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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 ВИНИТИ 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 ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

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. Корректура авторам не высылается, 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 compu-ter-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 საყურადღებოდ!

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, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის 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 ფჩხილებში 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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MACHINE LEARNING-BASED IDENTIFICATION OF KEY GENES AND DEVELOPMENT OF A PREDICTIVE NOMOGRAM FOR PERIODONTITIS DIAGNOSIS

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Abstract.

Background: Periodontitis is a prevalent chronic inflammatory disease affecting tooth-supporting tissues. Identifying molecular features that distinguish diseased from clinically healthy periodontal tissue sites may support biomarker discovery and improve molecular characterization of the disease.

Methods: Gene expression datasets GSE16134 (development set) and GSE10334 (external validation set) were obtained from the Gene Expression Omnibus database. Differentially expressed genes (DEGs) were identified using $|\log_2 \text{fold change}| > 2$ and $P < 0.05$. Nine machine learning algorithms—Random Forest (RF), Support Vector Machine (SVM), K-Nearest Neighbors (KNN), LASSO, Gradient Boosting Machine (GBM), Generalized Linear Model (GLM), XGBoost (XGB), Decision Tree (DT), and Neural Network (NNET)—were applied to screen feature genes. The top five RF-ranked feature genes were used to construct a nomogram model. Model performance was evaluated using ROC curve analysis, decision curve analysis, and calibration curves.

Results: We identified 12 DEGs, including 2 upregulated (AADACL2, DSC1) and 10 downregulated genes. RF and LASSO demonstrated the strongest and closely comparable discrimination among the nine algorithms. Five critical genes (IGHM, MZB1, DSC1, AADACL2, CXCL6) were identified. The integrated nomogram achieved an AUC of 0.900 (95% CI: 0.842-0.949) in the external validation dataset. Individual genes also showed satisfactory discriminative performance (AUC: 0.816-0.875).

Conclusions: This study established a machine learning framework for identifying periodontitis-associated genes and developed a five-gene nomogram with strong discriminative performance. The identified genes represent candidate molecular biomarkers, and the integrated signature may assist discrimination between diseased and clinically healthy periodontal tissue sites. Further patient-level and prospective validation is warranted before clinical implementation.

Key words. Periodontitis, machine learning, nomogram, biomarkers.

Introduction.

Periodontitis is a chronic inflammatory disease affecting the tooth-supporting tissues, characterized by progressive destruction of the periodontal ligament and alveolar bone, ultimately leading to tooth loss if left untreated [1]. According to the Global Burden of Disease Study 2019, severe periodontitis affects approximately 1.1 billion people worldwide, making it the sixth most prevalent human disease and imposing substantial economic and health burdens on healthcare systems globally [2]. Beyond its local effects on oral health, periodontitis has been increasingly recognized as a risk factor for various systemic diseases, including cardiovascular disease, diabetes mellitus, rheumatoid arthritis, and adverse pregnancy outcomes, underscoring its significance as a public health concern [3,4]. The pathogenesis of periodontitis involves complex interactions between pathogenic microbiota, host immune responses, and genetic susceptibility factors, resulting in dysregulated inflammation and tissue destruction [5]. Despite advances in understanding periodontitis etiology, early diagnosis and risk stratification remain challenging due to the heterogeneity of disease presentation and the lack of reliable molecular biomarkers.

Recent developments in high-throughput sequencing technologies and bioinformatics have revolutionized our ability to identify disease-associated genes and molecular signatures [6]. Gene expression profiling studies have revealed distinct transcriptomic alterations in periodontal tissues, providing insights into the molecular mechanisms underlying periodontitis pathogenesis [7,8]. However, translating these findings into clinically applicable diagnostic tools remains a significant challenge, as traditional differential expression analysis often generates extensive gene lists without clear prioritization of the most critical biomarkers [9]. Machine learning (ML) algorithms have emerged as powerful tools for feature selection and predictive model construction in biomedical research, offering superior performance in identifying key genes from complex genomic datasets [10]. Several studies have successfully applied ML approaches to various oral diseases, demonstrating improved diagnostic accuracy compared to conventional methods [11,12]. Nevertheless, comprehensive comparative analyses of multiple ML algorithms for periodontitis biomarker identification remain limited, and the development of validated predictive models for clinical application is still in its infancy.

Integration of multiple ML algorithms can enhance the robustness of feature selection by identifying genes that demonstrate high importance across different computational approaches [13]. Recent studies have shown that ensemble methods and comparative ML strategies can improve biomarker discovery and reduce algorithm-specific bias in small-sample studies [14,15]. Comparative evaluation of multiple ML algorithms for periodontitis-related gene signature identification remains limited, particularly when coupled with a compact nomogram integrating selected transcriptomic features.

In this study, we aimed to identify key genes associated with periodontitis through comprehensive ML-based feature selection and to construct a transcriptome-based model for discriminating periodontal tissue/site status. We analyzed gene expression data from the GEO database, applied nine different ML algorithms to identify informative genes, and constructed a

nomogram integrating the top-ranked feature genes. The model's discriminative performance was further evaluated in an external GEO dataset. Our findings provide a comparative machine learning perspective on periodontitis-associated molecular signatures and a basis for future validation of transcriptomic classification tools.

Materials and Methods.

Data Sources and Preprocessing:

Gene expression datasets related to periodontitis were retrieved from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/) using the keyword "periodontitis". GSE16134 was used as the development dataset and contains 310 gingival tissue samples from 120 patients, including 241 diseased/periodontitis sites and 69 control or clinically unaffected sites according to the source annotations. GSE10334 was used as an external validation dataset and contains 247 gingival tissue samples from 90 patients, including 183 diseased sites and 64 clinically healthy sites. Because the analytical outcome in this study was gingival tissue/site status, the sample/site rather than the individual patient was treated as the unit of analysis. Raw expression data were downloaded and processed using R software. For microarray data, background correction, normalization, and log2 transformation were performed using the limma package. Probe annotations were conducted using the corresponding platform annotation files from the GEO database. When multiple probes mapped to the same gene, the probe with the highest mean expression value was retained as the representative value for that gene. Legacy gene symbols present in the original platform annotation were retained for reproducibility, while updated nomenclature is noted in the text where relevant.

Identification of Differentially Expressed Genes:

Differential expression analysis between diseased and control/clinically healthy gingival tissue sites was performed using the limma package in R. Genes with $|\log_2\text{fold change (FC)}| > 2$ and a nominal P value < 0.05 were defined a priori as differentially expressed genes (DEGs). The relatively stringent fold-change threshold was used to prioritize genes showing large expression differences for subsequent exploratory machine learning analysis.

Machine Learning-Based Feature Selection:

To identify the most critical genes associated with periodontitis and evaluate their predictive performance, we applied nine machine learning algorithms to the identified DEGs: (1) Support Vector Machine (SVM) with radial basis function kernel, (2) Random Forest (RF) with 500 trees, (3) K-Nearest Neighbors (KNN) with k=5, (4) Least Absolute Shrinkage and Selection Operator (LASSO) regression with cross-validation, (5) Gradient Boosting Machine (GBM), (6) Generalized Linear Model (GLM) with binomial family, (7) XGBoost (XGB), (8) Decision Tree (DT), and (9) Neural Network (NNET).

All machine learning analyses were implemented using the caret package in R. The GSE16134 development dataset was randomly split at the sample/site level into training (70%) and testing (30%) subsets, consistent with the site-level classification objective of this study. The 70:30 hold-out split and 10-fold cross-validation served different purposes: the hold-out split provided separate subsets for model development and comparison, whereas 10-fold cross-validation was used for hyperparameter optimization during model training. Residual distributions and root mean square error (RMSE) were used as supplementary model-diagnostic measures, while area under the receiver operating characteristic curve (AUC) was treated as the primary measure of discriminative performance. The internal hold-out results were used principally for comparative evaluation of algorithms within the development dataset rather than as a stand-alone estimate of patient-level generalizability.

Construction and Validation of Nomogram Model:

The top five feature genes ranked by RF importance scores were selected to construct a parsimonious and interpretable nomogram using the rms package in R. Random Forest was used for feature ranking, whereas the nomogram represented a separate multivariable model integrating the five selected gene-expression predictors for the binary gingival tissue/site-status outcome. Each gene was assigned a corresponding point value based on its expression level, and the total points were converted to the model-estimated probability of a diseased periodontal tissue/site status. Model performance was assessed through multiple approaches: (1) decision curve analysis (DCA) was used to characterize potential net benefit across threshold probabilities relative to the 'treat all' and 'treat none' reference strategies; (2) calibration curves were generated to assess agreement between model-predicted and observed site-status probabilities, with bootstrap resampling (1000 iterations) used for bias correction; and (3) ROC curves were plotted, and AUC values with 95% confidence intervals (CI) were calculated to quantify discrimination. The calibration curve in Figure 3C represents internal bootstrap-corrected calibration within the development data and was not intended as an external calibration analysis.

External Validation:

To assess whether the identified feature genes retained discriminative value in a separate GEO dataset, validation was performed using GSE10334. The same preprocessing and normalization procedures were applied to the validation dataset to ensure consistency, and the same five-gene feature definition was retained without additional feature screening. ROC curve analysis was conducted for both individual feature genes and the integrated nomogram model. AUC values with 95% CI were calculated using the pROC package in R to evaluate site-level discrimination in the validation dataset. Accordingly, GSE10334 is referred to throughout this manuscript as an external validation dataset rather than as a prospective or participant-independent clinical cohort.

Statistical Analysis:

All statistical analyses were performed using R software (version 4.4). Continuous variables were compared between groups using Student's t-test, depending on data distribution assessed by the Shapiro-Wilk test. For differential expression analysis, the prespecified DEG criterion was $|\log_2 FC| > 2$ together with a nominal $P < 0.05$, consistent with the criteria reported in the Differential Expression Analysis section and Results. For machine learning model comparisons, performance

metrics were calculated with 95% confidence intervals. Because the primary analytical unit was the gingival tissue/site, the reported performance estimates and confidence intervals should be interpreted as site-level rather than patient-level measures.

Results.

Identification of Differentially Expressed Genes in Periodontitis:

To identify genes associated with periodontitis-related tissue status, we obtained the GSE16134 dataset from the Gene Expression Omnibus database and performed differential expression analysis between diseased and control/clinically unaffected gingival tissue sites. Using the prespecified filtering criteria of $|\log_2 \text{fold change (FC)}| > 2$ and $P < 0.05$, we identified 12 DEGs (Figure 1). Among these DEGs, 2 genes (AADACL2 and DSC1) exhibited elevated expression in diseased sites, while 10 genes (CXCL6, LOC100293211, IGLL5, IGK, IGHM, TENT5C [legacy symbol FAM46C], TNFRSF17, CD79A, MZB1, and SPAG4) showed reduced expression compared with control/clinically unaffected sites. LOC100293211 is retained here as the legacy microarray annotation although the corresponding NCBI record has subsequently been discontinued. Hierarchical clustering demonstrated clear separation between the two site-status groups based on the expression patterns of these 12 DEGs, indicating their potential relevance for tissue-level discrimination. Several downregulated genes were immunoglobulin-related genes (IGLL5, IGK, IGHM), suggesting that immune-cell composition and/or local humoral immune activity may differ between diseased and control periodontal tissues.

Machine Learning-Based Feature Selection and Model Performance Comparison:

To identify the most informative genes associated with periodontal tissue status and compare predictive algorithms, we applied nine machine learning algorithms—including SVM, RF, KNN, LASSO, GBM, GLM, XGB, Decision Tree (DT), and NNET—to the 12 DEGs identified from differential expression analysis. Model performance assessment revealed differences among algorithms (Figure 2A-C). The residual distribution analysis showed that LASSO had the lowest median residual value, followed by RF and SVM (Figure 2A), and the reverse cumulative distribution curves provided complementary diagnostic information (Figure 2B). ROC curve analysis showed that RF achieved the numerically highest AUC (0.823), closely followed by LASSO (AUC = 0.822), KNN (AUC = 0.818), GLM (AUC = 0.815), SVM (AUC = 0.806), and DT (AUC = 0.800) (Figure 2C). Given the negligible difference between RF and LASSO, these results were interpreted as broadly comparable rather than evidence of clear algorithmic superiority. Feature-importance analyses across the nine models identified recurring high-ranking genes, including IGK and CXCL6 in several algorithms (Figure 2D). Immune-related genes such as TENT5C (legacy symbol FAM46C), TNFRSF17, and CD79A also showed appreciable importance in several models.

Construction and Validation of Nomogram Based on Key Feature Genes:

Through the ROC curve comparison, RF achieved the numerically highest AUC among the evaluated algorithms and was selected for subsequent feature ranking and model construction. Because RF and LASSO showed nearly identical AUC values, the selection of RF was based on its combination of competitive discrimination and readily interpretable variable-importance ranking rather than on a claim of statistically proven superiority. The top five RF-ranked feature genes (IGHM, MZB1, DSC1, AADACL2, and CXCL6) were selected to provide a compact, interpretable signature for nomogram construction (Figure 3A). In this nomogram, each gene was assigned a point value according to its expression level, and the total points were used to estimate the probability that a gingival tissue/site belonged to the diseased category. The scoring scale showed the relative contribution of each predictor within the graphical model. Decision curve analysis indicated potential net benefit of the model over the reference strategies across the evaluated threshold range (Figure 3B); however, this analytical

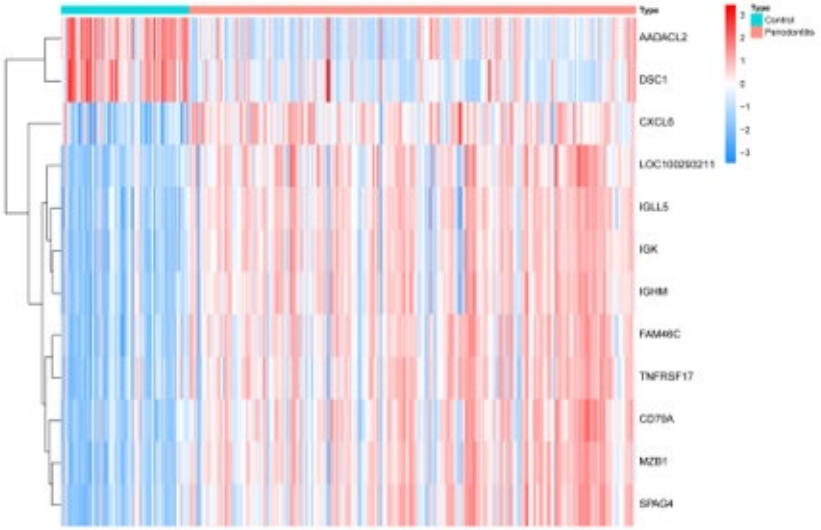


Figure 1. *Heatmap of differentially expressed genes between periodontitis and control groups.*

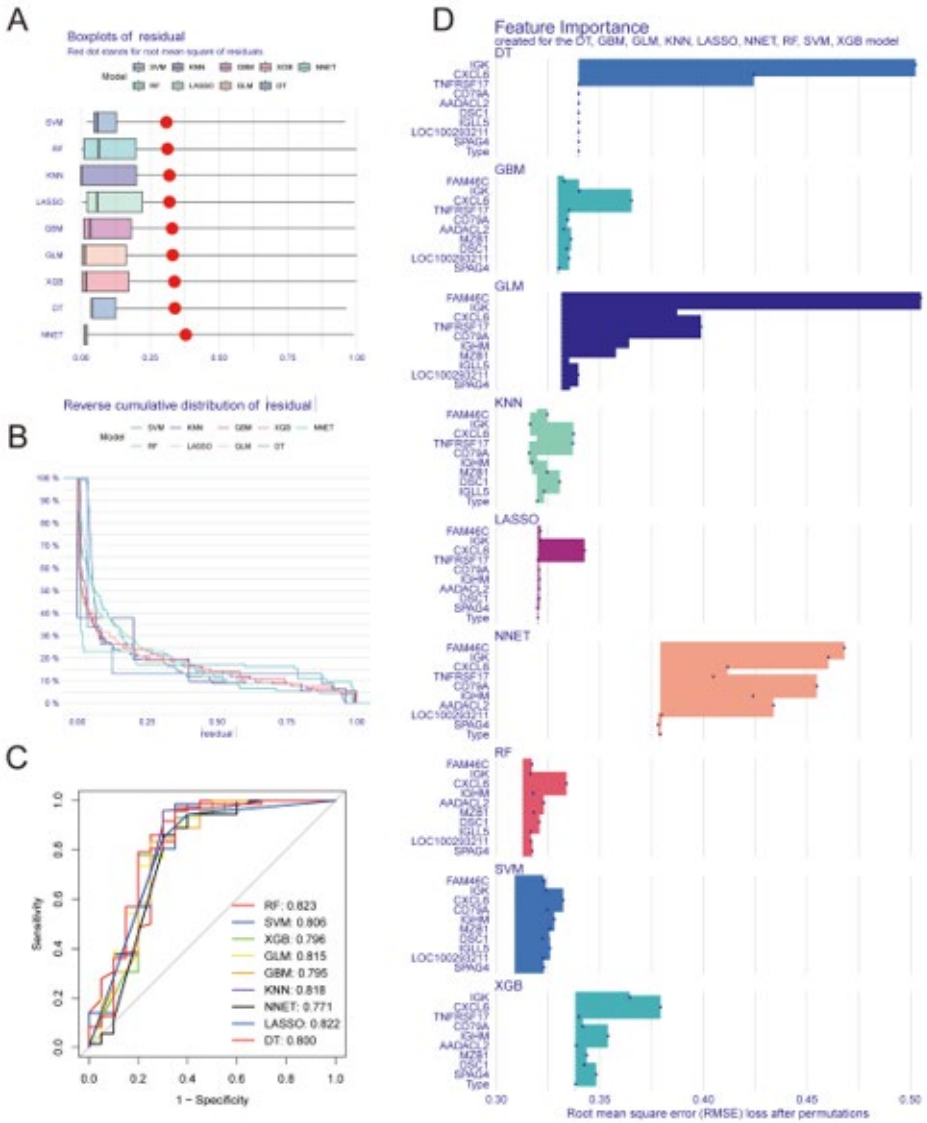


Figure 2. *Performance evaluation and feature importance ranking of nine machine learning algorithms for periodontitis gene signature identification. A, Boxplot showing residual distribution of nine machine learning models. B, Reverse cumulative distribution curves of residuals for each model. C, ROC curves comparing the discriminative performance of all nine models. D, Feature importance scores of the 12 DEGs across different machine learning algorithms based on root mean square error (RMSE) loss after permutations.*

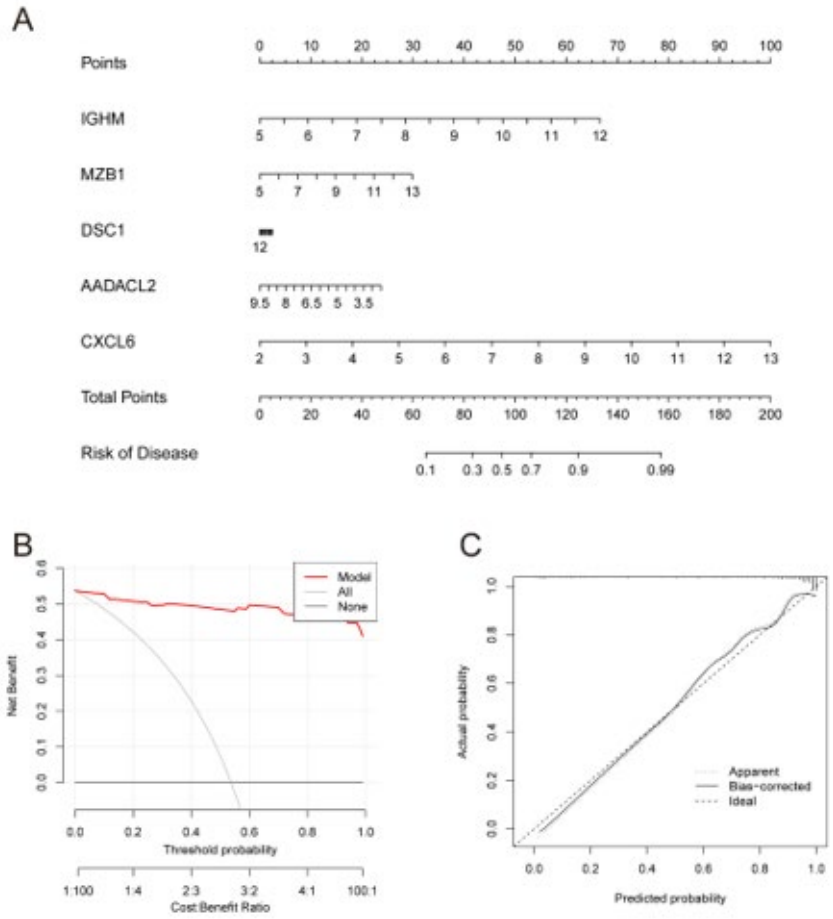


Figure 3. *Construction and validation of a nomogram model. A, Nomogram integrating IGHM, MZB1, DSC1, AADACL2, and CXCL6 for estimating the probability of diseased periodontal tissue/site status. B, Decision curve analysis showing model net benefit across the evaluated threshold probabilities relative to reference strategies. C, Internal bootstrap-corrected calibration curve assessing agreement between predicted and observed site-status probabilities in the development data.*

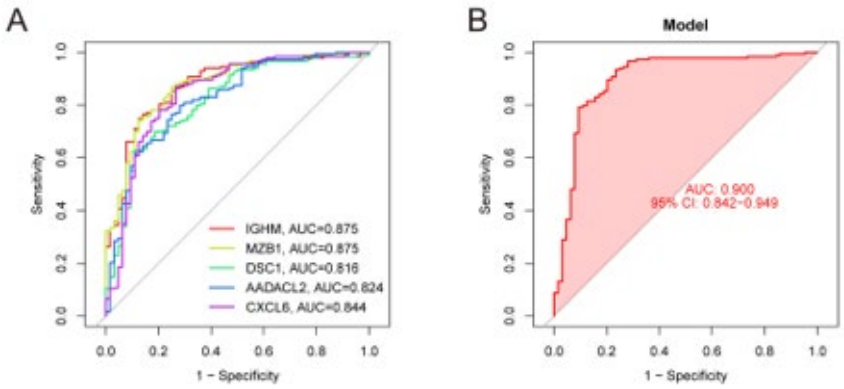


Figure 4. *Validation of individual feature genes and the integrated nomogram model in GSE10334. A, ROC curves evaluating the site-level discriminative performance of the five genes. B, ROC curve of the integrated nomogram model demonstrating its ability to distinguish diseased from clinically healthy gingival tissue sites.*

result should not be interpreted as direct evidence that a specific treatment decision would improve patient outcomes. The internal bootstrap-corrected calibration curve showed close agreement between predicted and observed site-status probabilities in the development data (Figure 3C). Together, these findings support the discriminative performance of the five-gene signature at the periodontal tissue/site level, while further clinical validation is required before patient-level implementation.

External Validation of Feature Genes and Nomogram Model:

To assess the robustness of the identified feature genes in a separate GEO dataset, we performed validation using GSE10334. ROC analysis showed that all five genes retained satisfactory site-level discrimination (Figure 4A). IGHM and MZB1 showed the highest individual AUC values (both AUC = 0.875), followed by CXCL6 (AUC = 0.844), AADACL2 (AUC = 0.824), and DSC1 (AUC = 0.816). The integrated five-gene nomogram achieved an AUC of 0.900 (95% CI: 0.842-0.949) in GSE10334 (Figure 4B), exceeding the AUCs of the individual genes and supporting the additive discriminative value of the multi-gene signature. AUC summarizes overall discrimination and does not, by itself, establish sensitivity or specificity at a particular operating threshold. These results therefore support the ability of the five-gene model to distinguish diseased from clinically healthy gingival tissue sites in the validation dataset, rather than establishing prospective patient-level risk prediction.

Discussion.

In this study, we conducted a comprehensive machine learning-based analysis to identify genes associated with periodontitis-related gingival tissue status and developed a five-gene nomogram for site-level discrimination. Through comparison of nine ML algorithms applied to DEGs from GSE16134, we identified five feature genes—IGHM, MZB1, DSC1, AADACL2, and CXCL6—with consistent discriminative value. The integrated nomogram achieved an AUC of 0.900 in the external GSE10334 validation dataset. These results support the potential utility of the five-gene signature for molecular discrimination of diseased versus clinically healthy periodontal tissue sites, while they should not be interpreted as evidence of longitudinal disease risk or prospective patient-level diagnosis.

The identified feature genes have biological functions plausibly related to periodontal inflammation and tissue homeostasis, but their associations should be interpreted cautiously in bulk gingival transcriptomic data. IGHM and MZB1 are related to B-cell and antibody-producing cell biology, and their lower expression in diseased tissue sites may reflect changes in local immune-cell composition and/or humoral immune activity rather than direct gene-specific causal effects. Previous studies have described altered B-cell and antibody responses in periodontitis [16,17]. CXCL6 is a CXC chemokine involved in neutrophil recruitment and inflammatory responses [18]. Importantly, CXCL6 was downregulated in our bulk-tissue DEG analysis; therefore, its predictive importance should not be equated with upregulation in the present dataset. Prior studies have nevertheless implicated CXCL6-related signalling in periodontal inflammation [19,20], suggesting that its direction and magnitude may depend on tissue composition, disease context, and analytical platform. DSC1 encodes desmocollin-1, a desmosomal cadherin involved in epithelial cell-cell adhesion, and altered expression may be associated with changes in epithelial integrity [21]. Overall, these genes should be viewed primarily as predictive transcriptomic associations in the current study rather than as established causal mediators.

Our ML-based analysis complements conventional differential expression analysis by providing a structured comparison of multiple classification approaches and feature-importance patterns. Among the nine algorithms evaluated, RF and LASSO showed the strongest and nearly identical AUC values, consistent with their common use in high-dimensional biomedical data. The recurrence of several genes among high-importance features across algorithms provides supportive, although not definitive, evidence for their relevance. The five-gene nomogram also showed higher discrimination than the individual genes in the validation dataset, supporting the value of combining multiple molecular features [22,23]. The calibration and decision-curve results provide additional internal characterization of the model, but they should be interpreted as model-performance evidence rather than proof of clinical utility or individualized treatment benefit [24,25].

Our study has several strengths. First, we compared nine ML algorithms rather than relying on a single modeling approach and used RF feature importance to derive a compact five-gene signature. Second, the selected genes and integrated model were evaluated in a separate GEO dataset (GSE10334), providing cross-dataset validation of site-level discrimination. Third, the nomogram offers an interpretable graphical representation of the multi-gene model. Several limitations should also be recognized. Both GEO datasets contain multiple gingival tissue sites contributed by individual patients; because our prespecified analytical unit was the tissue/site, the analyses and confidence intervals were not patient-clustered and should not be interpreted as patient-level risk estimates. In addition, GSE16134 and GSE10334 have been reported to originate from related gingival tissue archives, which may limit the degree of independence between datasets; accordingly, we refer to GSE10334 as an external validation dataset rather than an independent prospective cohort. DEG screening was performed as an exploratory biomarker-discovery step within GSE16134 before algorithm comparison, so the internal hold-out performance is best interpreted for comparative model assessment rather than as an unbiased patient-level generalization estimate. The cross-sectional nature of the data precludes inference regarding future disease occurrence or treatment response. Finally, bulk transcriptomic differences may partly reflect variation in tissue cellular composition, and functional studies are required before causal interpretations can be made.

Conclusion.

In conclusion, ML-based analysis of gingival transcriptomic data identified a five-gene signature associated with periodontal tissue status. The integrated nomogram demonstrated strong site-level discrimination in GSE16134 and retained favorable performance in the external GSE10334 dataset. These findings support the five-gene signature as a candidate molecular classifier of diseased versus clinically healthy periodontal tissue sites. Prospective studies with genuinely independent patient-level cohorts, explicit control of repeated sampling,

and integration of clinical variables are needed to determine its eventual clinical value [26-28].

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Conflicts of Interest.

The authors declare no conflicts of interest.

Data Availability.

The datasets analyzed in this study are publicly available in the Gene Expression Omnibus repository (https://www.ncbi.nlm.nih.gov/geo/) under accession numbers GSE16134 and GSE10334.

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