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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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Содержание:

Babry I. Oren, Marina I. Devdariani, Gela V. Beselia, Nino N. Sikharulidze, Manana G. Dashniani, Maia A. Burjanadze, Ia R. Kvachakidze, Marina I. Nebieridze, Lena Sh. Davlianidze, Lali M. Gumberidze, Nodar P. Mitagvaria.
ROLE OF ANTIOXIDANT FOLIUM EXPOSURE ON OXIDATIVE SRESS IN A VALPROIC ACID-INDUCED ANIMAL MODEL OF AUTISM……...6-15

Hajdi Gorica, Pavllo Djamandi, Gentian Vyshka.
DELAYED ONSET OF MYASTHENIA GRAVIS FOLLOWING COLECTOMY FOR ULCERATIVE COLITIS: A CASE STUDY……..16-17

Zhadyra Yersariyeva, Bagdad Suleyeva, Botagoz Turdaliyeva, Yeldos Tussipbayev.
HEMOSTASIS GENE POLYMORPHISM IN RETINAL VASCULAR OCCLUSION: A SYSTEMATIC REVIEW……..……..…18-28

Ilia Nakashidze, Nameera Parveen Shaikh, Shota Nakashidze, Aleena Parveen Shaikh, Sarfraz Ahmad, Irina Nakashidze.
EVALUATION OF TNF-A LEVELS IN MALE PATIENTS WITH STROKE: PROGNOSTIC IMPLICATIONS…….....…….29-32

Yerbolat Iztleuov, Marat Iztleuov, Altynbek Dushmanov, Gulmira Iztleuova.
PREVENTION IN THE PARENTAL GENERATION OF EXPOSED RATS: CONSEQUENCES OF TOXIC EXPOSURE TO CHROMIUM AND GAMMA IRRADIATION IN AN EXPERIMENTAL MODEL…….....……..33-45

Rashid Nassar, Nadine Khayyat, Michele Halasa, Fahad Hussain.
TRAUMATIC ANTERIOR SHOULDER INSTABILITY (TUBS): A NARRATIVE REVIEW OF CURRENT LITERATURE……..…46-50

Albadawi Abdelbagi Talha, Mawaheip A. Abdo Jeweser, Abubakr Ali Elamin Mohamed Ahmed, Abdelrahman Eldaw Mohammed, Elhadi Abdalla Ahmed, GadAllah Modawe, Sanaa Elfatih Hussein.
THE HBV AND HCV SEROPREVALENCE AMONG BLOOD DONORS IN Al-DAMAZIN STATE, SUDAN: A THREE-YEAR RETROSPECTIVESTUDY…….....……..…51-54

Hiba Salah Hasan, Teeb Ali, Kadhim Adnan Ali, Al hassan Ali, Hany A. Al-hussaniy.
MODELING DRUG–ORGAN INTERACTIONS AND OPTIMIZING IMMUNOTHERAPY: A QUANTITATIVE SYSTEMS PHARMACOLOGY AND ODRONEXTAMAB DYNAMICS…….....……..…55-60

Zilola Mavlyanova, Davron Ravshanov, Malika Ibragimova, Lola Irbutaeva, Khalimova Fariza, May K. Ismail, Shawgi A. Elsiddig, Marwan Ismail, Salma E R Mohamed, Sara Mohammed Ali.
PROGNOSTIC SIGNIFICANCE OF PROLIFERATION (KI-67) AND ANGIOGENESIS (CD34) MARKERS IN MENINGIOMAS FOR THE DEVELOPMENT OF REHABILITATION STRATEGIES…….....……61-65

A.R. Abzaliyeva, K.K. Kurakbayev, A.R. Ryskulova, Z.R. Abzaliyev, E. Tasmagambet, D.Zh. Saussanova.
TURNOVER INTENTIONS AMONG PHYSICIANS AND NURSES IN KAZAKHSTAN DURING THE COVID-19 PANDEMIC: A CROSS-SECTIONAL STUDY OF PSYCHOLOGICAL AND PROFESSIONAL CHALLENGES…….....…….66-72

A.A. Mammadov, A.N. Mustafayev, A.H. Aliyev.
RADIOLOGICAL IMAGING METHODS FOR ACCURATE DIAGNOSIS OF ABDOMINAL POSTOPERATIVE COMPLICATIONS…73-76

I.A. Lebedev, E.V. Zakharchuk, Yu.V. Boldyreva, I.A. Aptekar, E.I. Malinina.
OSSIFICATION OF THE POSTERIOR LONGITUDINAL LIGAMENT: A CASE REPORT AND LITERATURE REVIEW……..…….77-79

Zhanar Balmukhamedova, Gulmira Derbissalina, Aliya Dzholdasbekova, Dariga Blyalova, Luiza Murzakhalova.
SPECKLE-TRACKING ECHOCARDIOGRAPHY FOR EARLY DETECTION OF SUBCLINICAL SYSTOLIC DYSFUNCTION IN PERIMENOPAUSAL WOMEN WITHOUT APPARENT DIASTOLIC DYSFUNCTION…….....……80-86

Arkam Thabit Al Neama, Musab Mohammed Khalaf, Ahmed A.J. Mahmood.
PATTERNS OF ACETYLCHOLINESTERASE AND BUTYRYLCHOLINESTERASE ACTIVITY IN COMMON CARDIOVASCULAR PHENOTYPES…….....……87-94

Argjira Veseli, Shefqet Mrasori, Ivana Čuković-Bagić, Lul Raka, Kaltrina Veseli, Enis Veseli.
PARENTAL QUALITY OF LIFE WHEN RAISING CHILDREN WITH AUTISM SPECTRUM DISORDER: A NARRATIVE REVIEW…….....……...95-100

Anas Ali Alhur, Daliya T. Sendi, Miad M. AlZahrani, Layla T. Abusharha, Rahaf Y. Abudaak, Rahmah Alsinan, Rama R. Alharbi, Lamia Almadhi, Laila M. Alotaibi, Mona A. Hadadi, Shaima H. Alattas, Fatimah Almisbah, Fathi Almisbah, Abdulrahman Alrashed, Kawkab Alharbi.
EVALUATING THE TRUSTWORTHINESS OF CHATGPT-GENERATED HEALTH INFORMATION AMONG FUTURE HEALTH CARE PROFESSIONALS…….....……...101-106

Ting-Ting Wang, Yan Wang.
HUMANISTIC CARE NURSING FOR PATIENTS IN THE OPERATING ROOM DURING THE PERIOPERATIVE PERIOD: FULL-CYCLE CARE FROM PHYSIOLOGY TO PSYCHOLOGY…….....……107-109

Zauresh Barmanasheva, Mariya Laktionova, Anna Onglas, AyauIym Kossetova, Ivan Melnikov.
PREVALENCE AND RISK FACTORS OF UTERINE FIBROIDS IN WOMEN OF REPRODUCTIVE AGE: A FACILITY-BASED STUDY IN A MEGACITY…….....……110-120

Bolat Ashirov, Assel Kassymova, Jamilya Mansurova, Andrey Orekhov, Meiramgul Tokbulatova, Mirgul Kapakova, Zhanar Toktarova, Aisulu Zhunuspekova.
PROGNOSTIC MARKERS OF ISCHEMIC AND HEMORRHAGIC COMPLICATIONS IN PATIENTS WITH ATRIAL FIBRILLATION AFTER PERCUTANEOUS CORONARY INTERVENTION…….....……121-128

Khalilov Sh. Dzh.
ELECTROCARDIOGRAPHY CHARACTERISTICS OF THE PATIENTS WITH NON-ST-ELEVATION MYOCARDIAL INFARCTION (NS TEMI)……129-132

Salome Kordzaia, Elene Dolmazashvili, Khatuna Tsiklauri, Lasha Khmaladze, Nana Chikhladze.
FROM INFUSION REACTION TO IMMUNE CASCADE: A CASE OF SEQUENTIAL TAXANE AND CAPECITABINE TOXICITIES IN TRIPLE-NEGATIVE BREAST CANCER……133-136

Yu Zhu, Fandong Zeng, Weiwei Chang, Liying Wen, Lijun Zhu, Yuelong Jin.
AN EMPIRICAL STUDY ON THE ASSOCIATION BETWEEN ASPIRATION INDEX AND ACADEMIC PERFORMANCE AMONG PREVENTIVE MEDICINE STUDENTS……..137-142

Alaa O Ahmed, Mubarak S Karsany, Mohamed Elfatih Abdelwadoud, Mutaz Ali, Osama Mohamed, Amged Gaffer Mostafa, Hussam Ali Osman, Elryah I Ali, Elyasa Elfaki, Tagwa Yousif Elsayed Yousif, Ayman H. Alfeel, Mohammed Ibrahim Saeed.
MOLECULAR DETECTION OF HIGH RISK HUMAN PAPILLOMA VIRUS SUBTYPES IN CERVICAL SMEARS AMONG SUDANESE WOMEN……143-149

Tchernev G, Tchernev KG Jr, Krastev DS, Krastev NS, Kordeva S.
DERMATOLOGIC SURGERY ROUNDS: RECONSTRUCTIVE SURGERY EMPLOYING THE SHARK ISLAND FLAP FOR BASAL CELL CARCINOMA AFFECTING THE NASAL ALA……150-153

Saltanat Imanalieva, Bayan Sagindykova, Rabiga Anarbayeva, Murat Omirali, Gulnara Ospanova, Murat Ashirov.
CURRENT STATUS AND PROSPECTS FOR THE DEVELOPMENT OF PEDIATRIC DOSAGE FORMS BY THE EXAMPLE OF COMBINED MELOXICAM AND VITAMIN B12 TABLETS……154-167

Ahmed Miri Saadoon.
INCIDENCE OF PRESSURE SORE IN THE INTENSIVE CARE UNIT AT AL-DIWANYIA TEACHING HOSPITAL……168-171

Isoyan A.S, Danielyan M.H, Antonyan I.V, Azizyan N.H, Mkrtchyan A.A, Karapetyan K.V, Nebogova K.A.
MORPHOHISTOCHEMICAL ANALYSIS OF CORTICAL STRUCTURES IN AN EXPERIMENTAL MODEL OF PROLONGED COMPRESSION SYNDROME OF THE HIND LIMB IN RATS……172-179

Abdulaziz Alroshodi, Faisal A. Al-Harbi, Rasil Sulaiman Alayed, Fahad M. Alharbi, Khalid A Alkhalifah, Mayadah Assaf Alawaji, Ibrahim S. Alsabhawi.
FACTORS IMPACTING HEMODIALYSIS TREATMENT ADHERENCE IN END-STAGE RENAL DISEASE PATIENTS RECEIVING IN-CENTER HEMODIALYSIS IN QASSIM REGION……180-187

Gulshat Alimkhanova, Marat Syzdykbayev, Rinat Ashzhanov, Kulsara Rustemova, Maksut Kazymov, Rustem Kazangapov, Asem Kazangapova, Saule Imangazinova, Yernar Kairkhanov, Bazar Tuleuov, Sanzhar Khalelov, Roman Khripunov, Samatbek Abdrakhmanov, Abay Mijatov.
THE TRANSVERSUS ABDOMINIS PLANE BLOCK AS A METHOD OF MULTIMODAL OPIOID-SPARING POSTOPERATIVE ANALGESIA: A NARRATIVE REVIEW……188-194

Zhengmei Fang, Xiaoling Ran, Lijun Zhu, Yingshui Yao, Yuelong Jin.
THE IMPACT OF BMAL1 GENE POLYMORPHISM ON SLEEP QUALITY IN HEALTHY CHINESE YOUTH: A GENDER-SPECIFIC ANALYSIS……195-201

Muwafaq H. Zaya, Ahmed A. J. Mahmood, Musab M. Khalaf.
CROSS SECTIONAL EVIDENCE FOR OPPOSING EFFECTS OF HYPERGLYCAEMIA AND HYPERLIPIDAEMIA ON CHOLINESTERASEACTIVITIES……202-210

Erleta Muçaj, Erëza Durmishi, Serbeze Kabashi Muçaj, Leart Kuçi, Elza Muçaj, Gerta Durmishi.
CHALLENGES IN RADIOLOGICAL DIAGNOSIS: CRANIOPHARYNGIOMA VS ASTROCYTOMA……211-214

Uday Mahajan, Imran Khan, Ria Gupta, Meraj Akhtar, Vibhore Gupta, Edward Spurrier, Mohamed Kabary, Adnan Asif, Salman Shoukat Ali Parpia.
NAMING CONVENTIONS FOR UNIDENTIFIED PATIENTS IN EMERGENCY AND TRAUMA SETTINGS: A NARRATIVE REVIEW……..215-218

Xuexue Li, Wenjie Wen, Dandan Ren.
MOLECULAR MECHANISMS OF DIABETIC PERIODONTITIS: IDENTIFICATION OF KEY OXIDATIVE STRESS-RELATED GENES AND POTENTIAL THERAPEUTIC ROLE OF METFORMIN THROUGH MMP14 AND PXDN……....219-231

Davron Ravshanov, Zilola Mavlyanova, Kholmirzayev Bakhtiyor, Malika Tursunovna, Khalimova Fariza.
HISTOPATHOLOGICAL PREDICTORS AND FUNCTIONAL RECOVERY IN PATIENTS WITH INTRACRANIAL MENINGIOMAS……232-240

Aymuhambetov Y, Khismetova Z A, Iskakova N, Akhmetova K, Serikova-Esengeldina D, Shalgumbayeva G.M.
ASSESSMENT OF QUALITY OF LIFE IN BREAST CANCER PATIENTS BY USING EORTC QLQ-C30 QUESTIONNAIRE IN EAST KAZAKHSTAN REGION……241-248

Yujing Tao, Long Hua, Liu Zhang, Ying Feng, Liying Wen, Weiwei Chang.
THE CORRELATION BETWEEN STRESS, ACADEMIC PERFORMANCE, AND SLEEP DISTURBANCES AMONG HIGH SCHOOL STUDENTS IN ANHUI PROVINCE: A CROSS-SECTIONAL STUDY……249-257

Fahad AlAmr, Muhannad Essa S. Alghamdi, Ahmed Saeed A. Alghamdi, Osama Khamis A. Alghamdi, Hassan Mahfouz B. Alghamdi, Osama Mesfer S. Alghamdi, Abdullah Ali A. Almimoni, Abdulmalik Ahmed S. Al-Zahrani.
PREVALENCE AND ASSOCIATED RISK FACTORS OF NOCTURNAL ENURESIS AMONG CHILDREN AGED 5-18 YEARS IN ALBAHA REGION, SAUDI ARABIA……..258-263

Aya Saad Aldewachi, Mohammed I Aladul.
APPETITIVE TRAITS AND QUALITY OF LIFE IN WOMEN WITH OBESITY USING GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS: INSIGHTS FROM A PCOS-ENRICHED SAMPLE……264-269

George Shaburishvili, Nikoloz Shaburishvili, Georg Becker, Solomon Zeikidze, Bacho Tsiklauri.
INCIDENCE OF ADVERSE EVENTS RESULTING FROM BETA-BLOCKER TITRATION IN PATIENTS WITH HEART FAILURE…….270-279

Blushinova A.N, Orazalina A.S, Shalgumbayeva G.M.
INDUCED ABORTION IN KAZAKHSTAN: WOMEN'S PERCEPTIONS AND EXPERIENCES BASED ON CROSS-SECTIONAL STU DY……280-288

Qunru Hu, Liying Wen, Jingqi Zhang, Weiwei Chang, Yuelong Jin, Anshi Wang, Lijun Zhu.
IS CORE SELF-EVALUATION A PROTECTIVE FACTOR FOR COLLEGE STUDENTS'MARITAL ATTITUDES? THE MODERATING ROLE OF PSYCHOLOGICAL STATUS…….289-294

Gulfariza Gani, Ubaidilla Datkhayev, Kairat Zhakipbekov, Serzhan Mombekov, Murat Ashirov, Nurgali Rakhymbayev, Zhanerke Seitova.
STUDY OF THE CHEMICAL COMPOSITION AND ANTIMICROBIAL ACTIVITY OF SUBCRITICAL CO_2 EXTRACT FROM *EUPHORBIA HUMIFUSA* WILLD……295-302

Maysoon Mohammed Hassan, Mohammed Abdulwahab Ati Al-askeri, Naseer Kadhim Jawad.
PROGNOSTIC IMPACT OF EGFR2 AND KI-67 OVEREXPRESSION WITH DOWNREGULATION OF *miR-17* AND *miR-1307* IN FEMALE BREAST CANCER PATIENTS……303-313

Imzharov Talgat Abatovich, Zhakiev Bazylbek Sagidollievich, Sarkulov Marat Nukinovich, Pavlov Valentin Nikolaevich, Kurmangaliev Oleg Maratovich.
THE EFFECTIVENESS OF METAPHYLAXIS OF NEPHROLITHIASIS DURING PERCUTANEOUS NEPHROLITHOTRIPSY: A SYSTEMATIC REVIEW AND META-ANALYSIS……..314-322

Yan Wang, Ting-Ting Wang, Chang-Sheng He.
PROGRESS IN T-CELL IMMUNE RESEARCH ON HYPERLIPIDEMIC PANCREATITIS……323-326

Marwan I Abdullah.
MINING THE CELLMINER DATABASE TO IDENTIFY SHARED BIOMARKERS OF 5-FU AND OXALIPLATIN RESPONSE…...327-341

Shyngys Adilgazyuly, Tolkyn Bulegenov, Akmaral Mussakhanova, Tasbolat Adylkhanov, Kanat Abdilov, Zhannur Altybayeva, Gulmira Bazarova, Malike Kudaibergenova, Makpal Alchimbayeva, Aigul Utegenova, Gulnara Otepova.
ASSESSING THE INFLUENCE OF MEDICAL EDUCATION REFORMS ON ONCOLOGIST WORKFORCE AND LUNG CANCER MORTALITY IN KAZAKH-STAN: AN INTERRUPTED TIME SERIES ANALYSIS WITH PREDICTIVE MOD-ELING OF NATIONWIDE DATA FROM 1998 TO 2023……342-351

Wen-Wen Liu, Zhi-Juan Xu, Fang Xu.
NEW INSIGHTS INTO THE PATHOGENESIS AND TREATMENT ADVANCES OF AGE - RELATED MACULAR DEGENERATION……352-354

Zhamilya Zholdybay, Zhanar Zhakenova, Madina Gabdullina, Yevgeniya Filippenko, Suria Yessentayeva, Galymzhan Alisherov, Aigerim Mustapaeva, Jandos Amankulov, Ildar Fakhradiyev.
^{68}GA-FAPI PET/CT IN DIAGNOSIS OF THE BREAST CANCER DEPENDING ON THE MOLECULAR SUBTYPES AND EXPRESSION STATUS OF HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 (HER2/NEU)……355-363

A.I. Rybin, V.E. Maksymovskyi, O.V. Kuznetsova, V.V. Osyk, A.S. Bohdan.
THE RESULTS OF LIFE QUALITY ASSESSMENT IN PATIENTS WITH PRIMARY OVARIAN CANCER DURING TREATMENT: EFFECT OF DIFFERENT TACTICS AND HIPEC……364-368

Miranda Sejdiu Abazi, Arbër Prokshaj, Shpëtim Prokshaj, Fitim Alidema, Nora Leci, Linda Abazi Morina.
ASSESSMENT OF PRACTICAL PERFORMANCE IN ORTHODONTIC CLASP FABRICATION AMONG DENTAL TECHNICIAN STUDENTS AT UBT: A REAL-TIME ANALYSIS OF WORKING TIME AND PERCEIVED STRESS……369-377

Abylay Baimakhanov, Ainash Oshibayeva, Temirkhan Kozhakhmetov, Nazarbek Omarov, Dinara Akhmetzhanova, Berikuly Duman.
RESULTS OF MEDICAL CARE FOR PERSONS WITH POLYTRAUMA IN ALMATY AND CORRECTION OF THE ORGANIZATIONAL APPROACH……...378-382

Khatia Mikeladze, Nino Chikadze, Nino Gachechiladze, Marina Tediashvili, Irina Datikashvili-David, Peter Lydyard, Nina Porakishvili.
SERUM IL-6, IL-12, AND IL-10 LEVELS IN EARLY-STAGE, UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS: INSIGHTS FROM GEORGIA……383-387

Musayeva H.H.
FREQUENCY OF COMPLICATIONS IN PATIENTS WITH ADENTIA (BASED ON ARCHIVAL DATA)……388-393

Hong-Xia Wang, Xiao-Xia Hou, Jie Xu.
NURSING RESEARCH ON EMERGENCY GASTROSCOPIC TREATMENT OF UPPER GASTROINTESTINAL FOREIGN BODIES……394-396

Tolegenova Z.Zh, Tokanova Sh.E, Baibussinova A.Zh, Kalikhanova K, Iskakova A.M, Shalgumbayeva G.M.
ASSESSMENT OF INFECTIOUS DISEASE RISK FACTORS, INCLUDING COVID-19, AMONG HEALTHCARE WORKERS IN EAST KAZAKHSTAN REGION……397-405

Bassam A. Al- jabery, Majid R. Al-bahrani.
ENVIRONMENTALLY SAFE $CsPbBr_3$/MXene/MWCNTs HYBRID NANOCOMPOSITES: OPTOELECTRONIC AND STRUCTURAL CHARACTERISTICS FOR POSSIBLE BIOMEDICAL AND HEALTH APPLICATIONS……..……406-414

Hasan AlAidarous.
PIGMENTED VILLONODULAR SYNOVITIS IN THE ANKLE OF A PEDIATRIC PATIENT: A CASE REPORT…….....……..…415-419

Kuat Zhussupov, Nazarbek Omarov, Sagit Imangazinov, Saule Imangazinova, Yernar Kairkhanov, Olga Tashtemirova, Rustem Kazangapov, Aldiyar Masalov, Darkhan Otkenov.
ENDOSCOPIC INJECTION HEMOSTASIS AND LOCAL TREATMENT OF GASTRODUODENAL BLEEDING. LITERATURE REVIEW AND OWN DEVELOPMENTS…….....……..…420-424

GEORGIAN MEDICAL NEWS
No 7-8 (364-365) 2025

MOLECULAR MECHANISMS OF DIABETIC PERIODONTITIS: IDENTIFICATION OF KEY OXIDATIVE STRESS-RELATED GENES AND POTENTIAL THERAPEUTIC ROLE OF METFORMIN THROUGH MMP14 AND PXDN

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Abstract.

Aim: Periodontitis and diabetes mellitus (DM) exhibit a bidirectional relationship, with oxidative stress potentially serving as a crucial pathological bridge. However, the underlying molecular mechanisms remain unclear.

Methods: We identified differentially expressed genes (DEGs) related to oxidative stress in periodontitis and diabetes. Consensus clustering was performed to identify disease subtypes. Machine learning algorithms, including Support Vector Machine, LASSO regression, and Random Forest, were employed to identify key regulatory genes. Molecular docking was conducted to explore the potential interaction between metformin and target proteins.

Results: We identified 17 overlapping genes associated with oxidative stress, diabetes, and periodontitis. Two distinct molecular subtypes were identified with significant differences in immune cell infiltration patterns. Four key genes (FOS, MMP14, CD38, and PXDN) were identified as potential therapeutic targets. The nomogram based on these four genes showed excellent diagnostic performance (AUC = 0.931). Molecular docking analysis revealed strong binding affinities between metformin and two targets (MMP14: -5.6 kcal/mol; PXDN: -5.2 kcal/mol).

Conclusions: Our study provides novel insights into the molecular mechanisms linking periodontitis and diabetes through oxidative stress, identifying potential therapeutic targets and suggesting a possible mechanism for metformin's therapeutic effects in diabetic periodontitis.

Key words. Periodontitis, diabetes, oxidative stress, machine learning.

Introduction.

Periodontitis is a multifactorial chronic inflammatory disease, characterized by the destruction of the attachment of bones and connective tissues around the teeth (including periodontal destruction and alveolar bone resorption), which can lead to tooth loss in severe cases [1]. The imbalance in the microbiota of periodontal tissues during its development, also known as ecological imbalance, leads to an imbalance between the activities of osteoblasts and osteoclasts [2,3]. Periodontitis, the sixth most common disease in humans, poses a major threat to human health and affects more than 750 million people worldwide [4]. Periodontitis has been found to have strong associations with various systemic conditions, including metabolic disorders like diabetes, autoimmune diseases, and even cancer. Diabetes mellitus, a prevalent chronic condition, is marked by ongoing inflammation and disruptions in metabolic processes [5]. Studies have shown that the immune system in individuals with diabetes is hyperresponsive, and the activation of innate immune cells, such as macrophages, plays a crucial role in insulin resistance and contributes to the pathogenesis of diabetes and the progression of its complications [6].

Both periodontitis and diabetes place a heavy burden on global public health and finances, and a large body of evidence confirms the bidirectional relationship between periodontitis and diabetes [7]. Periodontitis is the sixth most common complication of DM and a risk factor for DM. Previous epidemiologic studies have reported an approximately threefold increased risk of periodontitis in diabetic patients compared to non-diabetic patients. This study showed that it was associated with an increased prevalence and severity of periodontitis depending on the status of diabetes [8]. It has been shown that periodontitis induces insulin receptor desensitization and exacerbates DM through excessive inflammatory response. In addition, DM is a major risk factor for periodontitis and can exacerbate disease progression [9]. Mechanistically, DM causes oxidative stress and alveolar bone resorption due to the accumulation of AGEs and inflammatory cytokines [10]. Excessive reactive oxygen species (ROS) can significantly increase the expression levels of pro-inflammatory factors, leading to periodontal tissue destruction. This affects the development and progression of periodontitis [11]. Since oxidative stress plays an important role in maintaining and establishing the immune-inflammatory response, they may be the “bridge” between periodontitis and DM. Increased oxidative stress has been implicated in the pathogenesis of insulin resistance, through inhibition of insulin signaling and dysregulation of adipokines. On the other hand, a number of studies have shown that drugs that restore oxidative stress function may be beneficial in the treatment of periodontitis and DM [12]. For example, metformin, a drug widely recognized for its ability to decrease hepatic glucose production and improve insulin sensitivity, may also reduce periodontal damage by promoting fatty acid oxidation and alleviating oxidative stress [13]. Therefore, it is plausible to propose that oxidative stress serves as a key pathological link between diabetes and periodontitis, making it a potential target for therapeutic strategies. There is also a need to delve into the role of oxidative stress in the pathogenesis of periodontitis in DM.

With the advancement of modern sequencing technologies, bioinformatics analysis allows for the exploration of disease relationships and pathogenic mechanisms, enabling more convincing conclusions to be drawn [14].While current research has highlighted the potential role of oxidative stress

in the pathological features of periodontitis and diabetes respectively [15], there remains a need to further investigate the complex relationship between oxidative stress-related genes and these comorbidities. Therefore, this study used an integrated analytical approach to explore key genes and signaling pathways in periodontitis and diabetes. The goal was to provide new insights into the molecular mechanisms linking oxidative stress with diabetic periodontitis. Additionally, we aimed to identify potential therapeutic targets for personalized treatment. Through the application of multiple machine learning algorithms and molecular docking analysis, we sought to elucidate the molecular basis of this relationship and evaluate potential therapeutic interventions.

Materials and Methods.

Data Acquisition and Preprocessing:

The periodontitis microarray datasets were retrieved from the Gene Expression Omnibus (GEO) database. The GSE10334 dataset included 183 periodontitis samples and 64 normal samples, while GSE16134 contained 69 normal and 241 periodontitis samples. Differentially expressed genes (DEGs) were identified using the R package "limma," with criteria of p-values < 0.05 and |log2(FC)| > 0.585. Crossover genes were screened by overlapping periodontitis differentially expressed genes, oxidative stress-responsive gene sets (downloaded from Gene Set Enrichment Analysis (GSEA)), and diabetes-related gene sets (downloaded from DisGeNET).

Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis:

GO annotation analysis (biological processes, molecular functions, and cellular components) and KEGG pathway enrichment analysis of DEGs and crosstalk genes were performed using R's "ClusterProfiler" software package for the selected human species, and the results are presented. GO catalogs and KEGG catalogs were selected based on p-value from smallest to largest. Bar and bubble plots were used to visualize the results.

Protein-Protein Interaction (PPI) Network Analysis:

To build a reliable PPI network, we utilized the well-respected STRING database, a well-established resource for protein interactions. We incorporated DEGs into the STRING database to predict direct and indirect functional interactions, setting the confidence level threshold at 0.4, ensuring that the network contained highly plausible and significant interactions.

Unsupervised Cluster Analysis:

Unsupervised cluster analysis was conducted with the R package "ConsensusClusterPlus" to identify different subtypes. The consensus clustering algorithm was run 1000 times to confirm cluster robustness. Gene expression and immune property differences among subtypes were compared using the Kruskal test. Principal component analysis was performed using the R package "PCA".

ROC Curve Analysis:

To assess the sensitivity and specificity of genes for diagnosis, ROC curves were created from the pROC package in R. The ROC curves were then calculated with 95% confidence intervals. A high discriminatory power in clinical diagnosis was defined when the AUC was >0.7, while a high discriminatory power in clinical diagnosis was defined when the AUC was >0.9.

Construction and Validation of the Nomogram:

The nomogram was constructed using the characteristic genes and their corresponding expression levels in the normal and periodontitis groups. The nomogram can serve as an important tool for the clinical diagnosis of periodontitis. Additionally, a diagnosis model for periodontitis based on diagnostic markers was built using the "rms" R software. The values of candidate genes were quantified as "points", and the total score was determined by summation. Subsequently, a cumulative scoring system was applied to calculate the probability of the occurrence of periodontal disease. The diagnostic efficacy of the nomogram in identifying periodontitis was evaluated by the receiver operating characteristic curve and its corresponding area under the curve. Moreover, the clinical applicability of the nomogram was evaluated through decision curve analysis (DCA).

Correlation Analysis of Immune Characteristics:

Single sample gene set enrichment analysis (ssGSEA) was used to estimate the abundance of specific infiltrating immune cells and the activity of related immune responses. An enrichment score was calculated to reflect the extent of gene set enrichment in each sample. Gene sets for infiltrating immune cells were sourced from prior studies, while immune response gene sets were obtained from the Immport database.

Identification of Characteristic Genes by Machine Learning Algorithms:

To identify potential candidate genes for the diagnosis of periodontitis, three machine learning prediction models were employed in this study: the Random Forest (RF) model, the Support Vector Machine (SVM) model, and the Least Absolute Shrinkage and Selection Operator (LASSO) regression model. The SVM model was constructed using the "e1071" package in R language. Subsequently, the "randomForest" package in R language was used to perform a classification analysis on the important genes obtained through screening. The LASSO regression analysis was carried out using the "glmnet" package in R language. Meanwhile, we plotted the relationship curve between the LASSO regression coefficients and log(λ). Finally, a classification model of periodontitis - related regulatory factors based on multiple logistic regression was constructed.

Molecular docking:

Molecular docking was performed using the CB - Dock2 online platform [18]. All settings were kept at the default options. The molecular structures of the compounds were obtained from the PubChem database, while the protein structures of MMP14 and CD38 were obtained from the RCSB Protein Data Bank. The protein structures of HXDN and FOS were derived from the AlphaFold Protein Structure Database.

Statistical Analysis:

The data are presented as the mean ± standard deviation (Mean ± SD). The Student's t - test was used for statistical comparisons between two groups. A significance threshold of $p < 0.05$ was applied to determine statistical significance. Statistical analyses were performed using GraphPad Prism.

Results.

Screening of Differentially Expressed Genes:

After performing batch correction, the confounding batch effects between the GSE10334 and GSE16134 datasets were significantly minimized. Through data mining and processing, 683 crosstalk DEGs were identified. The top 50 most significantly down-regulated and up-regulated genes were visualized using a heatmap (Figure 1A). The Venn diagram showed that 17 overlapping targets in these three datasets were potential targets related to the differentially expressed genes of diabetes, oxidative stress, and periodontitis (Figure 1B).

Enrichment analysis:

To investigate the biological functional pathways that might be affected, we further investigated the potential functions of these 17 intersecting targets by GO and KEGG analysis. The results of GO significant enrichment are demonstrated in Figure 2A and 2B, in which the biological processes related to response to oxidative stress, endoplasmic reticulum lumen and antioxidant activity binding were significantly enriched. KEGG pathway analysis further revealed that these intersecting targets were mainly enriched in the TNF signaling pathway and IL-17 signaling pathway (Figure 2C). This finding highlights a complex network of interactions between multiple signaling pathways and molecular events during the development of diabetic periodontitis. In order to more comprehensively illustrate the specific components of the enrichment pathways, we show the genes involved in each pathway and the molecular processes they participate in detail in Figure 2D. Among them, Figure 2E particularly presents the specific involvement of each molecule in the TNF signaling pathway and its interaction pattern.

Identification of disease subtypes:

Based on the expression profiles of 17 DEGs, we used an unsupervised clustering method for disease pattern identification. Through the analysis, k=2 was determined as the optimal number of clusters, and the samples were successfully classified into two unique subtypes (Figure 3A-C). The results of principal component analysis (PCA) showed significant differences between these two modification patterns (Figure 3D), further validating the heterogeneity of disease modification patterns.

Immunological characterization:

In order to deeply explore the immunological characteristics of the two subtypes, we performed a comparative analysis of their infiltrating immune cell abundance and immune response activity. The results showed that the infiltration level of a variety of immune cells was significantly higher in subtype B, including activated B cells, activated CD4+ T cells, activated CD8+ T cells, activated dendritic cells, γδ T cells, immature B cells, myeloid-derived suppressor cells (MDSCs), mast cells, natural killer T cells, natural killer cells, plasma cells, dendritic cells, regulatory T cells, T follicular helper cells, type 1 T helper cells and type 2 T helper cells (Figure 4A). Correlation analysis further revealed the existence of differential association patterns between the 17 regulatory factors and specific immune cell types; a result visualized in the heatmap (Figure 4B). In terms of immune response characteristics, subtype B exhibited significant activation of multiple immune pathways, including antigen-presenting cell (APC) costimulation, chemokine receptor (CCR) signaling pathway, immune checkpoints, cytolytic activity, human leukocyte antigens (HLAs), pro-inflammatory responses, expression of MHC class I molecules,

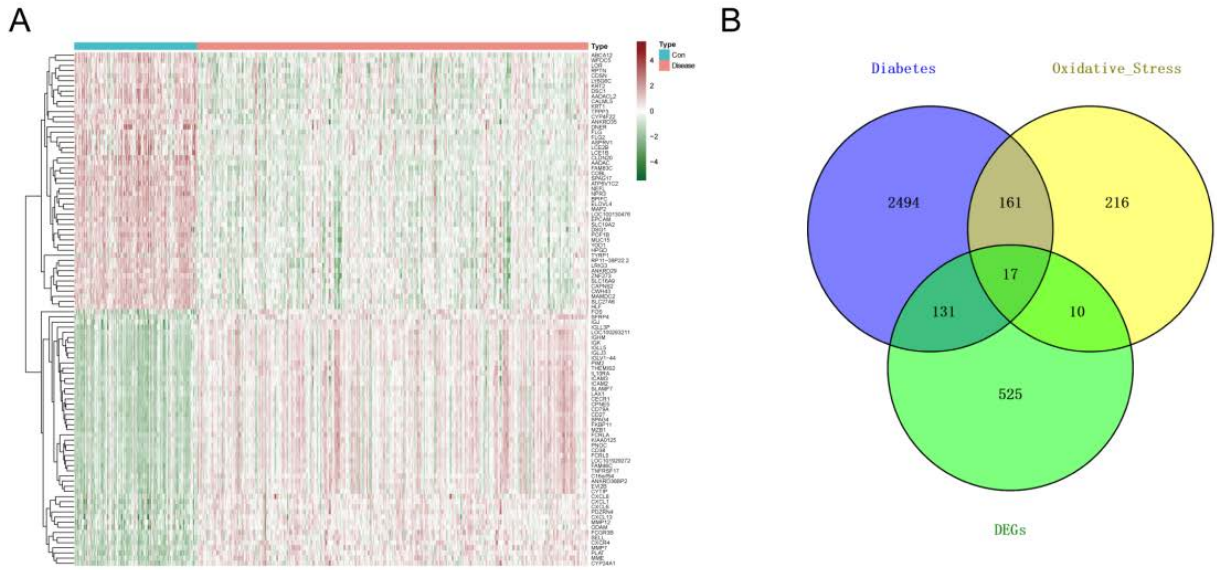


Figure 1. Analysis of variances. *(A) Heatmap representation of gene expression levels across various conditions, with the color scale indicating the level of expression. (B) Venn diagram illustrating the intersection of genes associated with diabetes, oxidative stress and differentially expressed genes.*

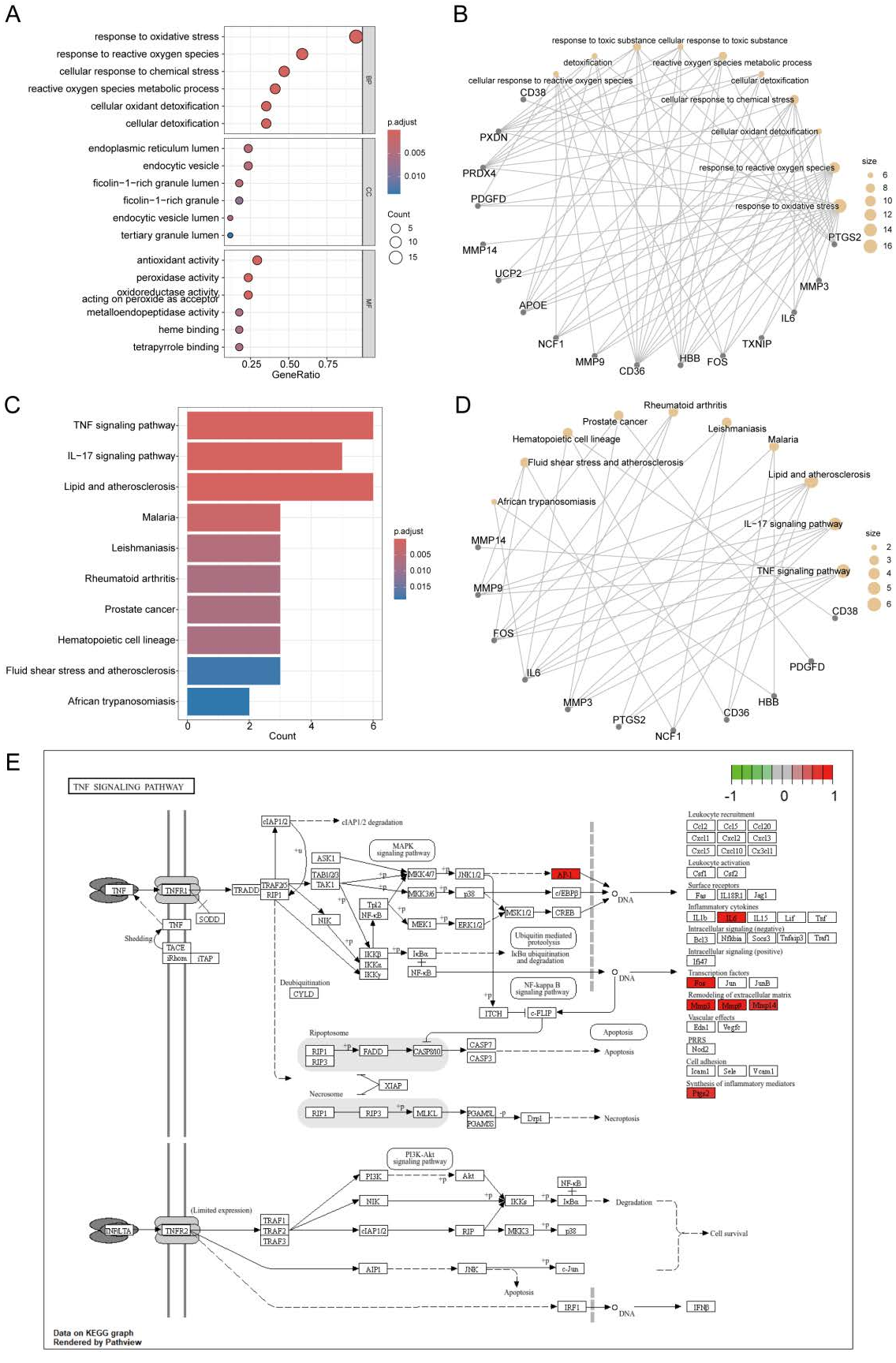


Figure 2. Enrichment analysis. *(A) Dot plot of GO enrichment analysis showing biological processes associated with DEGs. (B) Network diagram illustrating interactions between DEGs and biological processes. (C) Bar chart of top KEGG pathways enriched by DEGs. (D) Network diagram depicting DEG relationships with specific pathways. (E) Pathway map of the TNF signaling pathway, rendered using Pathview.*

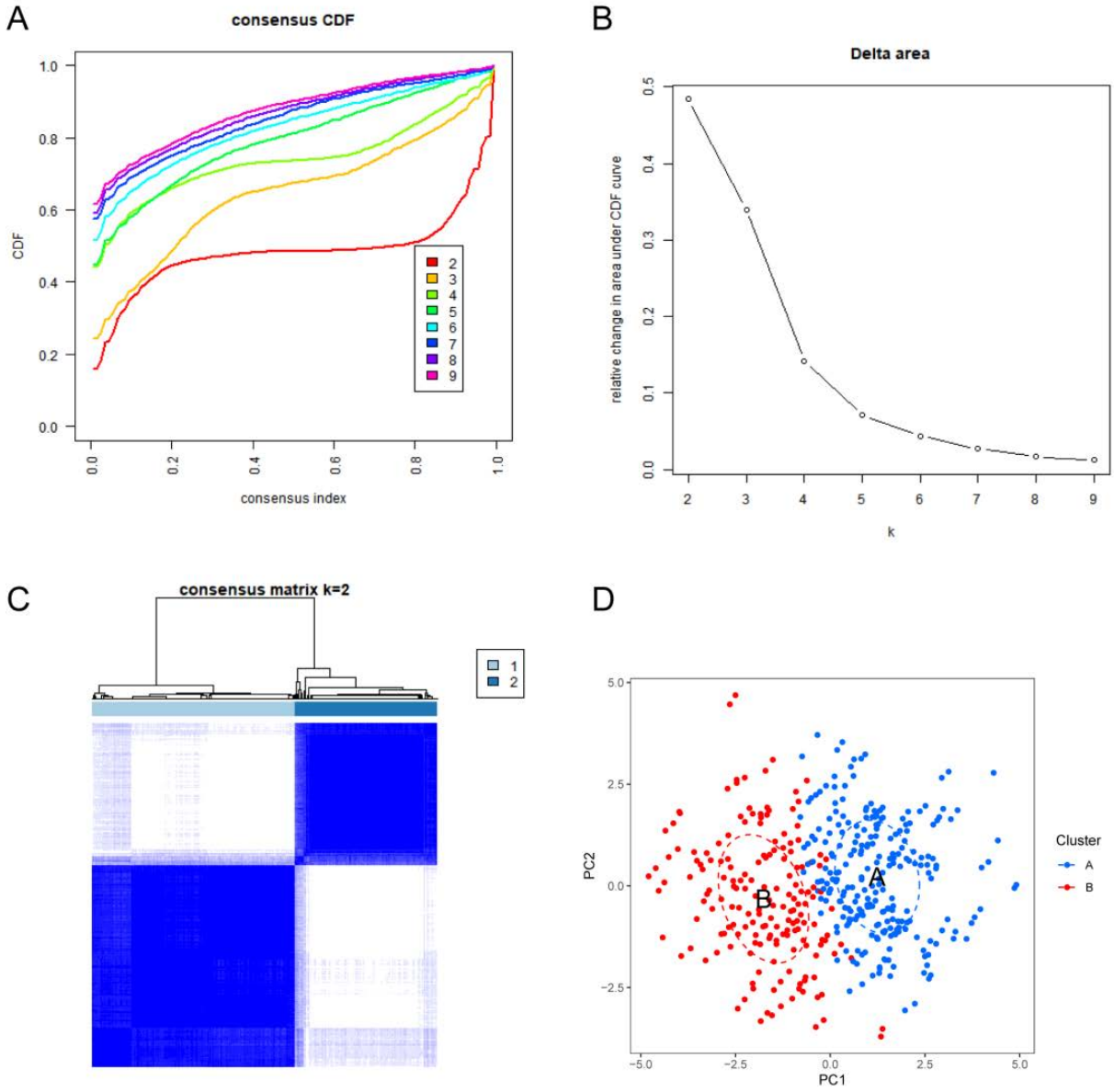


Figure 3. Consensus clustering analysis. *(A) Consensus cumulative distribution function (CDF) across multiple runs, illustrating the convergence of consensus indices for varying k values. (B) Delta area plot showing the average change in total delta-CDF curves as a function of k, indicating stabilization with increasing k. (C) Consensus matrix heatmap for k=2, displaying the hierarchical clustering and consensus levels among data points. (D) PCA scatter plot of the OR clusters, with distinct groupings labeled as A (blue) and B (red).*

T-cell costimulation, T-cell costimulation, and type II interferon (IFN) responses (Figure 4C). Further correlation analyses (Figure 4D) demonstrated the pattern of association between these regulatory factors and immune characteristics. Together, these results suggest that different subtype patterns have a unique spectrum of immunologic features.

Machine learning analysis:

To deeply reveal the molecular mechanisms of genes in the regulation of oxidative stress, we integrated and applied three machine learning methods (SVM, LASSO regression, and RF) for the identification of key target genes. 15 potential candidate target genes were successfully screened out by the SVM analysis (Figure 5A-B). 16 potential key targets were identified by the LASSO regression analysis (Figure 5C-D). Meanwhile, RF analysis rank-ordered all genes based on gene importance index (Figure 5E).

To identify the most reliable targets, we used Venn diagrams to analyze the intersection of three sets of data: candidate genes identified by SVM, genes ranked in the top 8 (the juncture at which the decline in significance becomes pronounced) by RF importance, and targets screened by LASSO (Figure 5F). Through this multi-algorithmic integrated analysis strategy, we finally identified seven key targets involved in the regulation of oxidative stress in diabetic periodontitis.

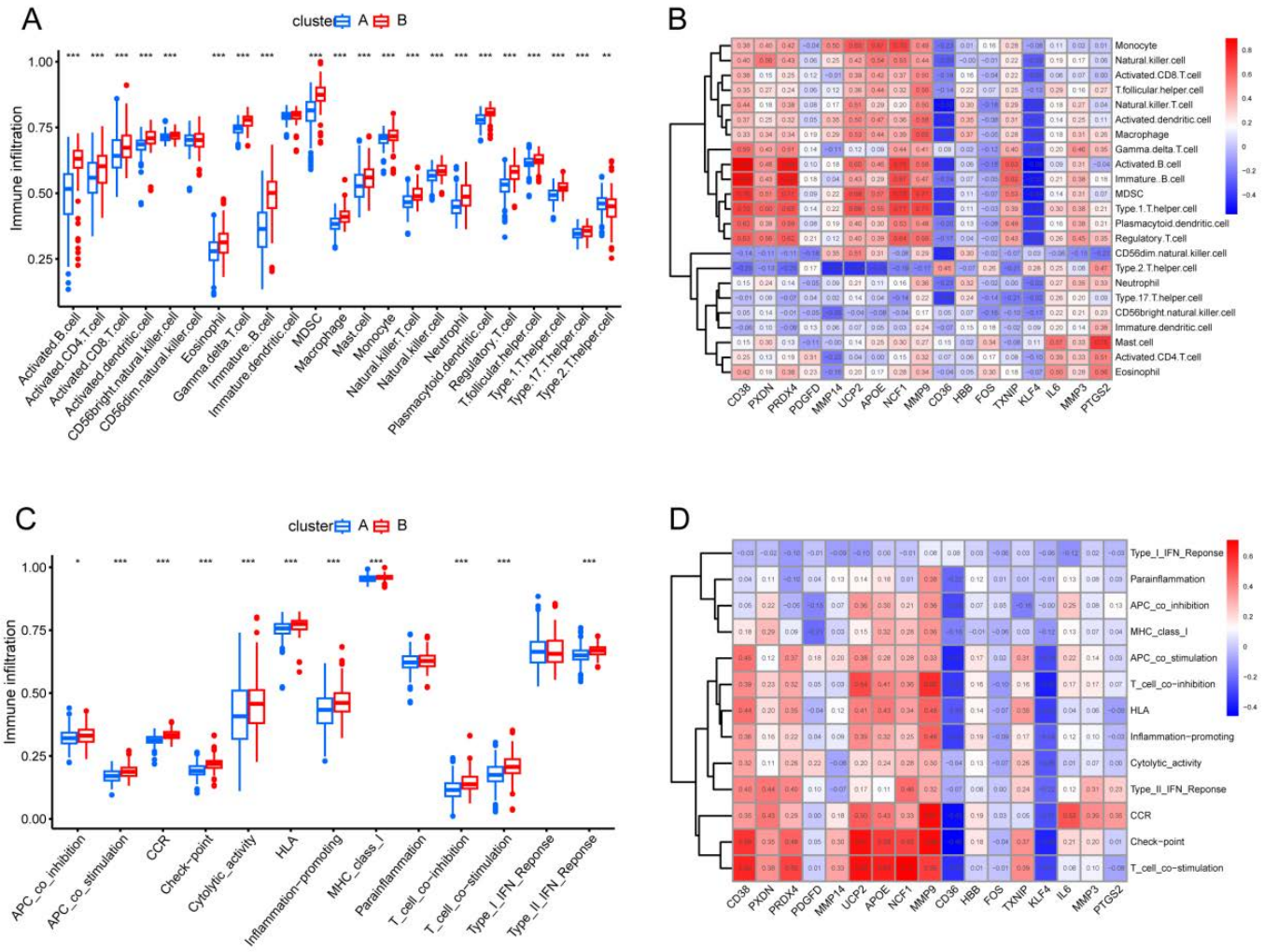


Figure 4. Immunological characterization analysis. *(A) Differences in abundance of 23 infiltrating immune cells. (B) Correlation between infiltrating immune cells and 17 DEGs. (C) Difference in activity of 13 immune responses in the two subtypes. (D) Correlation between immune responses and 17 DEGs.*

Screening key genes:

Based on the seven genes obtained from machine learning screening, we first constructed and visualized a PPI network using the STRING database (Figure 6A), which identified five genes with PPI interactions. Subsequently, we applied multivariate logistic regression analysis to construct classifiers for distinguishing healthy samples from disease samples (Figure 6B). In this multivariate analysis, among the five candidate genes, four genes (FOS, MMP14, CD38, and PXDN) met all selection requirements and were included in the final predictive model, while the APOE gene was excluded due to non-significant p-values ($p > 0.05$) in the multivariate analysis. To validate the differential expression of these four key genes between the disease group and the normal control group, we performed independent validation using the GEO dataset. The results showed that FOS, MMP14, CD38, and PXDN showed significant upregulation in the patient samples ($p < 0.05$; Figure 6C). Figure 6D demonstrates the distribution of the specific locations of these four key genes in the genome (FOS: chromosome 14, MMP14: chromosome 14, CD38: chromosome 4, PXDN: chromosome 2). Analysis of the ROC showed that these four genes were diagnostically sound in distinguishing between healthy and diseased states, highlighting their important role in the development of periodontal disease (Figure 6E).

Construction and Validation of the Prediction Nomogram:

To predict the risk of periodontitis in patients, we constructed a prediction nomogram based on the core target genes (FOS, MMP14, CD38, and PXDN) (Figure 7A). ROC curve analysis showed that the AUC of this nomogram was 0.931, indicating its excellent prediction accuracy (Figure 7B). The slope of the calibration curve was close to 1, confirming that the nomogram had significant predictive efficacy (Figure 7C). In addition, the results of DCA showed that the nomogram had substantial net benefits in clinical applications (Figure 7D).

Molecular docking of Metformin with core target proteins:

We obtained the standard structure of metformin from the PubChem database (Figure 8A), and its molecular characterization parameters were detailed in Table 1. The

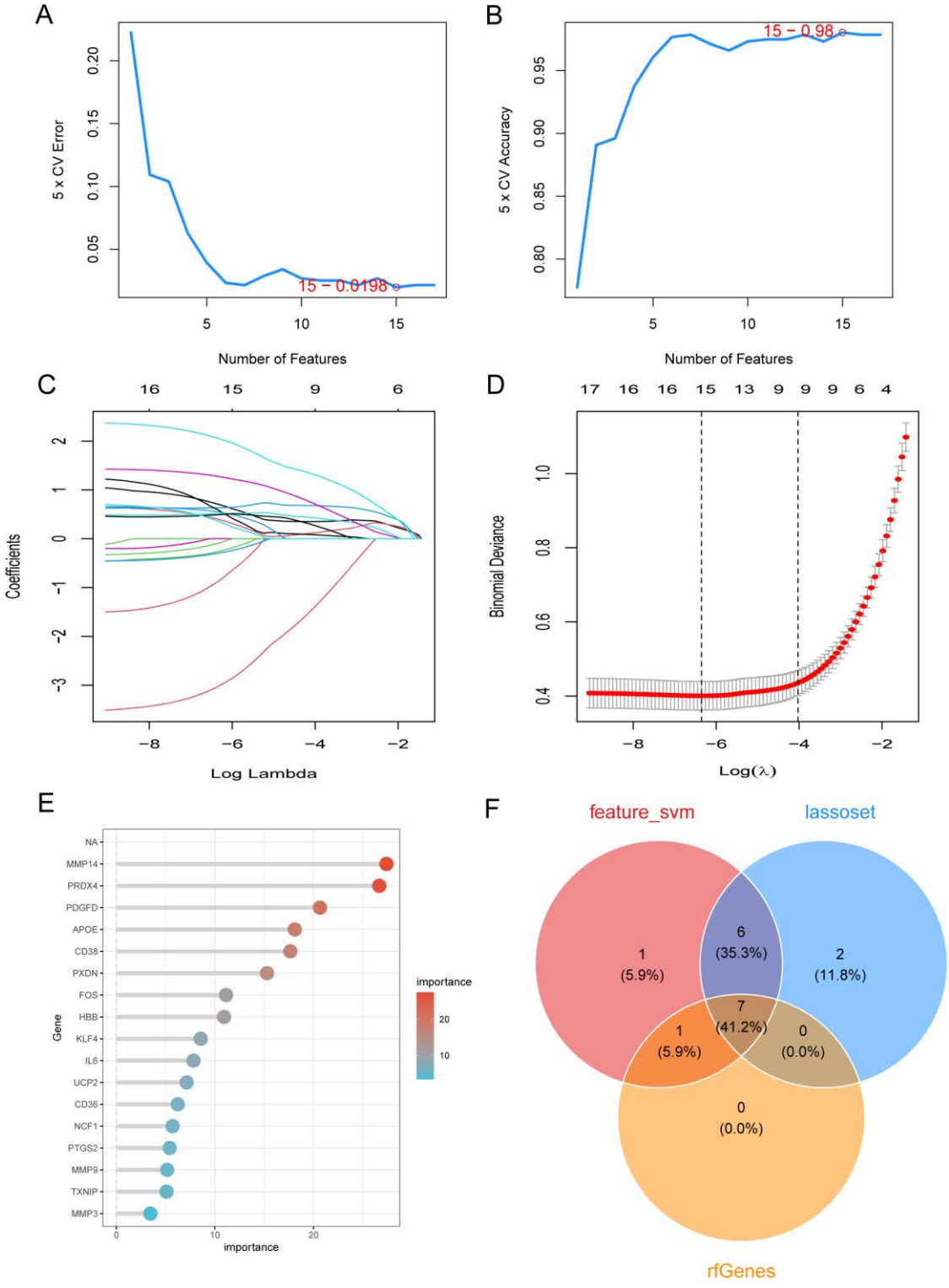


Figure 5. Three machine learning analyses. *(A) Cross-validation error as a function of the number of features, indicating the optimal number of features (dashed line) that minimizes the error. (B) Cross-validation accuracy plotted against the number of features, showing the peak accuracy at the optimal feature count. (C) Coefficient profiles from LASSO regression across different regularization strengths (log lambda), highlighting the selection of key features. (D) Brier distance as a function of log lambda, demonstrating the trade-off between model complexity and prediction error. (E) Feature importance plot showing the relative importance of each gene in the model, with size and color indicating higher importance. (F) Venn diagram illustrating the overlap of features selected by different models (feature_svm, lassoset, rfGenes), with numbers representing unique and shared features among the models.*

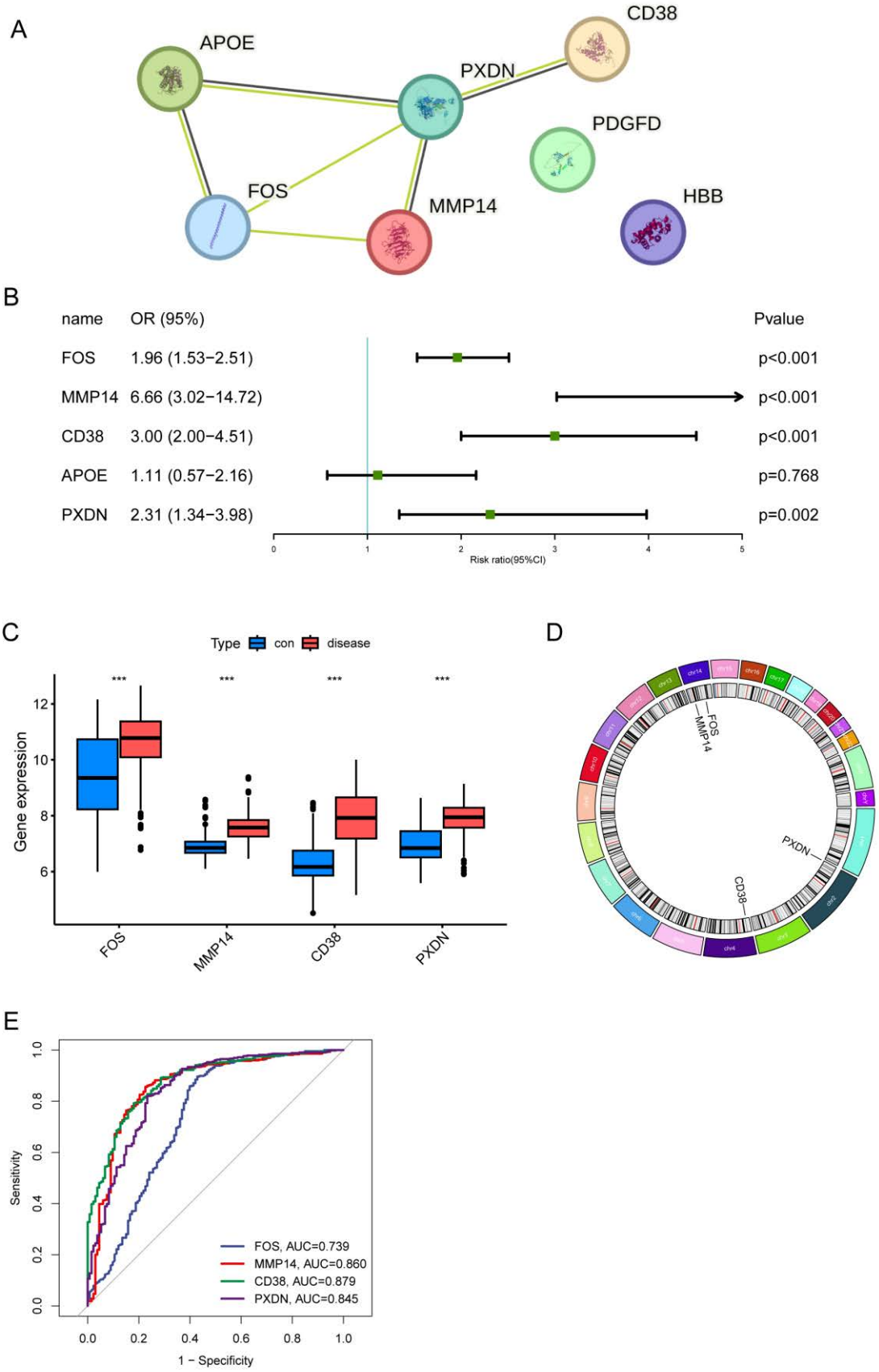


Figure 6. Screening of key genes. *(A) Network diagram illustrating interactions between key genes. (B) Forest plot showing odds ratios and 95% confidence intervals for each gene. (C) Box plot comparing gene expression levels between groups. (D) Circular heatmap displaying gene expression profiles across samples. (E) ROC curves for each gene.*

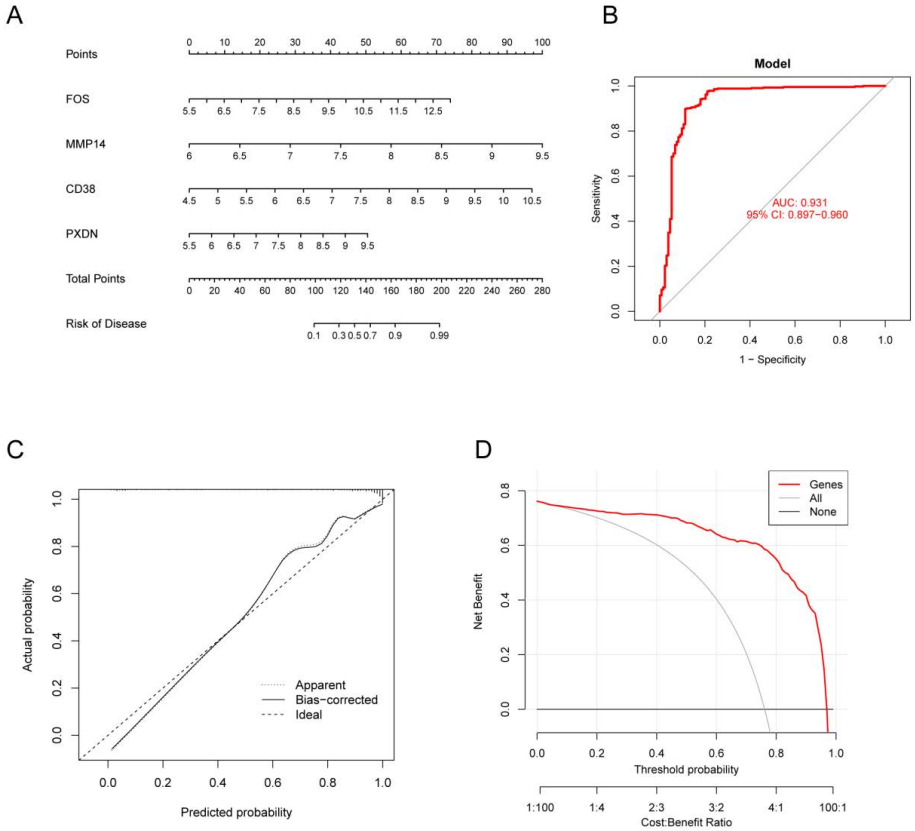


Figure 7. Clinical predictive model development and performance validation. *(A) Nomogram for predicting disease risk based on the expression levels of FOS, MMP14, CD38, and PXDN. (B) ROC curve for a combined model using multiple genes. (C) Calibration plot comparing predicted probabilities with actual outcomes. (D) Decision curve analysis evaluating the net benefit of the predictive model.*

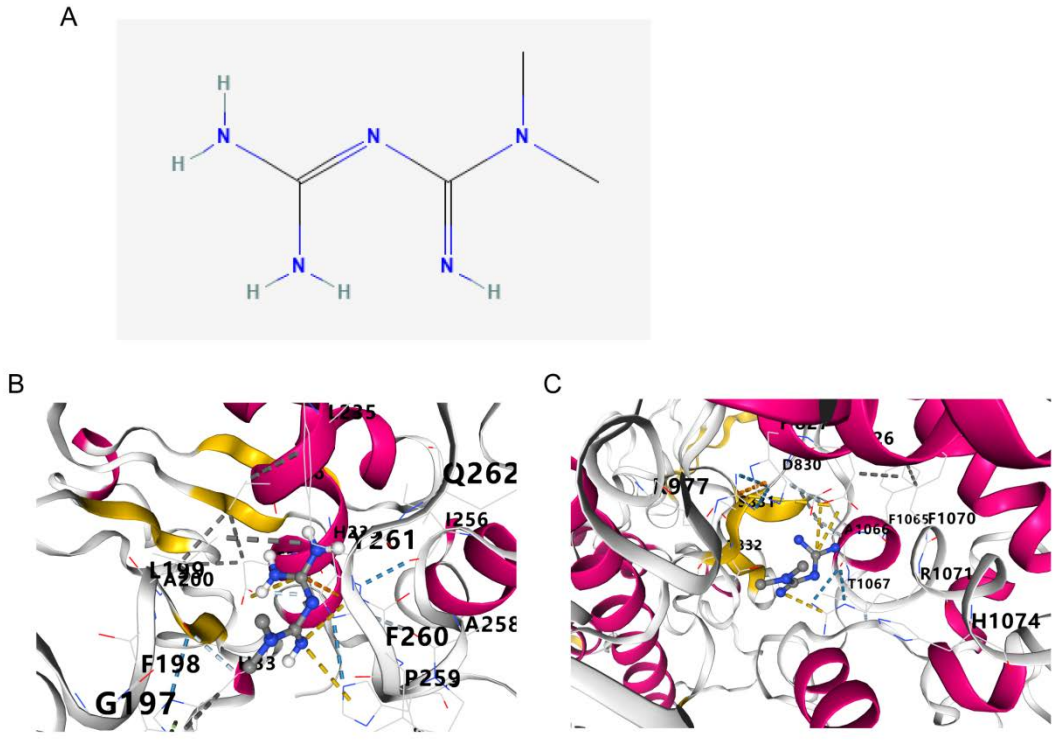
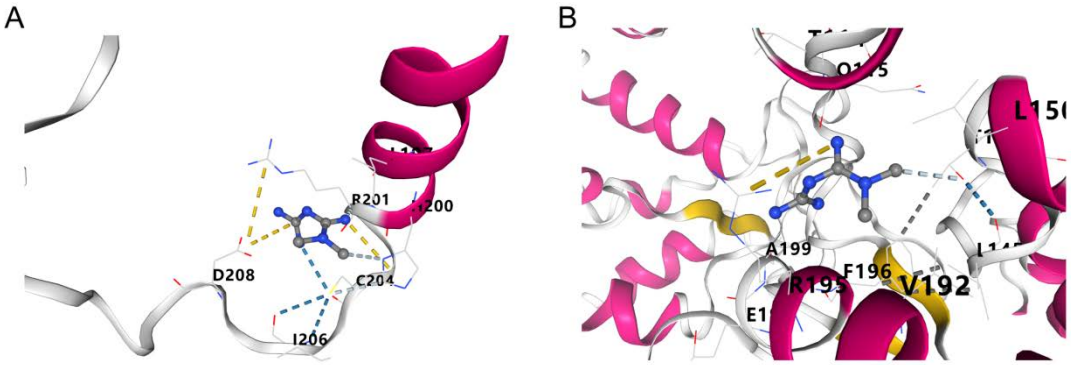


Figure 8. Molecular docking results *(A) Structure of Metformin. The Image sourced from the PubChem website. (B) Molecular structure of the MMP14-Metformin complex showing the binding site with key interacting residues. (C) Alternative conformation of the PXDN-Metformin complex highlighting the same residues and interactions.*



Supplementary Figure 1. Molecular docking results *(A) Molecular structure of the FOS-Metformin complex showing the binding site with key interacting residues. (B) Alternative conformation of the CD38-Metformin complex highlighting the same residues and interactions.*

Table 1. *Detailed information about Metformin (CID:4091) molecule (https://pubchem.ncbi.nlm.nih.gov/compound/4091).*

Property Name	Property Value	Reference
Molecular Weight	129.16 g/mol	Computed by PubChem 2.2 (PubChem release 2021.10.14)
Molecular Formula	C4H11N5	Computed by PubChem 2.2 (PubChem release 2021.10.14)
SMILES	CN(C)C(=N)N=C(N)N	Computed by OEChem 2.3.0 (PubChem release 2024.12.12)

potential interactions between Metformin and the core target genes (FOS, MMP14, CD38, and PXDN) were molecularly docked and analyzed using CB-DOCK2 software (Figure 8B-C, Supplementary Figure 1). Notably, the binding energies of Metformin with MMP14 and PXDN were low (MMP14-Met: -5.6 kcal/mol; PXDN-Met: -5.2 kcal/mol). The docking results showed that Metformin exhibited strong binding affinity with both MMP14 and PXDN, and the binding energies were lower than -5.0 kcal/mol [16], which revealed the stable interactions between the compounds and the targets.

Discussion.

Periodontitis and diabetes are widespread conditions that involve multiple genes and signaling pathways. Clinically, both periodontitis and T2DM act as risk factors for each other, demonstrating a bidirectional relationship [17,18]. However, the molecular mechanisms linking these two diseases have not been fully elucidated. Oxidative stress, a common pathological feature of both diseases, may play a key role in their interaction [19]. However, the underlying mechanisms leading to this connection are not fully understood. In this study, 17 differential genes associated with periodontitis, diabetes and oxidative stress were systematically identified by integrating multiple datasets. Enrichment analysis showed that these genes were mainly enriched in the TNF and IL-17 signaling pathways, and four core genes (FOS, MMP14, CD38, and PXDN) were further screened by multiple analytical methods, among which MMP14 and PXDN showed strong binding affinity to metformin, suggesting that metformin may influence the disease process by regulating the expression of these genes. These findings not only deepen our understanding of the pathogenesis of diabetic periodontitis, but also provide new molecular targets for exploring the therapeutic mechanism of metformin in this disease.

In this study, we integrated gene expression profiling datasets for four specific groups (GSE30528 and GSE96804) and analyzed these datasets using R. A total of 683 DEGs were identified using the limma package, including 448 up-regulated and 235 down-regulated genes. By overlapping the periodontitis differentially expressed genes, oxidative stress-responsive gene set, and diabetes-associated gene set, 17 differentially expressed genes were obtained that were associated with periodontitis, diabetes, and oxidative stress all. KEGG enrichment analyses pointed to the IL-17 signaling pathway and the TNF signaling pathway. During the development of periodontitis, neutrophil extracellular trapping networks (NETs) can trigger the upregulation of IL-17/Th17 responses and bone destruction [20]. TNF is a pro-inflammatory cytokine that plays a crucial role in various inflammatory pathways, including the recruitment, activation, and survival of immune cells [21]. Increased expression of the TNF signaling pathway during the development of periodontitis has also been widely reported. In addition, diabetes also enhances the expression of proteins associated with the TNF-α pathway (TNF-α, NF-κB). Therefore, we hypothesized that diabetes and periodontitis may have a cross-over development by affecting the IL-17 signaling pathway and the TNF signaling pathway.

Molecular subtyping is a strategy that has been widely applied in malignancies. Tailored treatment plans can be developed based on different molecular types, thereby improving patients' prognoses [22]. Based on the expression profiles of these 17 DEGs, we identified two distinct molecular subtypes of periodontitis, which may provide a novel classification strategy for the disease. Our immunological analysis revealed significant differences in immune cell infiltration between these subtypes, with subtype B showing notably higher levels of various immune cells, including activated B cells, CD4+ T cells, CD8+ T cells, dendritic cells, and other immune cell populations. This finding aligns with previous research suggesting that immune cell alterations play a crucial role in the relationship between T2DM and periodontitis. The elevated expression of multiple immune cell types in subtype B, particularly the increased

presence of dendritic cells and T helper cells, indicates a more pronounced inflammatory state that may contribute to disease progression. This molecular subtyping approach, similar to strategies widely used in cancer research, could potentially guide the development of personalized therapeutic interventions for different patient groups with diabetic periodontitis.

An important finding of this study is the successful screening of four core targets (FOS, MMP14, CD38, and PXDN) by integrating machine learning methods, protein-protein interaction analysis, and logistic regression methods. Among them, FOS, as a transcriptional activator of the AP-1 complex, plays a key role in regulating multiple signaling pathways and gene expression related to cell proliferation and apoptosis [23]. In addition, FOS genes have been associated with inflammatory responses [24]. Studies have shown that activation of AP-1 (c-Fos/c-Jun) transcription promotes osteoclastogenesis, which in turn leads to alveolar bone loss [25,26]. Matrix metalloproteinase 14 (MMP14) is a membrane type I collagenase that plays a crucial role in the postnatal development of mesenchymal tissues [27]. Previous studies have demonstrated its developmental function during adipogenesis [28]. However, there is still a relative paucity of studies on the role of MMP14 in periodontal disease.CD38 is widely expressed in a variety of tissues and is an important molecule in the regulation of NAD+ metabolism, extracellular nucleotides and intracellular calcium homeostasis [29]. In infection-induced inflammation, CD38 is induced to be expressed upon cellular activation and is involved in regulating processes such as cell recruitment and adaptive immune response.CD38 plays a key role in the immune response of macrophages, neutrophils and T cells. It has been found that during certain chronic inflammatory processes such as aging, the expression level of CD38 is elevated, accompanied by a decrease in NAD levels [30]. Notably, there is a correlation between decreased CD38 expression in neutrophils and altered neutrophil function in patients with limited invasive periodontitis [31]. Peroxidase (PXDN) encodes a heme-containing enzyme secreted into the extracellular matrix, where it contributes to matrix formation [32]. As a cell surface peroxidase associated with the extracellular matrix, in cancer cells, the interaction of PXDN with HO-1 promotes tumor invasion by decreasing the expression of the extracellular matrix proteins fibronectin and laminin [33]. Findings suggest that PXDN has a role in promoting tumor development in oral squamous cell carcinoma (OSCC) [34]. However, studies on the role of PXDN in periodontitis and diabetic periodontitis are still pending.

Metformin, as a first-line therapeutic agent for type 2 diabetes recommended by national guidelines, not only has significant glucose-lowering effects, but may also have other potential health benefits [35]. Current studies have shown that metformin acts mainly by inhibiting the mitochondrial respiratory complex and can improve cellular autophagy and oxidative stress status by activating the AMPK signaling pathway [36]. However, its exact target of action and detailed molecular mechanisms have still not been fully elucidated. In the present study, the results of molecular docking analysis revealed that metformin has a significant binding affinity for MMP4 and PXDN, with binding energies all below -5.0 kcal/mol. This finding is of great significance, suggesting that metformin is able to spontaneously bind to these two key protein targets, which may be one of the important molecular mechanisms by which it regulates the development of diabetes-related periodontal diseases. This result not only provides a new perspective for understanding the mechanism of action of metformin in diabetic periodontal disease, but also provides a theoretical basis for further development of targeted therapeutic strategies.

Overall, this study systematically investigated the role of oxidative stress in the pathogenesis of diabetic periodontitis with several remarkable features and innovative findings. First, by integrating multiple datasets and applying various bioinformatics analysis methods, we successfully identified four core genes (FOS, MMP14, CD38, and PXDN) and verified their reliability in the disease process. Secondly, the predictive column line graphs constructed based on these four key genes demonstrated good predictive efficacy and provided a potential practical tool for clinical risk assessment. In addition, our molecular docking analysis suggests that metformin may potentially interact with MMP14 and PXDN proteins, which could provide a theoretical basis for understanding its possible mechanism of action in diabetic periodontitis. However, this study still has some limitations: first, the findings are mainly based on data analysis and lack experimental validation in an independent cohort; second, although the binding sites of metformin with key proteins have been identified, their specific molecular regulatory mechanisms still need to be further corroborated by in vitro and in vivo experiments. Future studies could focus on the functional validation of these findings and explore their application value in clinical individualized therapy.

Conclusion.

This study comprehensively explored the molecular mechanisms linking periodontitis and diabetes, particularly focusing on oxidative stress-related pathways. Through systematic analysis, we identified four key genes (FOS, MMP14, CD38, and PXDN) that play crucial roles in the pathogenesis of diabetic periodontitis. The TNF and IL-17 signaling pathways emerged as significant mediators in this disease connection. Notably, we discovered two distinct subtypes of periodontitis with different immune cell infiltration patterns, suggesting potential personalized therapeutic approaches. The molecular docking analysis revealed that metformin shows strong binding affinity with MMP14 and PXDN, indicating these proteins might be potential therapeutic targets. Our findings provide new insights into the molecular basis of diabetic periodontitis and suggest potential therapeutic strategies for this complex condition. These results not only deepen our understanding of the relationship between diabetes and periodontitis but also offer new perspectives for developing targeted treatments.

Declarations.

Ethical Approval: Not applicable.

Consent for publication: Not applicable

Data availability:

The data that support the findings of this study are available upon request from the corresponding author, upon reasonable request.

Competing interests:
The authors declare that they have no competing interest.
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