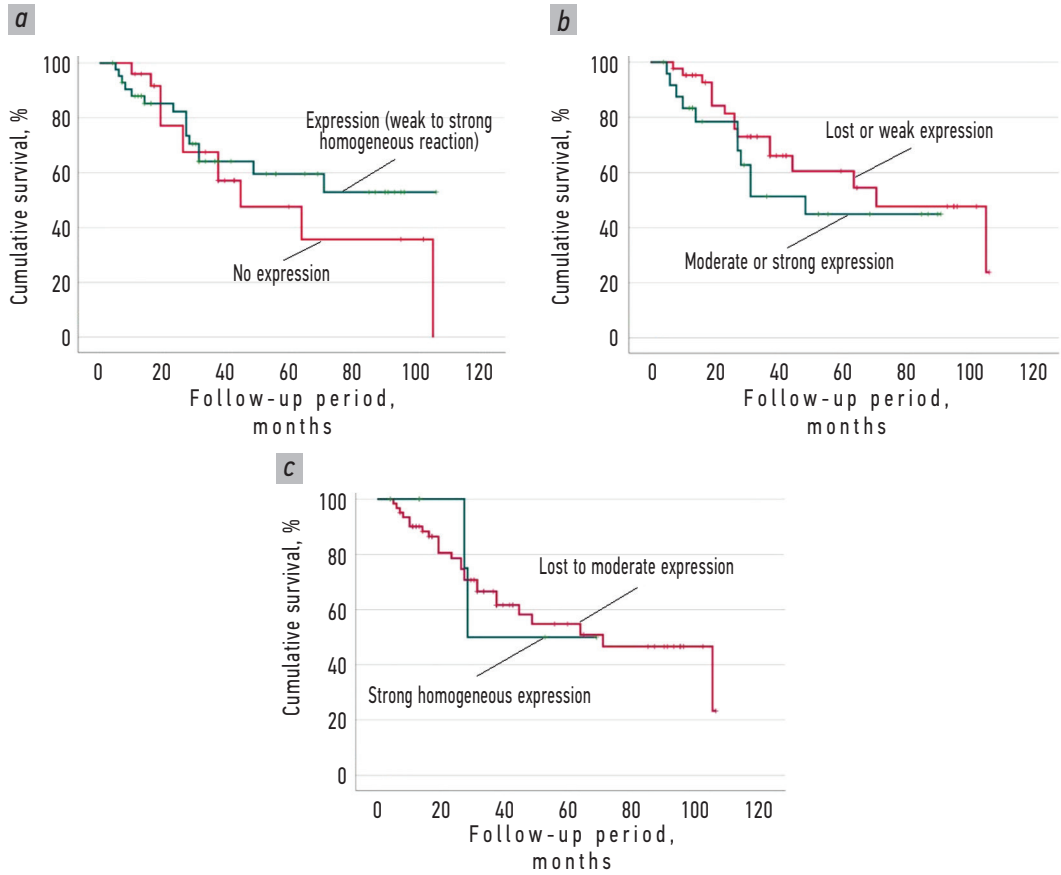

Fig. 4. Kaplan–Meier curves of overall survival: *a*, criterion 1, log-rank test: $\chi^2 = 0.62$, $p = 0.431$; *b*, criterion 2, log rank: $\chi^2 = 0.933$, $p = 0.334$; *c*, criterion 3, log rank: $\chi^2 = 0.007$, $p = 0.932$.

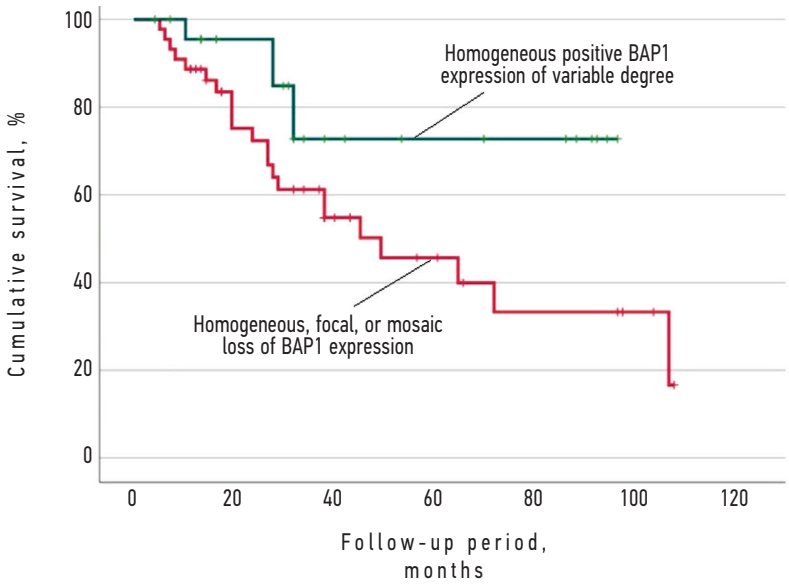

Fig. 5. Kaplan–Meier survival curves for patients with uveal melanoma, criterion 4. Log-rank test: $\chi^2 = 4.344$; $p = 0.037$.

DISCUSSION

Molecular genetic methods to assess the UM prognosis are currently limited. Postoperative management of patients with UM is often based on clinical and morphological examinations. However, each tumor is unique and typically consists of different cell subpopulations having their inherent morphological, genetic, and epigenetic features. Thus, a tumor is most often morphologically heterogeneous, which challenges the prognosis. However, it is known that the higher the epithelioid cell proportion, the worse the survival [14].

Previous studies demonstrated significant intratumor heterogeneity in both phenotype and genotype of UM [15–19]. Herwig-Carl et al. [16] studied heterogeneity of the effect of epigenetic factors (global levels of histone acetylation, DNA methylation, and ubiquitination) on expression of many different proteins in tumor cells. The authors demonstrated that the cells with the greatest metastatic potential were located on the tumor periphery and in the scleral emissarial channels. The *BAP1* gene plays an important role in epigenetic regulation of UM metastatic activity [20]. Pandiani et al. [17] found several different transcription profiles using single-cell RNA sequencing in a tumor, which indicates cells with different functions and variable intratumor metastatic potential. In general, tumor heterogeneity is associated with poor prognosis [21–24]. However, data on the prognostic value of heterogeneous BAP1 expression in UM have not yet been obtained. We aimed to determine BAP1 expression using IHC in different tumor areas and revealed heterogeneity of expression and distribution of this marker in most of the tumor volume. We found Russian studies of BAP1 expression in aspirated material after fine-needle aspiration using immunocytochemistry and molecular genetic methods and compared their data. The results showed no prognostic value of BAP1 expression determined by immunocytochemistry [25, 26]. In our point of view, the above results are explained by the fact that 100 tumor cells were tested without considering the sampling area, and therefore tumor heterogeneity.

Published data showed that the histological tumor type is associated with survival of patients with UM [27, 28]. We did not find a statistically significant dependence of patient survival on the morphological characteristics of UM. This can most probably be caused by the large tumor size and small sample size. Assessment of the effect of genetic and morphological factors on overall survival of patients with UM revealed that the *BAP1* status affects the disease outcome significantly greater than the histological type of tumor cells. Mortality risk in the case of lost BAP1 expression, both complete and partial (if intratumor heterogeneity occurs), is significantly higher than in epithelioid-cell or mixed tumor types. The prognostic value of this genetic factor is significant even if focal or mosaic loss of BAP1 expression is considered, whereas risk stratification only by averaged intensity of BAP1 expression does not provide a statistically significant result.

CONCLUSION

The assessment of prognosis of patients with UM should be based not only on clinical and morphological, but also on genetic criteria. Our study showed a special practical value of IHC of BAP1 expression for prognosis.

It also demonstrated the importance of intratumor heterogeneity of both morphological and genetic characteristics of UM. Nevertheless, further studies are warranted to analyze possible patterns of spatial distribution of prognostically unfavorable genetic factors within the tumor, which can significantly contribute to new methods for determining UM prognosis.

ADDITIONAL INFO

Author contributions: I.D. Kim: conceptualization and study design, data collection, data analysis and interpretation, statistical analysis, and writing—original draft; E.E. Grishina: conceptualization and study design, writing—review & editing, final approval of the version to be published, writing—original draft; G.R. Setdikova: conceptualization and study design, writing—original draft, writing—review & editing, and data analysis and interpretation. All the authors approved the final version of the manuscript to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval: The study was approved by the independent ethics committee of the Moscow Regional Research and Clinical Institute (Protocol No. 2 dated 2023 Feb 02). All participants provided written informed consent prior to inclusion in the study. The study protocol was not registered.

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Disclosure of interests: The authors have no relationships, activities, or interests for the last three years related to for-profit or not-for-profit third parties whose interests may be affected by the content of the article.

Statement of originality: No previously obtained or published material (text, images, or data) was used in this article.

Data availability statement: All data generated during this study are available in this article.

Generative AI: No generative artificial intelligence technologies were used to prepare this article.

Provenance and peer-review: This paper was submitted unsolicited and reviewed following the standard procedure. The peer review process involved two external reviewers, a member of the editorial board, and the in-house scientific editor.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. И.Д. Ким — существенный вклад в концепцию и дизайн работы, сбор, анализ и обработка материала, статистическая обработка данных, написание текста; Е.Е. Гришина — существенный вклад в концепцию и дизайн работы, редактирование, окончательное утверждение версии, подлежащей публикации, написание текста; Г.Р. Сетдикова — существенный вклад в концепцию и дизайн работы, написание текста, редактирование, анализ и обработка материала. Авторы одобрили версию для публикации, а также согласились нести ответственность за все аспекты работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и добросовестностью любой ее части.

Этическая экспертиза. Проведение исследования одобрено независимым комитетом по этике при ГБУЗ МО «Московский областной научно-исследовательский клинический институт им. М.Ф. Владимирского» (протокол № 2 от 02.02.2023). Все участники исследования добровольно подписали форму информированного согласия до включения в исследование. Протокол исследования не регистрировали.

Источники финансирования. Отсутствуют.

Раскрытие интересов. Авторы заявляют об отсутствии отношений, деятельности и интересов за последние три года, связанных с третьими лицами (коммерческими и некоммерческими), интересы которых могут быть затронуты содержанием статьи.

Оригинальность. При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).

Доступ к данным. Все данные, полученные в настоящем исследовании, доступны в статье.

Генеративный искусственный интеллект. При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.

Рассмотрение и рецензирование. Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали два внешних рецензента, член редакционной коллегии и научный редактор издания.

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