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Assessment of surgical journals listed in the TR Index in the context of primary care and surgical literature

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ABSTRACT

Aims: In general surgery and family medicine speciality training, it is emphasised that physicians should understand the approach to surgical diseases, be familiar with these diseases, and keep up to date by accessing new literature. To achieve this, physicians must recognise, access, and follow surgical journals. In this context, it is aimed to evaluate the surgical journals in the TR Index in order to provide convenience and guidance to physicians in our study.

Methods: Our study is descriptive and the number of annual publications, language of publication, format of publication, publication language, publication format, and publication of 96 journals, the subject area of which is surgery, which were available on the TR Directory Internet Site (https://trdizin.gov.tr/) on 20.04.2025. year, the number of published articles, the number of citations received, the citation average, the number of self-citations, the rate of self-citation, the number of cited articles, and the types of articles published.

Results: Considering the annual publication numbers of the journals, 49% (n=47) of the journals were published four times a year, 53.13% (n=51) were published in English-Turkish, 54.17% (n=51) of the journals were the most common publication format. 52) electronically, 5.21% (n=5) never published an article, 11.46% (n=11) were never cited, 22.92% (n=22) had no self-citation, 12.50% (n=12) did not publish cited articles, and 61.16% (n=27 724) research articles were published most frequently in these journals.

Conclusion: The frequent use of English in the journals examined may be due to their inclusion in the TR Index and the specific standards required there. The promotion of electronic publishing in the TR Index through improvements may have influenced the frequent use of electronic formats. It was observed that some journals did not publish any articles, did not receive citations, or did not publish articles that received citations. This may be related to the timeliness of the data in the TR Index, as well as the structure of the journals examined. Our study is limited in that it only includes TR Index data. There is a need for broader descriptive studies that include other indices, databases, and relevant journal websites that measure the scientific impact of journals, as well as evaluations of the opinions, attitudes, and behaviours of surgeons and family physicians on this subject. However, the findings obtained may contribute to family physicians and surgery-related clinicians making more informed decisions regarding literature tracking and journal selection.

Keywords: Bibliometric analyses, journal article, medical education, primary care, surgery

INTRODUCTION

One of the oldest branches of surgical medicine, it is a field where knowledge and skill complement each other, combining both science and art, based on repairing diseases, injuries, and structural abnormalities that cannot be cured with medication or other treatment methods through surgery, or by removing the diseased organ.[1]

The main objective of surgical speciality training is to ensure that physicians undergoing training gain professional competence, acquire the knowledge and skills they need to practice their profession, and develop the ability to engage in lifelong learning and maintain competence through this training.[2]

Core Curriculum for General Surgery Residency Training Within the Turkish Board of Medical Specialities Curriculum Development and Standard Setting System (TUKMOS). Within the structured educational activities, it is emphasised

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that those undergoing general surgery residency training must receive training and become competent in areas such as presentations, seminars, case discussions, article discussions, and file discussions.[3]

The primary goal of healthcare systems is to improve the quality of life and standards of service provided to individuals by increasing the accessibility and inclusiveness of primary healthcare services.[4] The efficient use of primary healthcare services will reduce the burden of disease on society, enabling secondary and tertiary healthcare institutions to provide services and training at higher standards.[5] Within this scope, the family medicine practice (FMP) has been designed to refer patients to the appropriate department and centre, to prevent unnecessary visits and overcrowding at the second and third levels.[6] In this regard, a study conducted in Turkiye found that there was a decrease in three of the 14 diagnoses used in general surgery after the implementation of FMP. Family physicians who received training under FMP and kept up to date may have contributed to this situation.[7]

Family medicine is an academic and scientific discipline with its own educational content, evidence-based and clinical practices, and a clinical speciality focused on primary care.[8] The Core Curriculum for Family Medicine Residency Training is determined by the Turkish Board of Medical Specialities Curriculum Development and Standard Setting System (TUKMOS) and is specified as a one-month rotation in general surgery. This section discusses the procedural competency objectives of "abscess drainage," "emergency approach to surgical diseases and application of referral criteria," "debridement," "local anaesthesia," and "suturing/removing sutures," as well as the desired competency levels. The same curriculum emphasises the necessity for family physicians to receive training and become competent in areas such as presentations, seminars, case studies, articles, and file discussions within structured education activities.[9] In this context, family physicians should have access to literature on surgical topics they encounter and have been trained in, and should keep themselves updated through surgical journals.

The TR Index, developed by the National Academic Network and Information Centre (ULAKBİM) of the Scientific and Technological Research Council of Turkiye (TÜBİTAK), is an index developed in accordance with international standards to provide researchers with electronic access to national and scientific content. It has been searchable via its website since August 2000.[10] In 2018, ULAKBİM introduced a new interface providing online access to the scientific community, and with these improvements, new features such as the Online Journal Monitoring System (ODİS) were added to the TR Index.[11]

As stated in both family medicine and general surgery residency training, physicians undergoing speciality training should know how to approach surgical diseases, be knowledgeable about surgical diseases, and update their knowledge by accessing new literature related to these diseases. In order to accomplish all of this, it is important for family physicians, especially surgeons, to be familiar with, have access to, and follow journals that publish surgical-related content. In this context, our study aims to facilitate access to surgical literature for clinicians working in primary care, especially family physicians, and to provide guidance on appropriate publication sources by evaluating surgical journals listed in the TR Index. Therefore, the systematic evaluation of journals publishing surgical content serves as an important guide for family physicians working in primary care in accessing current and reliable information sources.

METHODS

The study was conducted in accordance with the relevant ethical principles and publication ethics standards. Our study does not involve the use of techniques such as surveys or interviews, nor does it employ quantitative or qualitative approaches. Furthermore, it does not involve the use of humans or animals for clinical, scientific, or experimental purposes. It was conducted by reviewing the literature related to publicly available data in the TR Index. Therefore, there is no ethical violation.

Our study is descriptive in nature and evaluates journals in the field of surgery listed on the TR Index website (https://trdizin.gov.tr/). Since the TR Index is a dynamic database that is continuously updated, all data used in this study were retrieved at a single time point on April 20, 2025. The study was conducted using the most up-to-date data available on the TR Index on the specified date. All statistical analyses performed in this study were descriptive/bibliometric in nature; no comparative or inferential statistical analyses were conducted. To be included, journals were required to be actively indexed in TR Index at the time of data collection and to have accessible and sufficiently complete bibliometric data available in the database. These data included annual publication count, publication language, publication format, year of establishment, total number of published articles, total number of citations received, average citations per article, number and rate of self-citations, and the number of articles receiving citations.

Initially, 101 journals classified under the subject area "surgery" were identified and screened. However, five journals were excluded because their bibliometric data were missing, incomplete, inaccessible, or insufficiently reported on the TR Index website for the purposes of analysis. Additionally, the database was reviewed for potential duplicate records, and any such entries would have been excluded to prevent data redundancy. After applying these criteria, a total of 96 journals were included in the final analysis.

Statistical Analysis

IBM SPSS v.24 software package was used for statistical analyses. Descriptive statistics were calculated for continuous variables, including mean, standard deviation, minimum, and maximum values, while categorical variables were expressed as counts and percentages.

RESULTS

Looking at the annual publication numbers of the 96 journals examined in our study, 48.96% (n=47) of the journals publish four times a year, 53.13% (n=51) publish in English–Turkish, and the most common publication format is electronic at 54.17% (n=52), as shown in **Table 1**.

The journals under review began publication between 1916 and 2020, with 13.54% (n=13) most frequently starting in 2018. The number of articles published by the journals ranged from 0 to 3829, with a median of 337.00, and 5.21% (n=5) did not publish

Table 1. Information on the annual number of publications, publication language, and publication format for journals

	Frequency (n)	Percentage (%)
Annual publication frequency		
3 issues per year	37	38.54
4 issues per year	47	48.96
5 issues per year	1	1.04
6 issues per year	8	8.33
12 issues per year	3	3.13
Total	96	100.0
Publication language		
English-Turkish	51	53.13
Turkish	5	5.21
English	40	41.67
Total	96	100.0
Publication format		
Electronic	52	54.17
Electronic-printed	32	33.33
Printed	12	12.59
Total	96	100.0

any articles. The number of citations they received ranged from 0 to 2007, with a median of 54.00, and 11.46% (n=11) received no citations. The number of self-citations ranged from 0 to 660, with a median of 4.50, and 22.92% (n=22) had no self-citations. The number of articles receiving citations ranged from 0 to 1008, with a median of 34.00, and 12.50% (n=12) did not publish any articles that received citations. Information regarding the number of articles published in journals, the number of citations received, the average number of citations, the number of self-citations, the self-citation rate, and the number of articles that received citations is shown in Table 2.

Table 2. Data on the number of published articles, citations, citation averages, self-citations, self-citation rates, and cited articles were analyzed

	Min-max	Median (Q1-Q3)
Number of published articles	0-3829	337.00 (156.00-586.00)
Number of citations received	0-2007	54.00 (7.00-287.70)
Citation average	0-2,84	0.10 (0.00-0.40)
Number of self-citations	0-660	4.50 (1.00-20.50)
Self-citation rate	0-100	6.90 (1.60-24.40)
Number of articles cited	0-1008	34 (5.20-133.00)

Min: Minimum, Max: Maximum

When articles published in journals were examined by type, it was found that research articles were published most frequently at 61.16% (n=27,724). Information about the types of articles published in journals is provided in Table 3.

Table 3. Information on the types of articles published in journals

Article types	Frequency (n)	Percentage (%)
Research article	27 724	61.16
Case reports	9902	21.84
Reviews	2581	5.69
Letter to editors	1026	2.26
Others*	4092	9.02
Total	45 325	100

* Other (editorial, short communication, letter, book review, correction, etc.)

DISCUSSION

In our study, when looking at the annual publication numbers of the journals, 48.96% (n=47) of the journals publish four times a year, 53.13% (n=51) publish in English-Turkish, the most common publication format is electronic at 54.17% (n=52), 5.21% (n=5) do not publish any articles, 11.46% (n=11) received no citations, 22.92% (n=22) had no self-citations, 12.50% (n=12) did not publish any articles that received citations, and 61.16% (n=27,724) of the articles published in these journals were research articles.

In addition to being specified in the curricula of speciality training, journals also hold an important place in scientific publishing. Physicians undergoing speciality training should update their knowledge by accessing current literature. When examining the distribution of the most frequently published topics in a study that researched publications with Turkish addresses in citation indexes, it was found that the most productive scientific field in terms of publication count was "surgery."[12] In a study examining 253 scientific electronic journals in Turkiye, the frequency of publication was analysed, revealing that 39% (n=98) publish four times a year and 38% (n=96) publish twice a year.[13] In this context, our study examined 96 surgical journals, and it was determined that 49% of the journals examined (n=47) published four issues per year and showed similar characteristics to other studies. It was determined that the annual publication range of the journals was wide and that the number of publications varied among the journals. The wide range and variability in the annual number of publications may be due to the diversity of the journals included in the study, the data available in the TR Index, or the decisions made by the editorial boards of the journals included in the study.

When examined in terms of publication language, approximately 95% of journals are published in English. A study that surveyed journals based in Turkiye found that 66% of the total number of publications were in English.[14] Another study examining publications based in Turkiye found that 97% of publications were in English.[12] The predominant use of English, the international language of publication, in Turkiye-based journals, its frequent use in journals indexed in TR Dizin, and the fact that journals under evaluation are included in TR Dizin and meet certain standards may be contributing factors.

TR Index has been searchable via its website since August 2000.[10] Additionally, in 2018, ULAKBİM promoted electronic publications by launching a new interface that provides online access to the scientific community and implementing new improvements such as the ODİS.[11] It has been observed that there has been an increase in the use of electronic resources since the 2000s, and that many online journals have emerged.[13] Additionally, researchers working in the scientific field want to access information wherever, whenever, and as easily as possible.[15] Our study found that the publication format of the journals is frequently electronic. This situation may stem from the circumstances mentioned above, as well as from the fact that the journals in our study are included in the TR Index and adhere to certain standards. On the other hand, the promotion of electronic publishing in the TR Index through improvements also seems to be a reason why the publication format of the journals included in the study is frequently electronic.

ODIS was launched in 2018 on the TR Index, enabling journals to be monitored online.[11] The years in which the journals in our study began publication vary, with 2018 being the most common year of launch. In a study examining scientific electronic journals in Turkiye, it was found that two-thirds of the journals began publication in 2000 or later.[13] As internet usage has become more widespread, the number of journals indexed in the TR Index accessible via the web has increased since 2000. The introduction of ODIS in the TR Index in 2018 may be a contributing factor to this trend.

The Higher Education Council (YÖK) has been compiling and publishing on its website a performance ranking of universities based on the number of articles included in Web of Science (WoS) since 2005 and information obtained from relevant institutions.[16] Research has found that since 1997, the increase in the number of articles has risen proportionally with the amount of publication incentives provided.[17] In addition to these factors, it is known that universities' transition to online librarianship has also contributed to the increase in publications.[18] Our study found that the range of the number of articles published by journals is wide. It was found that the range started from zero, and 5.21% of journals did not publish any articles. Considering the reasons listed above, this situation may be due to an error during the transfer of information to TR Index, the information about the journals we examined in TR Index not being up to date, or, if the information is up to date, the journals not publishing. Comprehensive and detailed studies are needed to fully determine the cause.

In Turkiye, only WoS group indexes are accepted by the relevant authorities for academic promotions and appointments.[19] In a study examining journals published in Turkiye and included in the WoS database, the median number of citations per journal was determined to be 654.[20] Turkiye lags behind European Union member countries, except for Romania, in terms of the average number of citations per publication.[21] Our study found that the median number of citations per journal was 54.00. This may be due to the fact that there are fewer journals in the TR Index compared to the WoS database, and thus fewer journals are evaluated, and the citation factors of journals in the TR Index are lower than those in the WoS.

Our study found that while the range of articles receiving citations is wide, the median is 34.00, and 12.50% of journals do not publish articles that receive citations. In the study, which examined approximately 39,000 articles, it was found that an average of 10 citations was made per article, and 39% of the articles received nine or fewer citations.[14,22] In a study evaluating journals published in Turkiye and indexed in WoS, it was determined that approximately 40% of all articles published received no citations.[12] The most important factors increasing the number of citations for articles based in Turkiye and reducing the number of articles receiving no citations were found to be the five-year impact factors of the journals in which the articles were published, their quarterly (Q) values, the number of sources cited in the references, and collaboration.[23] For these reasons, along with the small sample size in our study and the evaluation of journals with specific standards included in the TR Index, the number of citations per article may be high, and the number of articles without citations may be low compared to other studies.

Since the distribution of citations to articles does not follow a normal distribution, it is necessary to examine not only the median but also the number and proportion of articles that received no citations. In the study, which examined approximately 39,000 articles, it was found that 39% of the articles received no citations.[20] One of the most important indicators affecting citation counts is the journal impact factor. A one-unit increase in this factor increases the average citation count by 16-32% and reduces the average number of articles receiving no citations by 39-89%.[24] It was determined that 11.46% of the journals in our study received no citations. The reason for the low rate in our study may be due to the low impact factors of the journals examined, or it may be due to the small number of journals evaluated and the exclusion of journals from the scope of the study in cases where there were deficiencies in data, such as citations and publications. The exclusion of journal impact factors from our evaluation is one of the limitations of our study. Studies that include journal impact factors in their evaluation could more clearly reveal the reasons why journals do not receive citations.

Studies have found that the impact factors of certain journals have increased significantly in a short period of time due to the "citation circles" established between them. Therefore, it has been emphasised that when considering citations, the self-citation effect must be addressed separately.[25] In this context, self-citations were evaluated separately when assessing journals in our study. In a study examining the citation counts of journals published in Turkiye between 1970 and 2013, it was observed that the self-citation rate, which is approximately 10% in the WoS Index, was over 50% in journals published in Turkiye, even reaching 80% for some journals.[26] Our study shows that the ranges of self-citation counts and rates for the journals are wide, but the median values for citation counts and rates are low. This may be because the journals included in our study are indexed in the TR Index and meet certain standards. On the other hand, the fact that 22.92% of the journals in our study have no self-citations supports this finding.

In a study that examined the total number of publications, it was determined that between 1966 and 2009, there were 194,213 publications with a Turkish address, and 10,030 of these publications were published in Turkish journals.[14] Between 2006 and 2015, a total of 39,137 articles were published in journals published in Turkiye and indexed in WoS.[20] A total of 45,325 articles have been published in the journals examined in our study, and the number of articles published is related to the number and quality of the journals examined. The interface that allows journals to be monitored online in the TR Index began operating in 2018.[11] In our study, which examined journals that have increased significantly in number since 2018 and are mostly published in electronic format, the high number of articles published compared to other studies may be related to this situation. In addition, the fact that other studies were conducted in the past and our study was conducted in an environment where internet use has become widespread may also have contributed to this situation.

In a study examining the distribution of Turkiye-based publications in citation indexes by type, covering approximately 198,000 articles, the proportion of original articles (research articles) was determined to be 77.20%,

reviews 1.50%, and others 0.10% (editorials, short communications, letters, book reviews, and corrections are not included).[12] When examining the distribution of articles in our study, our findings are consistent with the aforementioned research, with research articles ranking first at 61.16%. The remaining 9.02% of articles in our study were classified as "other." The reason for this higher percentage compared to the other study may be the inclusion of publication types such as "editorial, short communication, letter, book review, and correction." Family physicians working in primary care need up-to-date literature for the initial assessment of surgical diseases and appropriate referral processes. This study provides indicative data on which publications family physicians may consider when following the surgical literature.

Limitations

This study has several limitations. It was restricted to journals indexed in the TR Index and reflects data obtained at a single time point (April 20, 2025); therefore, the findings represent a cross-sectional snapshot and may not capture subsequent updates or changes in journal metrics. The analysis relied solely on the accuracy and completeness of data reported in the TR Index, and any missing, delayed, or inconsistently reported information may have influenced the results. In addition, journals indexed in other national and international databases were not included, limiting generalizability. Finally, advanced bibliometric indicators such as impact factor and quartile rankings were not evaluated, and no inferential analyses were performed, preventing causal interpretation of citation performance.

CONCLUSION

As emphasized in the General Surgery and Family Medicine Residency Training Programs, physicians are expected to maintain competence in the management of surgical diseases by continuously following current literature. In this context, our study evaluated surgical journals indexed in TR Index and provides a structured overview of their publication and citation characteristics. A small proportion of journals were found to have no publications or citations, which may reflect database timeliness or journal-related factors.

By presenting an up-to-date national snapshot of surgical publishing, this study offers practical guidance for primary care physicians—particularly family physicians—in identifying accessible, active, and academically visible journals relevant to surgical practice. Thus, it contributes to more informed literature follow-up, supports evidence-based referral decisions, and serves as a foundation for future, broader bibliometric research.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study did not involve the use of surveys, interviews, or any quantitative or qualitative data collection methods. It did not include human participants or animal subjects for clinical, scientific, or experimental purposes. The study was conducted through a review of publicly accessible data available in the TR Index. Therefore, ethical committee approval was not required, and no ethical violation is present.

Informed Consent

Since the study was conducted by analyzing data publicly available on the TR Index, no informed consent was required.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: EŞ, ÖSTŞ, EU; Design: EŞ, ÖSTŞ, EU; Data Collection and/or Processing: EŞ, ÖSTŞ, EU; Analysis and/or Interpretation: EŞ, ÖSTŞ, EU; Literature Review: EŞ, ÖSTŞ, EU; Writing the Article: EŞ, ÖSTŞ, EU; Critical Review: EŞ, ÖSTŞ, EU.

REFERENCES

1. T.C. Milli Eğitim Bakanlığı. Hemşirelik–Cerrahi Hemşireliğine Giriş. Published 2012. Cited June 23, 2025. Available from: http://megep.meb.gov.tr/mte_program_modul/moduller_pdf/Cerrahiye%20Giri%C5%9F.pdf
2. Özkan OV. Genel cerrahi uzmanlık eğitim programı ve ultrasonografi eğitimi. *Turk J Surg*. 2008;24(3):164-165.
3. Tıpta Uzmanlık Kurulu. Tıpta Uzmanlık Kurulu Müfredat Oluşturma ve Standart Belirleme Sistemi (TUKMOS) Genel Cerrahi Uzmanlık Eğitimi Çekirdek Müfredatı. Published 2019. Cited June 22, 2025. Available from: https://tuk.saglik.gov.tr/Eklenti/34081/0/genelcerrahimufredatv24pdf.pdf
4. Yalman F, Bayat M, Çati K. Aile hekimliği uygulamasının hekimlerin sunmuş olduğu hizmetlerin kalitesine etkisi: Düzce örneği. *AIBU Sos Bilim Enst Derg*. 2015;14(3):1-28.
5. T.C. Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü. Türkiye'de aile hekimliği. Published April 14, 2022. Cited June 22, 2025. Available from: https://hsgm.saglik.gov.tr/tr/aile-hekimligi/tr-aile-hekimligi.html
6. Üstü Y, Uğurlu M. Bir analiz: aile hekimliği ülkemizde etkin kullanılıyor mu? *Ank Med J*. 2015;15(4):244-248. doi:10.17098/amj.94639
7. Atadağ Y, Aydın A, Kaya D, Köşker HD. Changes in causes of admission to tertiary health care center with family medicine implementation. *Turk Aile Hekim Derg*. 2016;20(4):141-151. doi:10.15511/tahd.16.04141
8. Türkiye Aile Hekimleri Uzmanlık Derneği. Aile hekimliği nedir? Published April 14, 2022. Cited June 22, 2025. Available from: https://tahud.org.tr/kurumsal/aile-hekimligi-nedir
9. Tıpta Uzmanlık Kurulu. TUKMOS Aile Hekimliği Uzmanlık Eğitimi Çekirdek Müfredatı. Published 2019. Cited June 22, 2025. Available from: https://dosyamerkez.saglik.gov.tr/Eklenti/34104/0/ailehekimligimufredatv24pdf.pdf
10. Türkiye Bilimsel ve Teknolojik Araştırma Kurumu Ulusal Akademik Ağ ve Bilgi Merkezi. TR Dizin. Published April 14, 2022. Cited June 22, 2025. Available from: https://trdizin.gov.tr/hakkinda/
11. Aslan A. TR Dizin. *Acta Med Alanya*. 2019;3(1):1-2. doi:10.30565/medalanya.557393
12. Al U. Türkiye'nin bilimsel yayınlarının sosyal ağ analizi yöntemiyle değerlendirilmesi. Published May 2012. Cited August 9, 2025. Available from: https://bby.hacettepe.edu.tr/bs/projeler/SOBAG-110K044.pdf
13. Küçük ME. Türkiye'de bilimsel elektronik dergiler. *Turk Kutuphaneciligi*. 2008;22(3):308-319.
14. Al U, Soydal İ. Atıf dizinlerindeki Türkiye adresli dergiler üzerine bir değerlendirme. *Bilgi Dunyasi*. 2011;12(1):13-29. doi:10.15612/BD.2011.219
15. Malinconico M. Electronic documents and research libraries. *IFLA J*. 1996;22(3):211-225. doi:10.1177/034003529602200308
16. Acar V, Bektaş M. Türkiye'nin bilimsel yayın üretimi. *Ank Egit Arast Hast Tip Derg*. 2021;54(2):331-340. doi:10.20492/aeahtd.946548

17. Arıoğlu E. Ülkemizin yayın sıralamasına eleştirisel bir bakış. *Bilim ve Utopya*. 2003;105(3):1-11.
18. Binici K. Türkiye'de yayın göçü: Web of Science ve ULAKBİM ulusal veri tabanlarında indekslenen yayınlar üzerine bir inceleme. *Bilgi Dunyasi*. 2012;13(1):165-181. doi:10.15612/BD.2012.173
19. Yaman H, Kara IH. Aile hekimliği uzmanlığı dergilerinin geleceği ve indeksler: çözüm önerileri. *Konuralp Med J*. 2014;6(2):1-4. doi:10.18521/ktd.46460
20. Tonta Y. Türkiye'de yayımlanan ve Web of Science'ta dizinlenen dergilerle ilgili bir değerlendirme. *Turk Kutuphaneciligi*. 2017;31(4):449-482. doi:10.24146/tkd.2017.21
21. Al U. Avrupa Birliği ülkeleri ve Türkiye'nin yayın ve atıf performansı. *Bilig*. 2012;62:1-20.
22. Al U. Bilimsel yayınların değerlendirilmesi: h-endeksi ve Türkiye'nin performansı. *Bilgi Dunyasi*. 2008;9(2):263-285. doi:10.15612/BD.2008.307
23. Tonta Y, Akbulut M. Uluslararası dergilerde yayımlanan Türkiye adresli makalelerin atıf etkisini artıran faktörler. *Turk Kutuphaneciligi*. 2021;35(3):388-409. doi:10.24146/tk.933159
24. Didegah F, Thelwall M. Which factors help authors produce the highest impact research? Collaboration, journal and document properties. *J Informetr*. 2013;7(4):861-873. doi:10.1016/j.joi.2013.08.006
25. Teodorescu D, Andrei T. An examination of citation circles for social sciences journals in Eastern European countries. *Scientometrics*. 2014;99(2):209-231. doi:10.1007/s11192-013-1210-6
26. Asan A. Türk dergilerinin Web of Science'teki yeri, impakt faktör ve h indeks. *Saglik Bilim Sureli Yayin*. 2013;11(1):53-74.

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Assessment of knowledge and awareness levels of healthcare professionals involved in newborn heel prick screening

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ABSTRACT

Aims: The aim of this study is to evaluate the knowledge levels of healthcare workers involved in newborn heel prick screening regarding the screening process, sample collection steps, and the diseases screened for.

Methods: This descriptive and cross-sectional study was conducted with 202 healthcare workers employed at Family Health Centres in Malatya province between 07.11.2024 and 07.02.2025. Data were collected using a structured questionnaire consisting of 35 knowledge questions covering the newborn screening process, heel prick blood sampling procedures, and the clinical characteristics and management of the screened diseases.

Results: 75.7% of participants were physicians, 12.9% were nurses, and 11.4% were midwives. The level of knowledge regarding the heel prick blood collection process was generally found to be high. A significant difference was found in the level of knowledge regarding the practice among the professional groups, with midwives and nurses being more successful than physicians (p=0.021). The level of knowledge regarding the screened diseases was found to be higher among physicians (p=0.003). However, general knowledge about rare diseases such as biotinidase deficiency, congenital adrenal hyperplasia, and spinal muscular atrophy was found to be low.

Conclusion: In this study, while the level of knowledge regarding the steps of heel prick blood collection was found to be adequate knowledge gaps were identified regarding the clinical characteristics and management of the screened diseases. It is recommended that up to date, disease-focused and profession-specific training programmes for healthcare professionals be promoted.

Keywords: Newborn screening, mass screening, blood specimen collection, healthcare professionals, metabolic diseases

INTRODUCTION

Congenital metabolic disorders (CMDs) are a group of diseases that are mostly autosomal recessive and rare, but they are a significant public health issue because they encompass a wide range of different metabolic disorders. The prevalence of CMD in our country is reported to range between 1:1500 and 1:3000.[1,2] If these diseases are not diagnosed early they can lead to severe neurological sequelae, developmental delay, and life-threatening complications. The incidence of genetically transmitted diseases increases, particularly in communities where consanguineous marriages are common. The rate of consanguineous marriage in Turkiye varies between 12.8% and 35% depending on the region, and is reported to be approximately 21% nationwide.[3,4]

The idea of detecting diseases before symptoms appear has pioneered the development of newborn screening programmes.[5] Under the National Newborn Screening Programme (UYTP) in Turkiye, heel blood samples are taken from all live-born babies; screening for phenylketonuria (PKU), biotinidase deficiency (BD), congenital hypothyroidism (CH), cystic fibrosis (CF), congenital adrenal hyperplasia (CAH) and spinal muscular atrophy (SMA) is carried out.[6]

The success of newborn screening largely depends on the heel blood sample being collected using the correct technique, stored appropriately, and delivered to the laboratory in a timely manner. Errors made during the sample collection process can lead to incorrect test results and the need for repeat sampling. This causes delays in diagnosis and treatment, increasing the risk of damage caused by the diseases. However, early diagnosis and rapid treatment are

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of vital importance in newborn screening programmes. Although the scope of newborn screening programmes has been expanded in recent years, the limited number of studies evaluating healthcare professionals' knowledge of newborn screening means that potential shortcomings in practice cannot be adequately identified. This situation makes it difficult to determine training needs and develop screening programmes. This study was designed to assess the knowledge and awareness levels of healthcare professionals involved in newborn heel prick screening.

METHODS

Ethical approval for the study was obtained from the İnönü University Non-interventional Clinical Researches Ethics Committee (Date: 22.10.2024, Decision No: 2024/5378). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants before completing the questionnaire.

This study was designed as a descriptive and cross-sectional study. The study was conducted between 07 November 2024 and 07 February 2025 among healthcare professionals working at Family Health Centres in Malatya province. The study population consisted of 405 healthcare professionals (250 physicians and 155 nurses/midwives) working in Family Health Centres in the province during the study period. No sampling method was applied, and it was aimed to reach the entire population. A total of 202 healthcare professionals (153 physicians, 26 nurses and 23 midwives) who voluntarily agreed to participate were included in the study. This corresponds to approximately 49.8% of the target population. Data were collected using a structured questionnaire consisting of sociodemographic questions and 35 knowledge questions developed based on the literature.[6-8,18,19] The knowledge questions were grouped into three domains:

- Knowledge about the newborn screening programme and heel prick blood sample collection procedures
- Knowledge about the diseases included in the national newborn screening panel
- Knowledge about the clinical characteristics, diagnosis and treatment approaches of these diseases.

The diseases covered in the questionnaire included PKU, CH, CF, BD, CAH, and SMA. Each correct answer was scored as 1 point, while incorrect answers and "I do not know" responses were scored as 0 points. The total knowledge score ranged from 0 to 35 points. Knowledge levels were classified according to the percentage of correct answers as follows: low knowledge (0–11 points, ≤33%), moderate knowledge (12-23 points, 34-66%), and high knowledge (24-35 points, ≥67%).

Statistical Analysis

The data analyses were performed using SPSS version 22.0. Descriptive statistics were expressed as frequency and percentage values. The Chi-square test was used to compare knowledge levels between occupational groups. A p-value <0.05 was considered statistically significant.

RESULTS

The sociodemographic characteristics of the participants are presented in Table 1. Of the participants, 75.7% were physicians, 12.9% were nurses, and 11.4% were midwives. The mean age of the participants was 40.4±8.6 years. Knowledge levels regarding the heel prick blood sampling process are presented in Table 2. The percentage of correct answers exceeded 85% for several items, particularly those related to completing the sample form and the appropriate timing of sample collection. A statistically significant difference was observed between occupational groups in terms of knowledge regarding the heel prick blood sampling procedure (p=0.021). Midwives and nurses demonstrated higher practical knowledge levels than physicians (Table 3).

Table 1. Sociodemographic characteristics of participants (n=202)

Characteristic	n	%
Gender		
Female	102	50.5
Male	100	49.5
Marital status		
Married	164	81.2
Single	38	18.8
Having children		
Yes	157	77.6
No	45	22.4
Occupation		
Physician	153	75.7
Nurse	26	12.9
Midwife	23	11.4
Professional experience		
0-5 years	25	12.4
6-10 years	48	23.8
≥11 years	129	63.9
Mean age (years)	40.4±8.6	

Table 2. Knowledge level regarding the heel prick blood collection process

Question/application step	Correct n (%)	Incorrect n (%)
Sample collection time (48-72 hours)	181 (89.6)	21 (10.4)
Removal of the first drop of blood	167 (82.7)	35 (17.3)
Complete filling of the sample form	188 (93.1)	14 (6.9)
Warming the foot	159 (78.7)	43 (21.3)
Baby order in multiple pregnancies	172 (85.1)	30 (14.9)
Proper drying of the sample	176 (87.1)	26 (12.9)

Table 3. Knowledge level regarding the heel blood collection process by profession and comparison

Occupation	High n (%)	Moderate n (%)	Low n (%)	p
Physician	98 (64.1)	41 (26.8)	14 (9.1)	
Nurse	21 (80.8)	4 (15.4)	1 (3.8)	
Midwife	19 (82.6)	3 (13.0)	1 (4.4)	
Total	138 (68.3)	48 (23.8)	16 (7.9)	0.021

Regarding knowledge of the screened diseases, physicians were found to have significantly higher knowledge levels than nurses and midwives (p=0.003) (Table 4).

Table 4. Level of knowledge regarding screened diseases by profession and comparison

Profession	High n (%)	Moderate n (%)	Low n (%)	p
Physician	109 (71.2)	33 (21.6)	11 (7.2)	
Nurse	13 (48.1)	9 (34.6)	4 (17.3)	
Midwife	10 (43.5)	9 (39.1)	4 (17.4)	
Total	132 (65.3)	51 (25.2)	19 (9.5)	0.003

Disease-specific correct response rates regarding the conditions included in the newborn screening panel are presented in Table 5.

Table 5. Knowledge level regarding diseases included in the newborn screening panel

Disease	Correct n (%)	Incorrect n (%)
Phenylketonuria	159 (78.7)	43 (21.3)
Congenital hypothyroidism	69 (34.2)	133 (65.8)
Biotinidase deficiency	127 (62.9)	75 (37.1)
Cystic fibrosis	152 (75.2)	50 (24.8)
Congenital adrenal hyperplasia	180 (89.1)	22 (10.9)
Spinal muscular atrophy	161 (79.7)	41 (20.3)

DISCUSSION

The success of newborn screening largely depends on the heel blood sample being taken using the correct technique, stored appropriately, and delivered to the laboratory in a timely manner. Errors made during the sampling process can lead to incorrect test results and the need for repeat sampling. In this study, healthcare workers' technical knowledge regarding the heel prick blood sampling process was generally found to be adequate. However, significant knowledge gaps were observed regarding the clinical characteristics and treatment processes of the screened diseases.

This study found that healthcare workers involved in newborn heel prick screening generally had sufficient practical knowledge, but there were gaps in their knowledge regarding certain congenital metabolic and genetic diseases. Notably, awareness of rarer diseases such as BD, CAH, and SMA was limited.

When disease-specific knowledge levels were analysed, the highest correct response rate was observed for CAH (89.1%), while knowledge regarding CH was relatively lower (34.2%). These findings indicate that awareness among healthcare professionals may vary considerably depending on the disease included in the screening panel (Table 5).

The collection of heel blood samples at the right time and using the appropriate technique is critical to the success of newborn screening programmes. In our study, the high level of knowledge among healthcare workers regarding the steps involved in sample collection suggests that practices in the field are largely carried out in accordance with standards. Similarly, Beyzadeoğlu and colleagues[8] reported a significant increase in the knowledge levels of healthcare workers who received in-service training on newborn screening. Erdim and İnal[18] also emphasised that nurses' responsibilities in the sample collection and dispatch process directly affect the accuracy of test results. However, the fact that the level of knowledge about the clinical characteristics and long-term outcomes of screened diseases is lower than that of the implementation steps indicates that theoretical knowledge is not as strong as practical knowledge in the field.[10] Bayrak's[11] study also reported that health care workers' knowledge levels about newborn screening programmes varied. Gürbüz[12] noted that family physicians require more training, particularly regarding rare metabolic diseases. These findings are consistent with the results of our study.

In a comparison between occupational groups, it was observed that midwives and nurses had a higher level of practical knowledge than doctors, whereas doctors were more knowledgeable about the theoretical aspects of diseases. This situation can be attributed to midwives and nurses taking a more active role in the sampling process in the field, while doctors focus more on the diagnosis and treatment processes. The literature also emphasises that nurses and midwives play a fundamental role in newborn screening.[9,13] With the expansion of the scope of newborn screening programmes in recent years, the variety of diseases encountered by healthcare professionals has also increased. In particular, the addition of SMA to the screening panel has created a new need for knowledge in the field. However, the relatively low level of knowledge about SMA in our study suggests that training in this area is not yet sufficiently widespread. Demirtaş and colleagues also reported that family physicians may experience a lack of knowledge about CF and other rare diseases.[14]

It should not be forgotten that newborn screening is not merely a technical process, but also involves informing, guiding, and psychosocially supporting families. Having a sick child places a serious psychological burden on families, and the communication skills of healthcare personnel are of great importance during this process.[15-17] Therefore, healthcare workers need to be supported not only with technical knowledge but also with communication and counselling skills. In addition, the correct interpretation of newborn screening results and their appropriate communication to the family are also important in preventing unnecessary anxiety. Failure to properly guide families in cases of suspicious results can lead to delays in the diagnostic process and a loss of trust among families. Therefore, healthcare professionals must also have sufficient knowledge about the clinical significance of screening results and the roadmap to be followed.

The content of training programmes should not be limited to sampling techniques; it should also cover the clinical characteristics of the diseases screened for, treatment approaches, and long-term follow-up processes. Sharing up-to-date information, particularly on rare diseases, will reduce knowledge gaps in the field. Regular in-service training, updating guidelines, and using digital training materials can support this process.

One of the strengths of this study is that it evaluated both the practical knowledge related to heel prick blood sample collection and the theoretical knowledge regarding the diseases included in the newborn screening programme. In addition, the study included different professional groups such as physicians, nurses, and midwives working in primary healthcare settings. This provided a comprehensive assessment of healthcare professionals' knowledge and awareness regarding newborn screening practices.

Limitations

This study has some limitations. The research was conducted in a single province, and the results cannot be generalised to the entire country. Furthermore, the data were collected through self- reported questionnaires. Nevertheless, our study provides important data in terms of revealing the knowledge levels of healthcare professionals involved in newborn screening programmes.

Consequently, in order to increase the effectiveness of newborn heel prick screening, regular, up- to-date and disease-focused training programmes for healthcare professionals need to be widely implemented. Raising awareness, particularly regarding rare metabolic and genetic diseases, will directly impact the success of early diagnosis and treatment processes.

CONCLUSION

This study found that healthcare professionals involved in newborn heel prick screening generally had sufficient practical knowledge, but there were gaps in their knowledge regarding certain congenital metabolic and genetic disorders. Notably, awareness of rarer disorders such as BD, CAH, and SMA was limited. The high level of practical knowledge among midwives and nurses involved in this process indicates that field practices are largely conducted in accordance with standards. In contrast, physicians were found to have stronger theoretical knowledge of diseases. This suggests that educational content should be differentiated for different professional groups. With the expansion of the scope of newborn screening programmes, the variety of diseases encountered by healthcare professionals has also increased. Therefore, training programmes should not be limited to sampling techniques alone; they should also cover the clinical characteristics of the diseases screened for, treatment approaches, follow up processes, and family information steps.

Consequently, it is recommended that regular, up to date, and disease focused in-service training programmes for healthcare professionals be promoted to increase the effectiveness of newborn heel prick screening. Raising awareness, particularly regarding rare metabolic and genetic diseases, will directly impact the success of early diagnosis and treatment processes and significantly contribute to newborns leading healthy lives.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval for the study was obtained from the İnönü University Non-interventional Clinical Researches Ethics Committee (Date: 22.10.2024, Decision No: 2024/5378).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights—including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

Concept: BKT, MEB; Design: BKT, MEB; Control: BKT, MEB; Resources: BKT, MEB; Materials: MEB; Data Collection and/or Processing: MEB; Analysis and/or Interpretation: MEB, BKT, EU; Literature Review: MEB, HYB, ŞY; Writing the Article: MEB, HYB, ŞY; Critical Review: MEB, HYB, ŞY, BKT, EU.

REFERENCES

1. Zeybek ÇA. Fenilketonüri tarama programı. *Sağlam Çocuk İzlemi Sempozyum Dizisi*. 2003;35:65-71.
2. Mıhçı E. Yenidoğan taramaları ve genetik. *Türkiye Klin*. 2020;(1):25-27.
3. Tunçbilek E. Akraba evlilikleri. Türkiye Nüfus ve Sağlık Araştırması. Ankara, Türkiye: Hacettepe Üniversitesi Nüfus Etütleri Enstitüsü; 2008.
4. Tanyalçın T. Yenidoğanlarda biyokimyasal tarama testleri. *Türk Biyokimya Derg*. 2002;27(2):69-78.
5. İçke S, Ekti Genç R. National newborn screening tests carried out with heel lance and their importance. *J Pediatr Res*. 2017;4(4):186-190. doi:10.4274/jpr.22932
6. Tunç C. Aydın il merkezinde fenilketonüri tarama programını yürüten hemşire ve ebelerin fenilketonüri konusundaki bilgi düzeylerinin saptanması [master's thesis]. Afyonkarahisar, Türkiye: Afyonkarahisar Kocatepe Üniversitesi; 2006.
7. Yıldız S, Balcı S, Görak G. Guthrie tarama testi için örnek alma uygulamalarının ve test sonuçlarının değerlendirilmesi. *Atatürk Üniv Hemşirelik Yüksekokulu Derg*. 2006;9(1):17-28.
8. Beyzadeoğlu B, Ekuklu G, Vatansever Ü, Özden D. Edirne ili sağlık ocakları ebe/hemşire ve hekimlerinin hizmet içi eğitim öncesi ve sonrasında fenilketonüri tarama programı konusundaki bilgi düzeyleri. Sağlık Platformu. Accessed October 15, 2024. https://www.saglikplatformu.com/ebe-hemsire-ve-hekimlerininhizmetici-egitim-oncesi/
9. Erdöl Ş, Sağlam H. Kalıtsal metabolik hastalıklara klinik yaklaşım. *Turkiye Klinikleri J Med Genet-Special Topics*. 2016;1(1):81-86.
10. Memorial Sağlık Grubu. SMA hastalığı nedir? SMA belirtileri, nedenleri ve tedavisi. Accessed November 6, 2024. https://www.memorial.com.tr/hastaliklar/sma-hastaligi-nedir-belirti-ve-tedavi-yontemleri-nelerdir
11. Bayrak R. Yenidoğan topuk kanı taramasında görev alan sağlık çalışanlarının konu ile ilgili bilgi düzeyleri [master's thesis]. Kırşehir, Türkiye: Kırşehir Ahi Evran Üniversitesi Sağlık Bilimleri Enstitüsü; 2021.
12. Bilginer Gürbüz B, Coşkun T. Yenidoğan döneminde metabolik taramalar. *Türkiye Klinikleri J Fam Med-Special Topics*. 2017;8(5):324-330.
13. Aile hekimliği uygulama yönetmeliği. Resmi Gazete. January 25, 2013;28539.
14. American Academy of Pediatrics Newborn Screening Task Force. Serving the family from birth to the medical home: newborn screening—a blueprint for the future. *Pediatrics*. 2000;106(2 suppl):389-422.
15. Conk Z, Başbakkal Z, Yardımcı F. Çocuk sağlığına genel bakış. In: Conk Z, Başbakkal Z, Bal Yılmaz H, Bolışık B, eds. Pediatri Hemşireliği. Ankara, Türkiye: Akademisyen Kitabevi; 2018.
16. Er DM. Çocuk, hastalık, anne-babalar ve kardeşler. *Çocuk Sağlığı ve Hastalıkları Derg*. 2006;49(2):155-168.
17. Eminoğlu FT. Fenilketonüri hastalığı nedir, kimlerde gözlenir, tedavi yaklaşımları nelerdir? Ankara Üniversitesi Hastaneleri. Accessed November 4, 2024. http://hastane.ankara.edu.tr/2019/10/07/fenilketonuri-hastaligi-nedir-kimlerde-gozlenir-tedavi-yaklasimlari-nelerdir/

18. Erdim L, İnal S. Yenidoğan tarama testlerinde örnek alınması ve gönderilmesinde hemşirelerin sorumlulukları. *Sağlık Bilimleri ve Meslekleri Derg.* 2018;5(1):102-106. doi:10.17681/hsp.323082
19. Centers for Disease Control and Prevention. Newborn screening sample collection guidelines. Accessed May 2, 2025.

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Retrospective evaluation of anemia in elderly patients receiving home health care services

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ABSTRACT

Aims: This study aimed to evaluate the morphological and etiological distribution of anemia in patients aged ≥65 years receiving home health care services and to investigate its associations with polypharmacy, comorbidities, and nutritional support.

Methods: This single-center, retrospective cross-sectional study included 306 patients followed by the home health care unit of a tertiary hospital in 2024. Demographic data, laboratory parameters, comorbidities, nutritional status, and medication use were analyzed. Statistical analysis was performed using SPSS v27.0, and $p<0.05$ was considered statistically significant.

Results: The mean age was 82.6±7.1 years, and 60.8% of participants were female. Normocytic anemia was the most prevalent morphological type (78.1%), followed by microcytic (19.6%) and macrocytic (2.3%) anemia. Anemia severity was classified as mild (42.8%), moderate (52.9%), or severe (4.2%). The most common etiological profile was mixed-type anemia, particularly the combination of iron deficiency anemia (IDA) and anemia of chronic inflammation (ACI) (36.9%). Polypharmacy was significantly associated with ACI ($p=0.044$), while chronic kidney disease was associated with a lower prevalence of isolated IDA ($p=0.024$).

Conclusion: Anemia in elderly patients receiving home health care services is predominantly normocytic and multifactorial. Optimal management requires a comprehensive approach that includes assessment of nutritional status, comorbidities, and polypharmacy.

Keywords: Aged, home care services, anemia, inflammation, iron deficiency anemia

INTRODUCTION

Anemia is one of the most common hematological problems encountered in the elderly population, and its prevalence increases markedly with advancing age. While the prevalence of anemia in community-dwelling older adults is reported to range from 10% to 20%, this rate may rise to 40-50% among elderly individuals who are hospitalized, reside in nursing homes, or receive home health care services.[1] Anemia is closely associated with decreased physical performance, cognitive impairment, increased risk of falls, higher rates of hospitalization, and increased mortality.[2] Therefore, early recognition and appropriate management of anemia in elderly patients constitute one of the fundamental components of preventive medicine and a holistic approach to care.

The etiological profile of anemia in older adults is more complex and often multifactorial compared to that in younger adults. Nutritional deficiencies, chronic inflammatory diseases, renal insufficiency, and age-related decline in hematopoietic reserve frequently coexist.[3] In particular, the concomitant presence of anemia of chronic inflammation (ACI) and iron deficiency anemia (IDA) complicates clinical assessment and leads to diagnostic uncertainty. This complex clinical picture indicates that anemia in elderly patients cannot be considered a disease with a single underlying cause.

In cases where iron deficiency coexists with vitamin B12 or folate deficiency, erythrocyte indices may appear normal, potentially creating a false sense of reassurance in clinical practice.[4] Therefore, especially in elderly individuals receiving home health care services, a detailed etiological evaluation is required when low hemoglobin levels are detected, even if the mean corpuscular volume (MCV) is within the normal range. In addition, polypharmacy is potentially linked to the pathogenesis of anemia through possible mechanisms such as impaired nutrient absorption, increased risk of gastrointestinal bleeding, or exacerbation of inflammatory processes.[5-8]

For these reasons, a comprehensive evaluation of the morphological and etiological characteristics of anemia in

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the elderly population receiving home health care services is of clinical importance. This study aims to identify the etiological subtypes of anemia in individuals aged 65 years and older followed within the scope of home health care services, and to investigate the associations between medication use, polypharmacy, chronic disease burden, and nutritional status and the severity and distribution of anemia.

While several studies have investigated anemia in the general geriatric population, research specifically targeting patients receiving structured home health care services has largely remained descriptive, focusing primarily on basic prevalence rates. The literature lacks comprehensive analyses that detail the etiological subtypes and their direct associations with anemia severity, polypharmacy, specific nutritional support methods, and individualized chronic disease burdens in this unique cohort. By addressing these gaps, this study aims to move beyond simple descriptive statistics and provide actionable clinical insights for optimizing patient-centered anemia management in home healthcare settings.

METHODS

This study was conducted with the approval of the Scientific Researches Ethics Committee of the İzmir Bozyaka Training and Research Hospital (Date: 31.07.2024, Decision No: 2024/40). All procedures were performed in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This single-center, retrospective, cross-sectional study was conducted at the home health care services unit of a tertiary hospital. A total of 306 patients aged 65 years and older who were enrolled in the home health care unit during 2024 and were diagnosed with anemia according to the World Health Organization (WHO) criteria based on laboratory findings (hemoglobin <13 g/dl in men and <12 g/dl in women) were included in the study. Data were collected retrospectively from the Hospital Information Management System, and patients' demographic characteristics, laboratory parameters, comorbidities, nutritional status, and medications in use were recorded.

Anemia was morphologically classified according to MCV as microcytic (<80 fL), normocytic (80-100 fL), or macrocytic (>100 fL). Polypharmacy was defined as the regular use of five or more different medications per day.[5] This specific threshold was chosen as it is the most widely established standard in geriatric literature, marking the critical point at which the risk of adverse clinical outcomes and drug-disease interactions significantly increases.

In the classification of anemia etiology, biochemical criteria were evaluated together with clinical conditions. In patients without chronic disease, serum ferritin <15 ng/ml or ferritin levels between 15-100 ng/ml accompanied by transferrin saturation (TSAT) <20% were considered indicative of IDA; in patients with chronic disease, ferritin <50 ng/ml or ferritin levels between 50-299 ng/ml with TSAT <20% were classified as IDA.[9] To minimize the confounding effect of inflammation on ferritin levels, TSAT was utilized as a mandatory co-marker. Anemia was attributed to iron deficiency (absolute or functional) only if TSAT was <20%, regardless of the absolute ferritin value, ensuring that simple hyperferritinemia was not misclassified.

Vitamin B12 levels <200 pg/ml and/or folate levels <3 ng/ml were accepted as suggestive of megaloblastic anemia (vitamin B12/folate deficiency).[10,11] Anemia developing in patients with renal failure, malignancy, infection, or inflammatory disease was defined as ACI.[12] Cases that could not be explained by any diagnostic evaluation were classified as unexplained anemia.

Mixed-type anemia was defined as the simultaneous presence of biochemical markers indicating more than one etiological mechanism in the same individual. Specifically, the most frequent combination was IDA overlapping with ACI. This was diagnosed when patients presented with low serum iron levels and low TSAT (<20%), alongside indicators of chronic inflammation such as elevated or normal ferritin levels (>100 ng/ml or >300 ng/ml depending on comorbidities) and a history of documented chronic inflammatory or infectious diseases.

Anemia severity was classified according to the hemoglobin thresholds defined by the WHO: mild anemia was defined as hemoglobin levels of 12.0-10.9 g/dl in female and 13.0-11.0 g/dl in male; moderate anemia as 8.0-10.9 g/dl; and severe anemia as <8.0 g/dl.[13,14]

The inclusion criteria were being 65 years of age or older and having a diagnosis of anemia based on WHO thresholds (Hb <13 g/dl in male and <12 g/dl in female). Patients were excluded from the study if they: 1) were under 65 years of age; 2) did not meet the WHO anemia criteria; 3) had missing laboratory tests essential for etiological evaluation; or 4) had incomplete medical records that prevented data acquisition during the retrospective file review process.

Statistical Analysis

Data were analyzed using SPSS v27.0 software. Categorical variables were compared using the Chi-square test, while continuous variables were analyzed using the Independent Samples t-test or the Mann–Whitney U test, depending on the normality of data distribution. A p value <0.05 was considered statistically significant. Due to the high prevalence of multimorbidity (99%) and the inherent overlap between the number of chronic diseases and polypharmacy in this frail elderly population, associations were primarily evaluated using univariate analyses. A multivariable model was not constructed to avoid potential multicollinearity issues.

RESULTS

The mean age of the 306 patients included in the study was 82.6±7.1 years (range: 65-97), and 60.8% were female. The patients had multiple comorbidities, with at least one chronic disease present in 99% of the cohort. The most common comorbid conditions were hypertension (75.8%), cardiovascular diseases (48.4%), and diabetes mellitus (41.2%), while chronic kidney disease (CKD) was identified in 31.7% of the patients. Regarding nutritional status, a total of 22.6% of the patients required additional nutritional support, including 19.0% who received oral nutritional supplements (ONS) and 3.6% who were fed via percutaneous endoscopic gastrostomy (PEG). Polypharmacy was present in the majority of patients (**Table 1**).

Hematological evaluation revealed that anemia morphology was normocytic in 78.1% of cases, microcytic in 19.6%, and

Table 1. Descriptive characteristics of the patients

Variable	Mean±SD	Median (Q1–Q3)	Min-max
Age (years)	82.55±7.06	83.5 (78.0-88.0)	65-97
Number of chronic diseases	3.22±1.39	3.0 (2.0-4.0)	0-9
	Subgroup	**n**	**%**
Sex	Female	186	60.8
	Male	120	39.2
Chronic disease	Present	303	99.0
	Absent	3	1.0
Comorbidities	Hypertension	232	75.8
	Diabetes mellitus	126	41.2
	Cardiovascular disease	148	48.4
	Neurological disease	122	39.9
	Chronic pulmonary disease	44	14.4
	Malignancy	36	11.8
	Chronic kidney disease (CKD)	97	31.7
	Endocrine disease	69	22.5
	Other comorbidities*	49	16.0
Enteral feeding (PEG-fed)		11	3.6
Oral feeding with ONS		58	19
Oral feeding (no supplementation)		235	76.8
Polypharmacy		197	64.4
Anticoagulant use		86	28.1
Antiplatelet use		135	44.1
ACE inhibitor or ARB use		107	35
Other antihypertensive drug use		216	70.6
Proton pump inhibitor (PPI) use		163	53.3
H2 receptor blocker use		20	6.5
Metformin use		40	13.1
Total		306	100.0

SD: Standard deviation, Min: Minimum, Max: Maximum, PEG: Percutaneous endoscopic gastrostomy, ONS: Oral nutritional supplement, ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker *Benign prostatic hyperplasia, rheumatologic, and orthopedic diseases.

macrocytic in 2.3%. Regarding anemia severity, 42.8% of patients had mild anemia, 52.9% had moderate anemia, and 4.2% had severe anemia (Table 2).

Table 2. Distribution of anemia types according to MCV and hemoglobin levels

Morphological type	Number	Percentage (%)
Microcytic (<80)	60	19.6
Normocytic (81-100)	239	78.1
Macrocytic (>100)	7	2.3
Severity level	**Number**	**Percentage (%)**
Mild anemia (>11 g/dl)	131	42.8
Moderate anemia (8-10.99 g/dl)	162	52.9
Severe anemia (<8 g/dl)	13	4.2
Total	306	100.0

MCV: Mean corpuscular volume

A statistically significant association was found between the presence of polypharmacy and anemia etiology. In particular, the prevalence of ACI was higher among patients with polypharmacy compared to those without polypharmacy (71.1% vs. 59.6%, respectively; p=0.044), indicating a significant relationship between polypharmacy and ACI.

In patients diagnosed with CKD, the prevalence of isolated IDA was significantly lower than in those without CKD (11.2% vs. 21.6%; p=0.024). The anemia observed in patients with CKD was more frequently related to chronic disease–associated or mixed etiologies rather than isolated iron deficiency.

As shown in Table 3, the prevalence of mixed-type anemia was significantly lower among individuals receiving oral nutritional supplementation (ONS) (39.7%) compared to those not receiving ONS (55.6%) (p=0.028). Similarly, while the rate of mixed-type anemia was 55.7% in individuals who maintained oral feeding without nutritional supplementation, this rate decreased to 42.3% in patients receiving enteral nutritional support via ONS or PEG, and this difference was found to be statistically significant (p=0.046). These findings suggest that adequate nutritional support may be associated with a lower prevalence of mixed-type anemia and that the multifactorial nature of anemia in home health care patients is closely related to nutritional status (Table 3).

Table 3. Association between the presence of mixed-type anemia and clinical and pharmacological variables (n=306)

Group	No mixed-type anemia n (%)	Mixed-type anemia present n (%)	p
Female	87 (46.8)	99 (53.2)	0.79
Male	58 (48.3)	62 (51.7)	
Not PEG-fed	140 (47.5)	155 (52.5)	0.896
PEG-fed	5 (45.5)	6 (54.5)	
No ONS	110 (44.4)	138 (55.6)	0.028*
ONS present	35 (60.3)	23 (39.7)	
Fed via PEG or ONS	41 (57.7)	30 (42.3)	0.046*
Orally fed (without ONS)	104 (44.3)	131 (55.7)	
No polypharmacy	59 (54.1)	50 (45.9)	0.079
Polypharmacy present	86 (43.7)	111 (56.3)	
No anticoagulant use	105 (47.7)	115 (52.3)	0.848
Anticoagulant use	40 (46.5)	46 (53.5)	
No antiplatelet use	78 (45.6)	93 (54.4)	0.485
Antiplatelet use	67 (49.6)	68 (50.4)	
No ACEi/ARB use	90 (45.2)	109 (54.8)	0.302
ACEi/ARB use	55 (51.4)	52 (48.6)	
No other antihypertensive use	44 (48.9)	46 (51.1)	0.734
Other antihypertensive use	101 (46.8)	115 (53.2)	
No PPI use	69 (48.3)	74 (51.7)	0.776
PPI use	76 (46.6)	87 (53.4)	
No H2R blocker use	139 (48.6)	147 (51.4)	0.107
H2R blocker use	6 (30.0)	14 (70.0)	
No metformin use	121 (45.5)	145 (54.5)	0.087
Metformin use	24 (60.0)	16 (40.0)	

Fisher Exact Chi-square test. PEG: Percutaneous endoscopic gastrostomy, ONS: Oral nutritional supplement, PPI: Proton pump inhibitor, ACEi/ARB: Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, H2R blocker: Histamine-2 receptor blocker

DISCUSSION

In elderly individuals receiving home health care services, the majority of anemia cases in our study were of moderate severity. We consider the identification of a predominantly multifactorial etiology as the primary contribution of our study; specifically, a substantial proportion of cases (36.9%) exhibited the coexistence of IDA and ACI. When contrasted with existing literature on general community-dwelling older adults our findings demonstrate a significant paradigm shift. This finding indicates that complex anemia patterns involving multiple mechanisms acting simultaneously are the standard clinical presentation, rather than the exception, in this population. In addition, anemia was normocytic in 78% of cases. In what may be described as a "normocytic anemia trap," a normal MCV may create the misleading impression that no underlying deficiency is present. Indeed, when iron deficiency (microcytosis) coexists with vitamin B12/folate deficiency or reticulocytosis (macrocytosis) in elderly patients, erythrocyte indices may remain within normal limits. Therefore, when anemia is detected in elderly patients receiving home health care services, iron studies and vitamin B12 levels should be evaluated even if the MCV is normal. In our cohort, a considerable proportion of normocytic anemias appeared to be related to underlying mixed etiologies that masked each other.

In our study, a statistically significant association was identified between polypharmacy and ACI. Polypharmacy is a well-recognized geriatric syndrome and is highly prevalent among older adults.[5] Medications may contribute to anemia through various mechanisms. In the context of age-related low-grade inflammation, also referred to as "inflammaging," increased cytokine levels (e.g., interleukin-6) stimulate hepcidin production, leading to iron sequestration within macrophages and the development of ACI.[3] In this regard, the concomitant use of multiple medications may indirectly affect hepcidin levels and iron metabolism, thereby adversely influencing anemia pathogenesis. The study by Kulkarni et al.[15] highlighted that medications such as metformin may modulate inflammatory responses in older adults through both metabolic and non-metabolic pathways. Consistent with these observations, our findings suggest that polypharmacy may shift anemia etiology toward chronic inflammation by increasing systemic inflammatory burden or reflecting an underlying inflammatory state. It is important to emphasize that the statistically significant relationship identified between polypharmacy and ACI ($p=0.044$) is an association and does not imply a direct causal effect. In clinical practice, polypharmacy is frequently a proxy for multimorbidity; therefore, the observed correlation likely reflects the cumulative impact of various chronic inflammatory conditions rather than the medications themselves. Our analysis serves to highlight this clinical link as a marker of complexity in home-care patients.

It should be noted that our analysis utilized the standard threshold of ≥5 medications to define polypharmacy. Employing a stricter alternative definition, such as excessive polypharmacy (≥10 medications), might have isolated a subgroup with extreme multimorbidity, potentially yielding an even stronger statistical association with ACI. However, assessing the standard threshold allowed us to capture the broader impact of medication burden on anemia pathogenesis without compromising the statistical power of the cohort. Therefore, careful review and, when appropriate, simplification of medication regimens should be considered an integral component of anemia management in elderly patients.

In patients with CKD, the etiology of anemia was found to differ markedly compared to those without CKD. While isolated IDA was rarely observed in the presence of CKD (only 11.2%), mixed-type anemia or combinations involving ACI became predominant in these patients. This finding is consistent with the multifaceted pathophysiology of anemia in CKD. In patients with CKD, serum ferritin levels may appear normal or elevated due to the inflammatory acute-phase response, thereby masking true depletion of iron stores.[3] Therefore, when anemia is detected in a patient with CKD, the possibility of functional iron deficiency should be considered even in the absence of low ferritin levels. In our study, the low prevalence of isolated iron deficiency in patients with CKD may reflect a state of functional iron deficiency in which iron utilization is restricted by inflammation and impaired renal function.

When comparing our findings with the existing literature, it becomes apparent that the home health care population has certain distinctive characteristics. Studies conducted in the general elderly population have typically reported IDA as the most common etiology. For example, in a cross-sectional study by Yıldız and Sarıçam[16] involving elderly patients attending an internal medicine outpatient clinic, the causes of anemia were reported as IDA in 45.6%, ACI in 15.5%, mixed anemia in 4.8%, and unexplained anemia in 27.2% of cases. Similarly, a study by Emiroğlu et al.[17] conducted among patients receiving home health care services reported prevalences of 43% for IDA, 16.2% for ACI, only 1.1% for the IDA+ACI combination, and 37.4% for unexplained anemia. In contrast, the prevalence of mixed-type anemia in our study was substantially higher, reaching 36.9%, compared with previous reports. This discrepancy may be attributed to the fact that anemia etiologies have often been classified as mutually exclusive categories in the literature, without adequately defining or acknowledging combinations of etiological factors. In clinical practice, the coexistence of IDA and ACI is frequently encountered; however, because such combinations were not considered as a separate category in earlier studies, they may have been underreported. In contrast, our study systematically evaluated all potential mechanisms in each case, classified mixed-type anemia in detail, and demonstrated that more than half of the patients exhibited multifactorial mechanisms contributing to anemia.

Another noteworthy finding of our study is that the prevalence of unexplained anemia (2.9%) was considerably lower than the average rates reported in the literature. In previous studies, the prevalence of unexplained anemia in the elderly population has generally been reported to range between 15% and 30%.[4,18] Owing to the retrospective design of our study, advanced diagnostic evaluations could not be performed in some cases; therefore, the true prevalence of unexplained anemia may have been underestimated. In routine clinical practice, the inability to perform advanced investigations such as serum hepcidin measurement, erythropoietin level assessment, or bone marrow biopsy may have led to the classification of some cases with unclear etiology under the "mixed-type" category. In other words,

in certain cases where the underlying cause could not be definitively identified, mild or nonspecific findings may have been attributed to multiple contributing factors, resulting in their classification as multifactorial anemia. This may have artificially lowered the observed rate of unexplained anemia while relatively increasing the prevalence of mixed-type anemia.

In elderly patients registered in home health care services, anemia most often presents as a multifactorial syndrome rather than a condition attributable to a single cause. This study emphasizes that anemia management in such a population cannot be limited to iron or vitamin replacement alone. When primary care physicians identify anemia in frail elderly patients receiving home health care services, they should review not only nutritional status and underlying chronic diseases but also the patient's medication list. Considering the inflammatory burden and adverse effects associated with polypharmacy, deprescribing of unnecessary or potentially harmful medications should be incorporated into the management plan. Even in cases suggestive of iron deficiency, accompanying chronic diseases or medication use may contribute to anemia, underscoring the need for a comprehensive approach.

Limitations

Our study has several limitations. First, its retrospective cross-sectional and single-center design prevents the establishment of temporal or definitive cause-and-effect relationships, such as between polypharmacy and the onset of anemia, and limits the generalizability of the results to broader populations. Second, the retrospective nature of the study precluded a systematic evaluation of specific markers for rare anemia etiologies; for instance, hemolytic markers and peripheral blood smears were not routinely available. Furthermore, the retrospective reliance on routine clinical records meant that several relevant variables, specifically inflammatory markers (e.g., C-reactive protein), nutritional indicators (e.g., serum albumin), and standardized geriatric assessment parameters (e.g., functional status, were not systematically available for the entire cohort, limiting a more multidimensional interpretation. Finally, our statistical approach was limited to univariate analyses. A multivariate regression analysis to adjust for confounding factors, such as age, sex, and the precise chronic disease burden, was not performed due to the high collinearity between variables like polypharmacy and the absolute number of comorbidities in this highly frail cohort. Therefore, the observed links should be interpreted with caution as clinical associations rather than independent causal relationships.

CONCLUSION

Anemia is a common, multifactorial health problem among elderly patients receiving home health care services. The primary contribution of this study is the identification of mixed-type anemia as the predominant etiological profile, a finding that contrasts with existing general population literature which typically emphasizes isolated nutritional deficiencies or isolated chronic disease anemia. In this frail cohort, the vast majority of cases exhibited normocytic morphology, and the concurrent presence of multiple etiological factors indicates that single-etiology diagnostic approaches are insufficient. Furthermore, polypharmacy was found to be significantly associated with ACI, serving as a clinical proxy for multimorbidity. These findings highlight that the evaluation of anemia in home health care patients should not be limited to hemogram parameters alone; rather, nutritional status, underlying chronic disease burden, and medication regimens must be addressed in a comprehensive, patient-centered manner.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with the approval of the Scientific Researches Ethics Committee of the İzmir Bozyaka Training and Research Hospital (Date: 31.07.2024, Decision No: 2024/40).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Concept: EK; Design: EK, OT; Data Collection and/or Processing: EK; Analysis and/or Interpretation: EK, OT; Literature Review: EK, OT; Writing the Article: EK; Critical Review: EK, OT.

REFERENCES

1. World Health Organization. The global prevalence of anaemia in 2011. Published 2015. Accessed August 15, 2025. https://iris.who.int/handle/10665/177094
2. Stauder R, Thein SL. Anemia in the elderly: clinical implications and new therapeutic concepts. *Haematologica*. 2014;99(7):1127-1130. doi:10.3324/haematol.2014.109967
3. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med*. 2005;352(10):1011-1023. doi:10.1056/NEJMra041809
4. Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. *Blood*. 2004;104(8):2263-2268. doi:10.1182/blood-2004-05-1812
5. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC Geriatr*. 2017;17(1):230. doi:10.1186/s12877-017-0621-2
6. den Elzen WPJ, Groeneveld Y, de Ruijter W, Souverijn JHM, le Cessie S, Assendelft WJJ. Long-term use of proton pump inhibitors and vitamin B12 status in elderly individuals. *Aliment Pharmacol Ther*. 2008;27(6):491-497. doi:10.1111/j.1365-2036.2008.03601.x
7. Viollet B, Guigas B, Garcia NS, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: an overview. *Clin Sci (Lond)*. 2012;122(6):253-270. doi:10.1042/CS20110386

8. Bharath LP, Agrawal M, McCambridge G, et al. Metformin enhances autophagy and normalizes mitochondrial function to alleviate aging-associated inflammation. *Cell Metab.* 2020;32(1):44-55.e6. doi:10.1016/j.cmet.2020.04.015
9. Aydın K, Savaşcı U. Diagnosis and treatment guideline for iron deficiency in adults. In: Erythrocyte Diseases and Hemoglobin Disorders Diagnosis and Treatment Guideline 2022. Turkish Society of Hematology; 2022:23-32.
10. Devalia V, Hamilton MS, Molloy AM; British Committee for Standards in Haematology. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. *Br J Haematol.* 2014;166(4):496-513. doi:10.1111/bjh.12959
11. Oymak Y, İlhan G. Diagnosis and treatment guideline for vitamin B12 deficiency. In: Erythrocyte Diseases and Hemoglobin Disorders Diagnosis and Treatment Guideline 2022. Turkish Society of Hematology; 2022:1-10.
12. Malkan ÜY, Güneş A, Şimşek Y. Diagnosis and treatment guideline for anemia of chronic disease. In: Erythrocyte Diseases and Hemoglobin Disorders Diagnosis and Treatment Guideline 2022. Turkish Society of Hematology; 2022:98-101.
13. World Health Organization. Guideline on Haemoglobin Cutoffs to Define Anaemia in Individuals and Populations. World Health Organization; 2024.
14. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Accessed November 5, 2025. https://www.who.int/publications/i/item/WHO-NMH-NHD-MNM-11.1
15. Kulkarni AS, Brutsaert EF, Anghel V, et al. Metformin regulates metabolic and nonmetabolic pathways in skeletal muscle and subcutaneous adipose tissues of older adults. *Aging Cell.* 2018;17(2):e12723. doi:10.1111/acel.12723
16. Yildiz J, Sarıçam O. The prevalence of anemia in elderly patients: a cross-sectional study. *J Health Sci Med.* 2022;5(2):440-444. doi:10.32322/jhsm.1054184
17. Emiroglu C, Görpelioglu S, Aypak C. The relationship between nutritional status, anemia and other vitamin deficiencies in the elderly receiving home health care. *J Nutr Health Aging.* 2019;23(7):677-682. doi:10.1007/s12603-019-1214-7
18. Joosten E, Pelemans W, Hiele M, Noyen J, Verhaeghe R, Boogaerts MA. Prevalence and causes of anaemia in a geriatric hospitalized population. *Gerontology.* 1992;38(1-2):111-117. doi:10.1159/000213310

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Review

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A syndromic review of the microbial features and patterns in diabetic foot ulcers

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ABSTRACT

Diabetic foot ulcers (DFUs) are a major complication of diabetes mellitus, frequently complicated by microbial infections that impede wound healing and substantially increase the risk of lower-extremity amputation and death. Understanding the microbial ecology, resistance patterns, and diagnostic landscape of DFUs is a clinical imperative. This syndromic review evaluates the significance of microbial infection in DFUs, appraises current diagnostic and therapeutic approaches, and explores how emerging strategies can improve clinical management outcomes. A comprehensive literature search was conducted across Scopus, PubMed, and Web of Science, supplemented by Google Scholar, yielding 55 relevant qualitative and mixed-method studies published between January 2000 and December 2025. Eligible studies presented primary microbiological characterization data, syndromic pattern descriptions, or antibiotic susceptibility findings. Studies not available in English, purely translational or laboratory-based findings without clinical correlates, and publications lacking a clear methodological framework were excluded. DFUs harbour diverse microbial communities, including gram-positive cocci (principally *Staphylococcus aureus*, including methicillin-resistant strains), gram-negative bacilli (*Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae*), obligate anaerobes (*Bacteroides fragilis, Peptostreptococcus* spp.), and fungi (*Candida* spp.). Biofilm formation is a central mechanism underlying chronicity and antibiotic resistance. Microbial profiles shift temporally from monomicrobial gram-positive colonization in acute ulcers to polymicrobial, anaerobe-enriched communities in chronic wounds. Geographic variation is pronounced: high-income regions are dominated by gram-positive pathogens, while low- and middle-income settings bear a disproportionate gram-negative burden. Resistance rates are alarmingly high, with methicillin-resistant *S. aureus* (MRSA), extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*, and multidrug-resistant (MDR) gram-negative rods posing the greatest therapeutic challenges. Advanced diagnostic tools, including 16S rRNA sequencing, shotgun metagenomics, MALDI-TOF mass spectrometry, and fluorescence imaging; increasingly employed alongside conventional culture to improve microbial identification and therapeutic precision. A comprehensive understanding of the dynamic microbial ecology of DFUs, incorporating temporal shifts, resistance patterns, the role of biofilms, and emerging diagnostic technologies; essential for guiding evidence-based therapeutic strategies. Integration of precision diagnostics and novel therapies, including bacteriophage therapy, antimicrobial peptides, and topical probiotics, holds meaningful promise for improving clinical outcomes in this high-risk population.

Keywords: Antibiotic resistance, diabetic foot infections, microbial ecology, MRSA, polymicrobial infections, wound microbiome

INTRODUCTION

Historical Context and Clinical Significance

The association between diabetes mellitus and foot gangrene was recognised as early as 1852, when Marchal de Calvi, and subsequently Thomas Hodgkin in 1854, documented this clinically devastating relationship. Early management was largely ineffective, consisting of bed rest, with ulcers recurring upon patient ambulation. A pivotal advance came with Frederick Teves, whose technique of callus debridement

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following linseed poultice application, combined with antiseptic treatment and felt padding to redistribute plantar pressure, demonstrated that recurrence could be meaningfully reduced.[1] Before the advent of insulin therapy, gangrene and diabetic coma were the leading causes of death in patients with diabetes. Paradoxically, following the discovery of insulin, mortality from coma declined, yet mortality from foot disease increased significantly, reflecting the longer survival of diabetic patients and the cumulative burden of chronic complications.[2]

Epidemiology and Global Burden

A DFU is defined as a full-thickness wound developing distal to the ankle in a patient with diabetes, associated with neurological abnormalities and frequently complicated by infection and ischaemia.[3] Of the estimated 537 million people worldwide living with diabetes, 19-34% will develop a DFU during their lifetime, with a recurrence rate approaching 65% within 3-5 years of the initial presentation.[3] Approximately 20% of those who develop a DFU will require lower-extremity amputation, either minor (below the ankle) or major (above the ankle), and 10% will die within one year of their first diagnosis (**Figure 1**).[4]

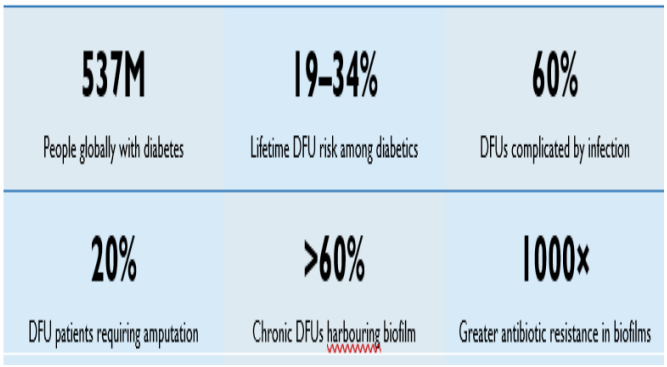

Figure 1. Key epidemiological statistics: the global burden of diabetic foot ulcers and microbial infection

The global prevalence of diabetes-related lower-extremity complications encompasses an estimated 131 million individuals, including 105.6 million with neuropathy alone, 18.6 million with active foot ulcers, and 6.8 million with amputations.[5] The disability burden, measured in years lived with disability (YLD), attributable to diabetic foot complications was estimated at 16.8 million YLDs (2.07% of all global YLDs) in 2016.[6] The economic impact is equally staggering: in the National Health Service (England), diabetic foot care consumes approximately 1% of the entire healthcare budget (approximately £1 in every £140 spent), while in the United States, diabetes directly costs $237 billion annually, with one-third of direct costs attributable to foot disease, and individual DFU patients incurring $11,710–$16,833 in incremental annual healthcare expenditure.[6,7]

Pathophysiology of Diabetic Foot Ulcers

DFU formation is precipitated by recurrent minor trauma to the foot, arising from persistent elevated plantar pressure, friction from poorly fitted footwear, gait abnormalities, or unrecognised injury (burns, punctures, ingrown toenails) to an insensate foot, that progresses via multifactorial pathophysiological pathways to a full-thickness wound.[8] These pathways are broadly classified as neuropathic, ischaemic, or mixed neuroischaemic, based on the dominant contribution of peripheral neuropathy (PN), peripheral artery disease (PAD), or both.[9]

Diabetic PN results from metabolic and microvascular injury under chronic hyperglycaemia, producing sensory, motor, and autonomic deficits. Sensory neuropathy eliminates protective sensation, pain, proprioception, and temperature, allowing minor trauma to go unrecognised, wounds to be repeatedly retraumatized, and ulcer formation to progress undetected. Motor neuropathy causes intrinsic muscle wasting, contributing to foot deformity and abnormal pressure distribution that creates additional ulceration points. Autonomic neuropathy impairs sweating, rendering skin dry and fissure-prone, and causes microvascular dysregulation that promotes local oedema and impaired tissue repair.[8] PAD superimposes on these deficits by causing diffuse, long-segment arterial occlusion that critically reduces perfusion, rendering wounds ischaemic, infection-prone, and refractory to healing.[9]

The Microbial Dimension: Infection as a Driver of Morbidity

Diabetic foot infection (DFI) complicates approximately 60% of DFUs and is the primary driver of emergency department visits and hospitalizations in this population.[10] Among those who develop DFI, the majority require operative intervention for debridement; 15-20% ultimately require amputation for adequate infection control.[11] In cases of severe infection or osteomyelitis, the amputation rate escalates to nearly 90%.[12] The microbial colonization of DFUs perpetuates a vicious cycle: infection causes local tissue swelling that worsens plantar pressure, microbial colonization of necrotic tissue prevents healthy granulation tissue formation, and polymicrobial communities form biofilms that are notoriously refractory to antimicrobial treatment, collectively deepening ulcer severity, increasing chronicity, and amplifying the risk of systemic sepsis, amputation, and death.[13,14]

Objectives and Rationale

With the global incidence of DFUs and their complications continuing to rise, a critical and systematic appraisal of the microbial features, resistance patterns, and management landscape is urgently needed. This syndromic review aims to: (i) delineate the microbial ecology and temporal patterns of DFU infection; (ii) critically evaluate current diagnostic approaches, from conventional culture to advanced molecular techniques; (iii) appraise antibiotic resistance trends and their clinical implications; (iv) assess established and emerging treatment strategies; and (v) identify research gaps and future directions to advance precision management of DFIs. The review is intended to serve as a comprehensive resource for clinicians, microbiologists, and researchers engaged in diabetic wound care (**Supplementary Table 1**).

METHODS

Literature Search Strategy

A systematic literature search was conducted across three primary electronic databases, Scopus, PubMed/MEDLINE, and Web of Science, applying a syndromic review framework to capture existing evidence on microbial features and patterns

Supplementary Table 1. Summary of the syndromic review framework: domains, scope, and clinical focus

Review domain	Clinical scope	Key questions addressed
Microbial ecology	Gram-positive, gram-negative, anaerobic, and fungal pathogens; temporal and geographic variation	Which organisms colonise DFUs? How do communities evolve with chronicity and geography?
Biofilm biology	Biofilm structure, EPS matrix, persister cells, quorum sensing, polymicrobial interactions	How do biofilms confer treatment resistance? What are the mechanisms of chronicity?
Antibiotic resistance patterns	MRSA (7–40%), ESBL-producers (10–20%), CRE (<5%), MDR *P. aeruginosa* (15–41%)	What resistance phenotypes predominate? What are reported prevalence ranges?
Diagnostic approaches	Culture (gold standard), PCR, 16S rRNA sequencing, metagenomics, MALDI-TOF, fluorescence imaging	What are the comparative advantages and limitations of available diagnostics?
Treatment strategies	Empirical vs. culture-guided antibiotics, serial debridement, bacteriophage therapy, AMPs, probiotics	What evidence supports empirical versus targeted therapy? What novel modalities show promise?
Emerging perspectives	Precision medicine, computational biology, microbiome biomapping, personalised algorithms	How can computational and molecular tools advance individualised DFU management?

DFU: Diabetic foot ulcer, EPS: Extracellular polymeric substance, MRSA: Methicillin-resistant *Staphylococcus aureus*, ESBL: Extended-spectrum beta-lactamase, CRE: Carbapenem-resistant *Enterobacteriaceae*, MDR: Multidrug-resistant, PCR: Polymerase chain reaction, rRNA: Ribosomal ribonucleic acid, MALDI-TOF: Matrix-assisted laser desorption/ionization time-of-flight, AMP: Antimicrobial peptide

in DFUs. Google Scholar was additionally interrogated to identify conference proceedings, grey literature, and relevant unpublished theses. Although this work does not constitute a formal meta-analysis, the multifaceted search approach was designed to comprehensively cover pathogen spectra, antibiotic resistance patterns, and associated clinical syndromes. Boolean operators (AND, OR) were applied throughout.

The Medical Subject Headings (MeSH) strategy employed the following primary terms and their variants: "diabetic foot ulcer," "diabetic foot infection," "diabetic foot microbiome," "wound microbiota," "biofilm," "antibiotic resistance," "MRSA," "ESBL," and "syndromic review." The search was limited to publications in English, spanning January 2000 to December 2025, to reflect the contemporary evidence base while capturing historically significant foundational studies.

Eligibility Criteria

Inclusion criteria: Studies were eligible for inclusion if they: (i) presented primary qualitative or mixed-method data on microbiological characterization of DFUs, including isolated pathogens and antibiotic susceptibility patterns; (ii) demonstrated relevant analysis of syndromic patterns and their clinical presentations or outcomes; (iii) were peer-reviewed publications, original research articles, systematic reviews, meta-analyses, or high-quality narrative reviews; and (iv) were published in English between January 2000 and December 2025.

Exclusion criteria: Studies were excluded if they: (i) were not available in English, regardless of their potential relevance; (ii) reported exclusively translational or laboratory-based findings without demonstrable clinical correlates; or (iii) lacked a clear methodological framework, including case reports, editorials, and commentaries or failed to provide sufficient primary qualitative microbiological data.

Limitations

The inherent limitations of this review are acknowledged. First, restriction to English-language publications introduces language bias and may result in underrepresentation of important research from non-English-speaking regions, particularly in low- and middle-income countries bearing the greatest DFU burden. Second, the heterogeneity of included study designs, sampling methodologies, microbiological processing standards, and reporting conventions limits direct cross-study comparisons. Third, publication bias is possible, as studies with significant microbiological findings are more likely to be published and indexed in the primary databases searched. These limitations have been carefully considered in interpreting and contextualizing the findings presented throughout this review.

MICROBIAL ECOLOGY OF DIABETIC FOOT ULCERS

DFUs represent a complex and dynamic microbial ecosystem, shaped by wound chronicity, host immune status, prior antibiotic exposure, local ischaemia, and geographical provenance. A comprehensive understanding of this ecology, encompassing the spectrum of pathogens, mechanisms of biofilm formation, and the clinical distinctions between polymicrobial and monomicrobial infections; foundational to effective management.[15]

The Microbial Spectrum of DFUs

DFUs harbour a diverse array of microorganisms, ranging from skin commensal colonisers in early wounds to complex polymicrobial communities in advanced chronic ulcers. The principal pathogen categories are summarized in **Table 1**.

Gram-positive bacteria: Gram-positive bacteria are the predominant initial colonisers of DFUs, particularly in acute or superficial presentations. *Staphylococcus aureus*, including methicillin-resistant strains (MRSA); consistently the most frequently isolated organism globally. *S. aureus* elaborates a broad arsenal of virulence factors, including protein A (immune evasion), hemolysins, leukotoxins, and exfoliative toxins, which collectively drive tissue destruction and impair host defenses. *Streptococcus* species, notably *S. pyogenes* and *S. agalactiae*, are frequently co-isolated, particularly in superficial infections, where they induce intense inflammatory responses via streptolysin and hyaluronidase production.[16] *Enterococcus faecalis* and *faecium*, intrinsically resistant to many antibiotics, are increasingly prevalent, particularly in patients with prior antimicrobial exposure.[17]

Gram-negative bacteria: Gram-negative organisms are more commonly implicated in chronic, deep, or hospital-acquired DFU infections, and frequently reflect prior antibiotic selection pressure or nosocomial acquisition. *Pseudomonas aeruginosa* is a particularly formidable pathogen due to its

Table 1. Common microbial pathogens isolated in diabetic foot ulcers and their clinical significance

Microorganism type	Representative pathogens	Clinical relevance
Gram-positive bacteria	*Staphylococcus aureus* (incl. MRSA), *Streptococcus pyogenes, Streptococcus agalactiae, Enterococcus* spp.	Predominant early/superficial ulcers; MRSA poses significant treatment challenge; induces intense inflammation via exotoxins and hemolysins
Gram-negative bacteria	*Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Proteus* spp.	Prevalent in chronic/deep ulcers; high intrinsic resistance; *Pseudomonas aeruginosa* forms robust biofilms; ESBL producers complicate therapy
Anaerobes	*Bacteroides fragilis, Peptostreptococcus* spp., *Clostridium* spp., *Fusobacterium* spp.	Under-detected due to culture limitations; synergize with aerobes; collagenase production degrades ECM; associated with ischemic/necrotic wounds
Fungi	*Candida albicans, Candida tropicalis, Candida parapsilosis, Aspergillus* spp. (rare)	Occur in immunocompromised hosts or post-prolonged antibiotic therapy; form resilient biofilms; often missed by routine screening

MRSA: Methicillin-resistant *Staphylococcus aureus,* ESBL: Extended-spectrum beta-lactamase, ECM: Extracellular matrix

high intrinsic resistance, potent biofilm-forming capacity, and production of pigments (pyocyanin, pyoverdin) that generate oxidative stress and inhibit epithelial repair. Members of *Enterobacteriaceae, E. coli, Klebsiella pneumoniae*, and *Proteus* spp.; commonly isolated in polymicrobial infections and may exacerbate wound malodor and inflammation. The emerging prevalence of ESBL and carbapenemase-producing strains within this group represents one of the most pressing therapeutic challenges in DFU management.[18]

Anaerobic organisms: Obligate anaerobes, though systematically underdetected due to the technical limitations of conventional culture, play a critical pathogenic role in DFUs, particularly in ischaemic, necrotic, or deeply penetrating wounds where reduced tissue perfusion creates microaerobic and anaerobic niches. *Bacteroides fragilis* and *Peptostreptococcus* spp. are the most frequently identified anaerobes. These organisms produce short-chain fatty acids, collagenase, and other extracellular matrix-degrading enzymes that deepen ulcer chronicity and synergize with facultative aerobes to amplify pathogenic potential and antibiotic resistance.[18,19]

Fungal pathogens: Fungal involvement in DFUs, while not routinely screened, is a clinically important consideration in immunocompromised patients or those exposed to prolonged broad-spectrum antibiotic therapy. *Candida albicans* is the most commonly reported species, with *C. tropicalis* and *C. parapsilosis* also documented. *Candida* spp. form resilient biofilms and are capable of co-infecting alongside bacterial communities, leading to mixed fungal-bacterial infections that frequently escape detection with standard diagnostic approaches and require specific antifungal treatment in addition to antibacterial management.[49]

Biofilm Formation and Its Role in Ulcer Chronicity

A defining pathological feature of chronic DFUs is the establishment of microbial biofilms, structured, sessile communities of microorganisms embedded within a self-produced extracellular polymeric substance (EPS) matrix, anchored to wound surfaces. Clinical evidence indicates that more than 60% of chronic wounds, including DFUs, harbour biofilm. The presence of biofilm is consistently associated with delayed epithelialization, heightened chronic inflammation, and inferior therapeutic outcomes.[13,14]

The EPS matrix, composed of polysaccharides, proteins, nucleic acids, and lipids, provides structural integrity and serves as a formidable physicochemical barrier. Within this architecture, cells exhibit pronounced phenotypic heterogeneity; a small subpopulation adopts a dormant persister state, rendering them highly refractory to antimicrobial action. Polymicrobial biofilms, incorporating both bacterial and fungal components, create a cooperative microenvironment supporting interspecies chemical signaling, genetic exchange via conjugation, and coordinated virulence expression through quorum sensing.[44]

Mechanisms of Biofilm-Associated Antibiotic Resistance

Microorganisms residing within biofilms are estimated to be up to 1,000 times more resistant to antibiotics than their planktonic (free-floating) counterparts. This resistance arises from multiple synergistic mechanisms, detailed in Table 2, which collectively render standard antibiotic regimens insufficient for biofilm eradication and necessitate combination pharmacological strategies alongside physical debridement.[35,36]

Table 2. Mechanisms of biofilm-associated antibiotic resistance in diabetic foot ulcers

Resistance mechanism	Mechanistic description	Clinical impact
EPS diffusion barrier	Extracellular polymeric substance matrix physically impedes antibiotic penetration; particularly effective against hydrophilic agents	Reduces effective antibiotic concentration at the infection site by up to 100-fold
Altered microenvironment	Oxygen, pH, and nutrient gradients within the biofilm reduce metabolic activity of bacteria in deeper layers	Renders bactericidal agents (e.g., β-lactams) ineffective against metabolically inactive bacteria
Efflux pump upregulation	Biofilm-resident bacteria upregulate multi-drug efflux pumps (e.g., MexAB-OprM in *Pseudomonas aeruginosa*)	Active extrusion of antibiotics before they reach target sites; contributes to MDR phenotype
Horizontal gene transfer	Close spatial proximity within biofilm facilitates conjugation and transfer of plasmid-encoded resistance genes	Rapid dissemination of MRSA, ESBL, and carbapenem-resistance genes across polymicrobial communities
Persister cell formation	Metabolically dormant subpopulations (1–5% of biofilm) exhibit high antibiotic tolerance without genetic resistance	Repopulate biofilm after antibiotic cessation; responsible for chronic relapsing infections
Quorum sensing	Bacteria communicate via chemical signals (N-acyl homoserine lactones) to coordinate biofilm maturation and virulence	Coordinated regulation of virulence factors; limits immune recognition; promotes biofilm structural integrity

MDR: Multidrug-resistant, MRSA: Methicillin-resistant *Staphylococcus aureus,* ESBL: Extended-spectrum beta-lactamase

Polymicrobial vs. Monomicrobial Infections

The microbial ecology of DFUs spans a continuum from monomicrobial infections, typically gram-positive cocci in acute, superficial ulcers, to complex polymicrobial communities in chronic, deep, or ischaemic wounds. This distinction carries significant diagnostic and therapeutic implications. In polymicrobial infections, synergistic pathogenicity is well documented: *S. aureus* exploits anaerobic microenvironments created by *Bacteroides* spp., while *P. aeruginosa* suppresses host immune responses, facilitating co-colonization by other organisms.[19,20] These interspecies interactions amplify virulence, accelerate biofilm maturation, and broaden resistance profiles. Table 3 systematically compares the key clinical and microbiological distinctions.

MICROBIAL PATTERNS AND THEIR CLINICAL SIGNIFICANCE

The microbial communities of DFUs are not static; they evolve dynamically in response to wound chronicity, treatment pressures, host factors, and environmental influences. Understanding these temporal, geographical, and severity-linked patterns is essential for guiding empiric antibiotic selection, anticipating resistance, and tailoring clinical management strategies.

Temporal Evolution: Acute vs. Chronic Ulcers

The microbial profile of a DFU undergoes a predictable, clinically significant transition from initial presentation to the chronic wound state. Early DFUs are typically colonised by skin commensal flora and are predominantly monomicrobial, with gram-positive organisms, principally *S. aureus* and β-hemolytic *Streptococcus* species, accounting for the majority of isolates. As ulcers persist, microbial diversity expands: chronic DFUs develop polymicrobial profiles with progressive enrichment in gram-negative organisms and obligate anaerobes, driven by increasing tissue hypoxia, necrosis, and biofilm maturation.[21,22] Critically, infection duration exceeding one month has been independently associated with MDR bacterial colonization (adjusted OR approximately 7.6).[21] Table 4 illustrates the quantitative microbial shift between ulcer stages, based on data from a large South China cohort.[24]

Geographic and Demographic Variation

Microbial profiles in DFUs exhibit substantial geographic heterogeneity, shaped by regional climate conditions, sanitation infrastructure, local antibiotic prescribing patterns, and population demographics. A landmark global meta-analysis identified *S. aureus* as the most prevalent isolate (~23% of isolates globally), followed by Pseudomonas aeruginosa, *E. coli*, and *Enterococcus* spp.[21] However, pronounced regional divergence was evident: high-income countries demonstrated a predominantly gram-positive burden (~62%), while low- and middle-income countries showed a predominantly gram-negative profile (~60%).[21,22] Tropical climates are associated with a higher prevalence of *P. aeruginosa*, linked to environmental reservoirs and warm, humid conditions that favor gram-negative survival and transmission.[23] Table 5 summarizes these regional differences.

Demographic factors further modulate microbial ecology. Older age, prolonged diabetes duration, prior hospitalization, and limited healthcare access are independently associated with higher rates of MDR colonization and polymicrobial infection.[24] These considerations underscore the imperative for clinicians to contextualize microbiological findings within the patient's geographic, clinical, and treatment history when formulating empiric antibiotic strategies.

Table 3. Comparative features of polymicrobial and monomicrobial infections in diabetic foot ulcers

Parameter	Polymicrobial infection	Monomicrobial infection
Frequency in DFUs	Predominant in chronic, deep, or ischemic ulcers (>60% of chronic wounds)	More common in acute, superficial presentations
Microbial composition	Combination of aerobic, anaerobic, and occasionally fungal species	Single dominant organism (typically *Staphylococcus aureus* or *Streptococcus* spp.)
Pathogenic synergy	Enhanced virulence through cross-species signaling; increased biofilm formation and quorum sensing	Localised virulence limited to one organism's repertoire
Antibiotic resistance	Greater resistance via interspecies gene transfer; broader resistance profiles	Resistance patterns typically limited to one species
Diagnostic challenge	High; standard cultures may miss fastidious/anaerobic components	Lower; easily identifiable by conventional culture
Treatment approach	Broad-spectrum or combination antibiotic therapy required; surgical debridement essential	Targeted narrow-spectrum antibiotics after identification
Clinical prognosis	Higher risk of treatment failure, recurrence, amputation, and mortality	Generally better outcomes with appropriate targeted therapy

DFU: Diabetic foot ulcer

Table 4. Temporal shift in microbial profile between acute and chronic diabetic foot ulcers

Ulcer stage	Gram-positive detection	Gram-negative detection	Predominant isolates
Early/acute DFU	~59.6%	~23.4%	*Staphylococcus aureus* (~43%), *Enterococcus* spp. (~11%), *Proteus* spp. (~8%)
Chronic DFU	~53.7%	~35.8%	*Staphylococcus aureus* (~34%), *Enterococcus* spp. (~13%), *Proteus* spp. (~13%)
Clinical implication	Declining dominance over time	Rising proportion; increasing antimicrobial challenge	Chronicity drives polymicrobial shift; MDR risk increases (adjusted OR ~7.6 for infection duration >1 month)

DFU: Diabetic foot ulcer, OR: Odds ratio

Table 5. Regional and geographic differences in diabetic foot infection microbiology

Region/setting	Gram-positive (%)	Gram-negative (%)	Notable microbiological trends
High-income countries	~62.4%	~37.6%	Higher rates of *Streptococcus* spp. and MRSA; access to advanced diagnostics alters apparent profiles
Low/middle-income countries	~40.4%	~59.6%	Greater *Enterobacteriaceae* and *Pseudomonas aeruginosa* burden; limited diagnostic infrastructure masks anaerobic burden
Tropical/subtropical climates	Lower	Higher	*P. aeruginosa* more prevalent; warm humid conditions favor gram-negative growth and environmental acquisition
Temperate/cooler climates	Higher	Lower	Predominantly gram-positive pathogens; MRSA remains clinically significant
Sub-Saharan Africa (Nigeria)	Mixed	Dominant	Multidrug-resistant organisms up to ~41%; ESBL-producers and MDR *Klebsiella* increasingly prevalent
South/Southeast Asia (Malaysia, China)	Mixed	Significant	Rising carbapenem-resistant *Enterobacteriaceae; Stenotrophomonas maltophilia* associated with major amputation risk

MRSA: Methicillin-resistant *Staphylococcus aureus,* ESBL: Extended-spectrum beta-lactamase, MDR: Multidrug-resistant

Association with Ulcer Severity and Wound Grade

Microbial complexity scales predictably with ulcer severity. Superficial ulcers (Wagner grade 1-2) typically involve aerobic pathogens, predominantly *S. aureus* and *Streptococcus* spp., with limited anaerobic burden. As ulcers penetrate deeper tissues (Wagner grade ≥3), the microenvironment becomes progressively hypoxic, creating favorable conditions for obligate anaerobes and polymicrobial communities. DNA sequencing studies corroborate this pattern, demonstrating markedly greater bacterial diversity at higher Wagner grades.[21,25] Ulcers complicated by peripheral ischaemia exhibit disproportionately elevated anaerobic and gram-negative burdens due to severely reduced tissue perfusion.[24] These severity-microbiome correlations have direct therapeutic implications: empiric broad-spectrum coverage (including anaerobic coverage) is warranted for grade ≥3 ulcers, pending definitive culture-guided therapy.

Antibiotic Resistance Patterns in Diabetic Foot Infections

Antimicrobial resistance represents one of the most clinically urgent challenges in DFU management. The three principal resistance phenotypes, MRSA, ESBL-producing Enterobacteriaceae, and MDR gram-negative rods; increasingly prevalent and correlate with treatment failure, prolonged hospitalization, and amputation risk.[21,22,25] Of note, antibiotic resistance rates in DFUs increased measurably during the COVID-19 pandemic period, likely reflecting reduced antimicrobial stewardship and disrupted outpatient care pathways.[25] Table 6 summarizes key resistance findings with their clinical implications.

The rise of MDR pathogens in DFUs emphasises the critical importance of stringent glycaemic control, rigorous wound hygiene, evidence-based antimicrobial stewardship, and culture-guided therapy over empiric prescribing. In regions with high MDR prevalence, local antibiograms should inform empiric regimens, and infectious disease specialist input should be sought for complex or treatment-refractory cases.[27]

DIAGNOSTIC APPROACHES FOR MICROBIAL IDENTIFICATION

Accurate and timely microbial identification in DFUs is foundational to guiding appropriate antimicrobial therapy, reducing empiric prescribing, and improving clinical outcomes. While conventional culture methods remain the clinical mainstay, their well-recognised limitations, particularly in detecting anaerobic, fastidious, or biofilm-embedded organisms, have driven the development and adoption of advanced molecular and point-of-care technologies. Table 7 provides a comprehensive comparison of available diagnostic modalities.

Table 6. Antibiotic-resistant pathogens in diabetic foot ulcers: prevalence, mechanisms, and clinical implications

Resistant pathogen/phenotype	Reported prevalence in DFUs	Key resistance mechanisms	Clinical implications and management
MRSA (methicillin-resistant *S. aureus*)	7–40% (regional variation); global mean ~18%	mecA gene-mediated PBP2a alteration; biofilm formation	Requires MRSA-active agents (vancomycin, linezolid, daptomycin); culture-guided therapy essential
ESBL-producing *Enterobacteriaceae*	10–20%; up to 12.2% in some series	Extended-spectrum beta-lactamase enzymes hydrolyze penicillins and cephalosporins	Carbapenem therapy required; associated with prolonged hospitalization and worse outcomes
Carbapenem-resistant *Enterobacteriaceae* (CRE)	Emerging; <5% globally but rising	KPC, NDM, OXA carbapenemases; porin loss	Limited therapeutic options; colistin or ceftazidime-avibactam; infection control critical
MDR *Pseudomonas aeruginosa*	15–41% in resource-limited settings	MexAB-OprM efflux pumps; AmpC beta-lactamases; biofilm	Combination therapy; antipseudomonal carbapenems or piperacillin-tazobactam; debridement essential
Vancomycin-resistant *Enterococci* (VRE)	Rare but increasing; ~2–8%	vanA/vanB gene-mediated cell wall modification	Linezolid or daptomycin required; associated with immunocompromised patients and prolonged therapy
MDR organisms (overall)	Up to ~41% in some regions; increased post-COVID-19 pandemic	Multiple co-existing resistance mechanisms	Stringent antimicrobial stewardship; multidisciplinary wound care; combination debridement + targeted therapy

DFU: Diabetic foot ulcer, MDR: Multidrug-resistant, ESBL: Extended-spectrum beta-lactamase

Table 7. Comparative diagnostic methods for microbial identification in diabetic foot ulcers

Diagnostic method	Method category	Advantages	Limitations
Conventional culture (tissue biopsy/swab)	Culture-based (gold standard)	Pathogen isolation; enables AST; cost-effective; widely available	3–5 day turnaround; misses fastidious/anaerobic organisms; swabs prone to superficial contamination; underestimates polymicrobial burden
Polymerase chain reaction (PCR)	Molecular–targeted	Rapid (hours); detects resistance genes (mecA, ESBL genes); high sensitivity for known targets	Limited to pre-specified targets; does not distinguish viable from nonviable organisms; cannot characterise full community
16S rRNA gene sequencing	Molecular–Broad-spectrum	Culture-independent; detects fastidious and unculturable bacteria; reveals full bacterial diversity	Poor species-level discrimination; lacks functional insight (no AST, virulence gene data); semi-quantitative
Shotgun metagenomic sequencing	Molecular–comprehensive	Full microbiome characterization; detects bacteria, fungi, viruses; identifies resistome and virulence genes	High cost; complex bioinformatics; requires specialised infrastructure; host DNA contamination
MALDI-TOF mass spectrometry	Spectrometry	Rapid, accurate species ID (even anaerobes); low per-sample cost (~$1); shorter time-to-identification vs conventional culture	Requires prior culture; limited in low-biomass samples; cannot reliably detect resistance genes
Fluorescence imaging (FL-imaging)	Point-of-care technology	Non-invasive; real-time bacterial burden visualization (>10^4 CFU/g); guides targeted debridement	Cannot detect anaerobes; affected by wound exudate/dressings; limited depth penetration; no species/resistance data
Third-generation sequencing (TGS/nanopore)	Advanced genomic technology	Direct DNA/RNA sequencing; no amplification bias; real-time results (hours); on-site compatible	High error rates; complex bioinformatics; difficulty separating microbial from host DNA; not yet routine
Loop-mediated isothermal amplification (LAMP)	Molecular–point-of-care	Simple, rapid (~60 min); low-cost equipment; high sensitivity; suitable for resource-limited settings	Limited pathogen range; requires primer design for each target; not suitable for broad-spectrum screening

rRNA: Ribosomal ribonucleic acid, AST: Antimicrobial susceptibility testing, ESBL: Extended-spectrum beta-lactamase, CFU: Colony-forming units

Conventional Culture-Based Methods

Tissue biopsy remains the gold standard for specimen collection in DFIs, providing access to deep tissue microorganisms, including those embedded within biofilm, with reduced risk of superficial contamination.[26] However, wound swabbing is more commonly practiced due to ease of use and patient tolerability. Surface swabs are prone to contamination from colonising skin flora and may fail to accurately represent the causative organisms in polymicrobial or anaerobe-rich infections. Standard culture on selective and differential media under aerobic and anaerobic conditions typically requires 3-5 days for definitive results and remains indispensable for antimicrobial susceptibility testing (AST).[27] Key limitations include systematic underestimation of polymicrobial and anaerobic components, and the inability to characterise biofilm-associated organisms without specialised processing.

Molecular and Advanced Diagnostic Technologies

Polymerase chain reaction (PCR): PCR enables rapid amplification and detection of specific microbial DNA sequences, with particular utility in identifying resistance determinants, notably the mecA gene in MRSA and ESBL-encoding genes in *Enterobacteriaceae*.[28] Multiplex PCR panels can simultaneously screen for multiple targets, significantly reducing time-to-result compared to culture. However, PCR is inherently limited to pre-specified, known targets and cannot differentiate viable from nonviable organisms or characterise the broader polymicrobial community. It also provides no direct information on antimicrobial susceptibility beyond resistance gene detection.

16S ribosomal RNA (rRNA) gene sequencing: 16S rRNA gene sequencing has emerged as the primary culture-independent method for characterising bacterial communities in DFUs. By targeting conserved yet variable regions of the prokaryotic 16S rRNA gene, this approach provides broad-spectrum bacterial detection and has revealed substantial, previously underappreciated microbial diversity in chronic DFUs, including detection of obligate anaerobes and fastidious organisms that escape conventional culture.[15,28] Limitations include relatively poor species-level discrimination between closely related taxa, the absence of functional information (virulence gene profiles, resistance genes), and the inability to quantify viable organisms or provide AST data.

Shotgun metagenomic sequencing: Shotgun metagenomics offers the most comprehensive characterization of the DFU microbiome, providing simultaneous, unbiased profiling of all microbial DNA, encompassing bacteria, fungi, viruses, and antimicrobial resistance genes (the "resistome"), directly from wound specimens.[15] Studies employing this approach have revealed the presence of resistance genes (ermA for macrolides, tetA for tetracyclines, ant1 for aminoglycosides) and virulence factors in chronic DFU infections.[28] The primary barriers to routine clinical adoption remain high cost, substantial computational infrastructure requirements, and the analytical challenge of distinguishing microbial from host DNA. As sequencing costs continue to decrease, metagenomics is positioned to become an increasingly central diagnostic tool in complex DFU management.

MALDI-TOF mass spectrometry: Matrix-Assisted Laser Desorption/Ionization Time-of-Flight (MALDI-TOF) mass spectrometry identifies bacterial and fungal isolates rapidly and accurately by generating unique protein spectral fingerprints matched against reference databases. It substantially shortens time-to-organism identification compared to biochemical phenotypic methods, is applicable to anaerobic organisms, and incurs very low per-sample costs (approximately $1).[29] Its principal limitation is the requirement for prior culture growth; it cannot be applied directly to clinical specimens with low bacterial loads or effectively characterise antimicrobial resistance profiles without supplementary molecular testing.

Point-of-Care and Emerging Technologies

Fluorescence imaging: Fluorescence (FL) imaging exploits the endogenous autofluorescence of bacterial metabolites, particularly porphyrins in *P. aeruginosa* and other organisms, to non-invasively visualize and semi-quantify bacterial burden (>10^4 CFU/g) in wounds in real time.[30] This tool enables targeted debridement of bacterially dense areas and supports antimicrobial treatment decision-making at the point of care. Its limitations include inability to detect non-fluorescent anaerobes, susceptibility to interference from wound exudate and dressings, and restricted depth penetration, limiting sensitivity for deep tissue infections.[31,32] FL imaging functions best as a complementary adjunct rather than a standalone diagnostic.

Third-Generation Sequencing and LAMP: Third-generation sequencing (TGS), exemplified by Oxford Nanopore MinION technology, enables direct, amplification-free DNA/RNA sequencing, yielding pathogen identification results within hours, a transformative advantage over culture-dependent methods.[29] Its capacity for on-site deployment and detection of epigenetic modifications further distinguishes it from prior sequencing generations. Current limitations include higher error rates than short-read platforms, the need for advanced bioinformatics expertise, and challenges in host-microbial DNA separation. Loop-mediated isothermal amplification (LAMP) offers a complementary point-of-care molecular approach with rapid results (~60 minutes), minimal equipment requirements, and applicability in resource-limited settings, though it is restricted to targeted pathogens.[52]

TREATMENT STRATEGIES AND CLINICAL CHALLENGES

Effective management of infected DFUs demands a multimodal, iterative approach that integrates infection control, biofilm disruption, wound bed preparation, and optimization of the wound-healing environment. This section appraises established and emerging therapeutic strategies, with particular attention to the critical distinction between empirical and culture-guided antibiotic prescribing, the essential role of debridement, and the clinical potential of novel adjunctive therapies.

Empirical vs. Culture-Guided Antibiotic Therapy

Empirical antibiotic therapy, initiated before definitive microbiological identification; common clinical practice, offering the advantage of rapid treatment initiation. However, it carries significant risks: misalignment with causative organisms, contribution to resistance selection, and suboptimal outcomes. A landmark study demonstrated that patients with mild DFU infections treated empirically were 1.87 times more likely to require hospitalization within 30 days compared to those receiving culture-guided therapy.[33] These data underscore the imperative of obtaining appropriate wound specimens, tissue biopsy where feasible, prior to antibiotic initiation, and of transitioning from empirical to targeted, culture-directed therapy as soon as results are available.[27,33] Empirical regimens, where necessary, should be informed by local epidemiological data, patient-specific risk factors (prior MRSA colonization, recent hospitalization, prior antibiotic exposure), and ulcer severity classification (**Supplementary Table 2**).

Debridement and Biofilm Disruption

Surgical and sharp debridement, the systematic removal of necrotic, devitalized, and infected tissue; a cornerstone of DFU management. Given the propensity of biofilms to reconstitute within 24–72 hours of disruption, serial debridement within a structured wound care protocol is essential rather than a one-time intervention.[34,35] Regular debridement confers multiple benefits: it mechanically disrupts biofilm architecture, removes the necrotic substrate that sustains microbial growth, reduces bacterial burden, stimulates cellular proliferation, activates growth factors, and transitions the wound from a chronic inflammatory state to an acute healing phenotype. When combined with appropriate antimicrobial coverage and systemic optimization, serial debridement remains the single most effective biofilm-targeted strategy available in routine clinical practice.[36]

Supplementary Table 2. Algorithm for empirical versus culture-guided antibiotic treatment in diabetic foot ulcer infections

Step	Clinical decision point	Action	Rationale
1	At first presentation: is tissue biopsy feasible?	YES → Obtain deep tissue biopsy before antibiotics NO → Obtain deep wound swab (Levine technique)	Tissue biopsy is the gold standard; minimises superficial contamination
2	Ulcer severity assessment (Wagner/IDSA grade)	Grade 1–2 (mild): Narrow-spectrum empirical cover (anti-staphylococcal) Grade ≥3 (moderate/severe): Broad-spectrum empirical cover, including anaerobic and gram-negative cover	Severity correlates with polymicrobial and anaerobic burden; guides initial empirical choice
3	Risk factors for MDR organisms present?	YES (prior MRSA, recent hospitalisation, prior antibiotics, travel to high-MDR region): Include MRSA-active agent (vancomycin, linezolid, daptomycin) NO: Standard empirical regimen per local antibiogram	Targeted empirical escalation reduces unnecessary broad-spectrum use while addressing MDR risk
4	Culture and susceptibility results available (day 3–5)	De-escalate to narrowest effective agent based on susceptibility data Discontinue agents with no susceptibility match	Culture-guided de-escalation reduces resistance selection and adverse effects; associated with lower hospitalisation rates
5	Inadequate clinical response at 48–72 hours?	Re-culture (repeat biopsy preferred) Seek infectious disease specialist input Consider MDR pathogens, biofilm, or fungal co-infection	Early reassessment prevents treatment failure and avoids delays in identifying resistant or fastidious organisms
6	Osteomyelitis suspected or confirmed?	Prolonged culture-guided antibiotic course (6 weeks) Orthopaedic/vascular surgical input Consider bone biopsy for definitive diagnosis	Osteomyelitis carries an amputation rate approaching 90%; requires specialist multidisciplinary management

MDR: Multidrug-resistant, MRSA: Methicillin-resistant *Staphylococcus aureus*

Novel and Adjunctive Therapeutic Strategies

Bacteriophage therapy: Bacteriophage (phage) therapy, the therapeutic application of bacteriophages (viruses that specifically infect bacteria) to treat antibiotic-resistant infections, represents a compelling re-emerging modality with particular relevance to DFU management. Phages exhibit exquisite host specificity, targeting pathogenic bacteria without disrupting commensal flora, and select strains produce depolymerases capable of degrading EPS matrices, enabling penetration of established biofilms. Early clinical experience is encouraging: a case series documented meaningful clinical improvement and limb salvage in patients with limb-threatening DFIs treated with topically applied bacteriophage preparations targeting MDR organisms.[37,38] While phage therapy is not yet standardized for routine DFU use, due to challenges in phage banking, regulatory pathways, and controlled trial evidence, it represents a high-priority investigational approach for infections refractory to conventional antibiotics.

Antimicrobial peptides (AMPs): Antimicrobial peptides are endogenous host defense molecules with broad-spectrum microbicidal activity and wound-healing properties. LL-37, the sole human cathelicidin AMP, has attracted particular clinical interest: beyond its direct antimicrobial effects, LL-37 promotes angiogenesis, modulates inflammatory cytokine signaling, and enhances re-epithelialization. A randomised double-blind controlled trial demonstrated that topical LL-37 cream significantly improved healing rates in DFU patients compared to placebo.[39] The capacity of AMPs to target multiple bacterial membrane components simultaneously reduces the likelihood of resistance development, distinguishing them mechanistically from conventional antibiotics.[40] Ongoing research is exploring AMP-loaded wound dressings and synthetic AMP analogues with enhanced stability and clinical applicability.

Topical probiotics: The therapeutic application of probiotics to wound surfaces, leveraging beneficial microbial competition to suppress pathogenic colonization and modulate local immune responses, represents an innovative and relatively underexplored management strategy. In a multicentre study, topical application of probiotics in a soybean-based vehicle achieved healing in over 80% of patients with small chronic DFUs within 16 weeks.[42] Proposed mechanisms include competitive exclusion of pathogens, production of bacteriocins and short-chain fatty acids, and immune modulation at the wound interface. While large-scale randomised evidence is lacking, topical probiotics represent a low-risk adjunctive option warranting further investigation, particularly in patients with recalcitrant or polymicrobial infections.

The Challenge of Recurrent and Treatment-Refractory Infections

Chronically recurrent DFU infections present a particularly daunting management challenge. The interplay of persistent hyperglycaemia, microvascular insufficiency, established biofilm communities, and escalating antimicrobial resistance creates a milieu profoundly hostile to healing. MRSA, ESBL-producing *Enterobacteriaceae,* and MDR *P. aeruginosa*, each capable of biofilm formation; disproportionately represented in treatment-refractory DFUs. Effective management requires a multidisciplinary approach integrating surgical debridement, metabolic optimization (aggressive glycaemic control, management of PAD), microbiologically guided systemic antibiotic therapy, and consideration of adjunctive novel therapies. Antimicrobial stewardship must be rigorously applied to avoid further resistance selection, and subspecialty input from infectious disease, vascular surgery, and orthopaedics is frequently required in complex cases.[27,33]

EMERGING PERSPECTIVES AND FUTURE DIRECTIONS

The field of DFU microbiology is undergoing rapid transformation, driven by advances in molecular diagnostics, computational biology, and a deeper mechanistic understanding of wound microbiome dynamics. Several emerging paradigms hold particular promise for improving clinical outcomes and advancing the science of DFU management (Figure 2).

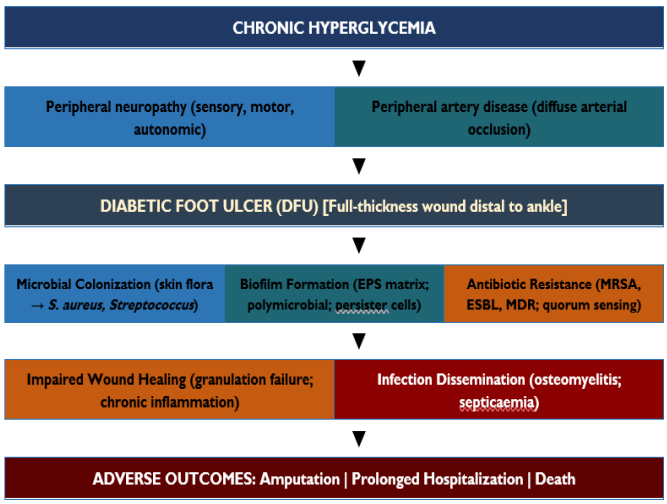

Figure 2. Pathophysiological cascade from diabetes to adverse foot outcomes
Schematic representation of the pathophysiological cascade linking chronic hyperglycaemia to diabetic foot ulcer formation, microbial colonization, biofilm establishment, antimicrobial resistance, and adverse clinical outcomes including amputation and death. EPS: Extracellular polymeric substance, ESBL: Extended-spectrum beta-lactamase, MDR: Multidrug-resistant, MRSA: Methicillin-resistant *Staphylococcus aureus*

Microbial Biomapping and Precision Diagnostics

Conventional culture-based approaches systematically underestimate the microbial diversity of DFU wounds by selectively cultivating aerobically dominant pathogens while overlooking the full spectrum of anaerobes, biofilm-embedded organisms, and fungi. Microbial biomapping, the spatially resolved, multi-omics characterization of the wound microbiome using culture-independent technologies such as 16S rRNA sequencing, shotgun metagenomics, and spatial transcriptomics, offers a transformative advance in diagnostic capability.[30,43] By identifying the complete pathogen portfolio, including fastidious and unculturable species, and mapping their spatial distribution within the wound, biomapping enables more accurate infection severity assessment, more precise antibiotic selection, and the identification of microbial signatures associated with clinical trajectories such as delayed healing or amputation risk.[42]

The integration of MALDI-TOF mass spectrometry as a rapid culture complement, combined with molecular resistance gene detection, can substantially narrow the time-to-targeted-therapy gap that is currently bridged by empirical

prescribing. The association between specific fastidious organisms, notably *Stenotrophomonas maltophilia* and major amputation outcomes exemplifies the clinical value of comprehensive microbiome characterization beyond standard culture.[42] As these technologies become more accessible and cost-effective, their integration into routine DFU diagnostic pathways represents a logical and evidence-supported evolution.

The Wound Microbiome and Host–Microbe Interactions

The DFU microbiome does not exist in isolation, it is in constant, dynamic dialogue with the host immune system, influencing and being influenced by local inflammatory mediators, antimicrobial peptide production, and adaptive immune responses.[53] Emerging research highlights how specific microbial community compositions shape the wound immune environment: certain microbiome configurations promote chronic inflammation and impaired healing, while others may support immune-mediated clearance and resolution. Understanding these host-microbiome interactions at the molecular level opens potential avenues for immunomodulatory interventions, microbiota-targeted therapies, and biomarker-based prognostic stratification.[50]

The fungal component of the DFU microbiome, the mycobiome; an underappreciated contributor to wound chronicity. Fungal communities in chronic wounds are dynamic, prevalent, and have been independently associated with delayed healing.[49] Routine integration of fungal culture and molecular detection into DFU microbiological workup is warranted, particularly in patients with prolonged antibiotic exposure, immunosuppression, or recalcitrant wounds unresponsive to antibacterial treatment.

Personalised Medicine and Standardisation Imperatives

The heterogeneity of DFU microbial ecology, across patients, geographies, and wound stages, makes a "one-size-fits-all" antimicrobial strategy inherently inadequate. Precision or personalised medicine approaches, informed by comprehensive microbiological profiling, patient-specific risk stratification, and predictive modelling, represent the future paradigm of DFU management.[50] Machine learning algorithms applied to microbiome data, clinical variables, and treatment responses have demonstrated preliminary capacity to predict outcomes and guide antimicrobial selection. Future advances in point-of-care molecular diagnostics will further enable bedside implementation of personalised treatment decisions.

A critical prerequisite for advancing the field is methodological standardisation. The current literature is characterised by substantial heterogeneity in sampling techniques (swab vs. biopsy), processing protocols, sequencing platforms, bioinformatics pipelines, and outcome reporting standards. This variability profoundly limits cross-study comparisons and the synthesis of robust, generalizable conclusions. The development and adoption of standardized protocols, across sampling, sequencing, and data interpretation; essential for creating validated microbial databases, reliable risk-stratification tools, and reproducible research that can meaningfully inform clinical practice guidelines.[51-54]

CONCLUSION

DFUs remain one of the most clinically consequential and economically burdensome complications of diabetes mellitus. Microbial infection, driven by a dynamic, evolving ecosystem of gram-positive and gram-negative bacteria, obligate anaerobes, fungi, and their polymicrobial interactions within biofilm communities; the pivotal factor that distinguishes manageable wounds from those that progress to amputation and death. This syndromic review has mapped the microbial ecology of DFUs across temporal, geographic, and severity dimensions; critically appraised conventional and advanced diagnostic modalities; evaluated established and novel treatment strategies; and identified the research and clinical practice gaps that must be addressed to improve outcomes. Computational biology, encompassing bioinformatic analysis of metagenomic datasets, machine learning-driven predictive modelling, and network-based pathway analysis, enables the integration of complex microbiome data with clinical variables to identify resistance determinants, predict treatment outcomes, and stratify patients according to infection severity. Through these analytical frameworks, computational biology transforms raw sequencing data into actionable clinical intelligence, bridging the gap between molecular diagnostics and personalised therapeutic decision-making in diabetic foot care.

The evidence supports several clear clinical imperatives: tissue biopsy and culture should be obtained before initiating antibiotic therapy whenever feasible; culture-guided therapy demonstrably reduces hospitalization risk compared to empirical prescribing; serial debridement remains irreplaceable as a biofilm management strategy; and the empiric antibiotic regimen must be informed by local resistance epidemiology, ulcer severity, and patient risk factors. The integration of molecular diagnostic tools, 16S rRNA sequencing, shotgun metagenomics, MALDI-TOF, and FL imaging, into clinical pathways can substantially enhance the precision and timeliness of microbiological characterization.

Looking forward, precision medicine, anchored in comprehensive microbiome profiling, advanced diagnostics, and personalised treatment algorithms, represents the most promising paradigm for overcoming the limitations of current management. Novel therapies, including bacteriophage therapy, antimicrobial peptides, and topical probiotics, offer genuine clinical potential and merit rigorous investigation through well-designed randomised controlled trials. Critically, achieving the standardisation of microbiological assessment protocols across institutions and geographies is a foundational prerequisite for the generation of comparable, reproducible evidence that can translate into meaningful advances in DFU clinical practice guidelines. Interdisciplinary collaboration across microbiology, infectious disease, vascular surgery, wound care, and computational biology will be essential to realise this vision and reduce the devastating global burden of diabetic foot complications.

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Peer Review Process

This review was externally peer-reviewed.

Conflict of Interest

The authors declare no conflicts of interest.

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REFERENCES

1. Connor H. Some historical aspects of diabetic foot disease. *Diabetes Metab Res Rev.* 2008;24(Suppl 1):S7-13. doi:10.1002/dmrr.838
2. Bliss M. The discovery of insulin. Chicago: University of Chicago Press; 1982.
3. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. *N Engl J Med.* 2017;376(24):2367-2375. doi:10.1056/NEJMra1615439
4. Hoffstad O, Mitra N, Walsh J, Margolis DJ. Diabetes, lower-extremity amputation, and death. *Diabetes Care.* 2015;38(10):1852-1857. doi:10.2337/dc15-0536
5. Zhang Y, Lazzarini PA, McPhail SM, van Netten JJ, Armstrong DG, Pacella RE. Global disability burdens of diabetes-related lower-extremity complications in 1990 and 2016. *Diabetes Care.* 2020;43(5):964-974. doi:10.2337/dc19-1614
6. Kerr M, Barron E, Chadwick P. The cost of diabetic foot ulcers and amputations to the National Health Service in England. *Diabet Med.* 2019;36(8):995-1002. doi:10.1111/dme.13973
7. Edmonds M, Manu C, Vas P. The current burden of diabetic foot disease. *J Clin Orthop Trauma.* 2021;17:88-93. doi:10.1016/j.jcot.2021.01.017
8. McDermott K, Fang M, Boulton AJM, Selvin E, Hicks CW. Etiology, epidemiology, and disparities in the burden of diabetic foot ulcers. *Diabetes Care.* 2023;46(1):209-221. doi:10.2337/dci22-0043
9. Sidawy AN, Perler BA, eds. Rutherford's vascular surgery and endovascular therapy. 9th ed. Philadelphia, PA: Elsevier; 2019.
10. Rice JB, Desai U, Cummings AKG, Birnbaum HG, Skornicki M, Parsons NB. Burden of diabetic foot ulcers for Medicare and private insurers. *Diabetes Care.* 2014;37(3):651-658. doi:10.2337/dc13-2176
11. Fang M, Hu J, Matsushita K, Selvin E, Hicks CW. Long-term consequences of diabetic foot infection: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetes.* 2022;71(Suppl. 1):126-OR.
12. Lavery LA, Ryan EC, Ahn J, et al. The infected diabetic foot: re-evaluating the Infectious Diseases Society of America diabetic foot infection classification. *Clin Infect Dis.* 2020;70(8):1573-1579. doi:10.1093/cid/ciz489
13. Høiby N, Bjarnsholt T, Moser C, et al. ESCMID guideline for the diagnosis and treatment of biofilm infections 2014. *Clin Microbiol Infect.* 2015;21(Suppl 1):S1-S25. doi:10.1016/j.cmi.2014.10.024
14. James GA, Swogger E, Wolcott R, et al. Biofilms in chronic wounds. *Wound Repair Regen.* 2008;16(1):37-44. doi:10.1111/j.1524-475X.2007.00321.x
15. Sadeghpour Heravi F, Zakrzewski M, Vickery K, Armstrong DG, Hu H. Bacterial diversity of diabetic foot ulcers: current status and future prospectives. *J Clin Med.* 2019;8(11):1935. doi:10.3390/jcm8111935
16. Shahi SK, Kumar A. Isolation and genetic analysis of multidrug-resistant bacteria from diabetic foot ulcers. *Front Microbiol.* 2016;6:1464. doi:10.3389/fmicb.2015.01464
17. Mashaly M, Ibrahim M, Khafagy W. Aerobic bacteria isolated from diabetic foot ulcers of Egyptian patients: types, antibiotic susceptibility pattern and risk factors associated with multidrug-resistant organisms. *Germs.* 2021;11(4):570-580. doi:10.18683/germs.2021.1292
18. Noor S, Zubair M, Ahmad J. Diabetic foot ulcer: a review on pathophysiology, classification and microbial etiology. *Diabetes Metab Syndr Clin Res Rev.* 2015;9(3):192-199. doi:10.1016/j.dsx.2015.04.007
19. Morsli M, Salipante F, Magnan C, Dunyach-Remy C, Sotto A, Lavigne JP. Direct metagenomics investigation of non-surgical hard-to-heal wounds: a review. *Ann Clin Microbiol Antimicrob.* 2024;23(1):39. doi:10.1186/s12941-024-00698-z
20. Ahmed A, Boateng J. Treatment of mixed infections in wounds. In: Therapeutic Dressings and Wound Healing Applications. 2020:91-113.
21. Macdonald KE, Jordan CY, Chartered MJ, et al. The microbiology of diabetic foot infections: a meta-analysis. *BMC Infect Dis.* 2021;21:770. doi:10.1186/s12879-021-06516-7
22. Hadi P, Kaur T, Raja RA, et al. Distribution of causative microorganisms in diabetic foot infections: a ten-year study in Malaysia. *Antibiotics.* 2023;12(4):687. doi:10.3390/antibiotics12040687
23. Winski H, Kaul DR, Foxman B. Correlating climate conditions with *Pseudomonas* prevalence in diabetic foot infections (US). *Open Forum Infect Dis.* 2024;11(11):ofae621. doi:10.1093/ofid/ofae621
24. Sun J, Zheng P, Li L, et al. Microbial distribution and antibiotic susceptibility in diabetic foot infections in South China. *Front Endocrinol.* 2023;14:1113622. doi:10.3389/fendo.2023.1113622
25. Kalan LR, Meisel JS, Loesche MA, et al. Strain- and species-level variation in the microbiome of diabetic wounds is associated with clinical outcomes and therapeutic efficacy. *Cell Host Microbe.* 2019;25(5):641-655. doi:10.1016/j.chom.2019.03.006
26. Adeyemo AT, Kolawole AA, Aderemi-Williams RI, et al. Multicentre study of multidrug-resistant bacteria in infected diabetic foot ulcers in Nigeria. *Afr J Lab Med.* 2021;10(1):1261. doi:10.4102/ajlm.v10i1.1261
27. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 IDSA clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis.* 2012;54(12):e132-e173. doi:10.1093/cid/cis346
28. Huang Y, Xiao Z, Cao Y, et al. Rapid microbiological diagnosis based on 16S rRNA gene sequencing in diabetic foot infections. *Front Microbiol.* 2022;13:1021955. doi:10.3389/fmicb.2022.1021955
29. Anwar K, Hussein D, Salih J. Antimicrobial susceptibility testing and phenotypic detection of MRSA isolated from diabetic foot infection. *Int J Gen Med.* 2020;13:1349-1357. doi:10.2147/IJGM.S278574
30. Schmidt BM. Emerging diabetic foot ulcer microbiome analysis using cutting-edge technologies. *J Diabetes Sci Technol.* 2022;16(2):353-363. doi:10.1177/1932296821990097
31. Armstrong DG, Edmonds ME, Serena TE. Point-of-care fluorescence imaging reveals extent of bacterial load in diabetic foot ulcers. *Int Wound J.* 2023;20(2):554-566. doi:10.1111/iwj.14080
32. Koo DY, Namgoong S, Han SK, Dhong ES, Jeong SH. Diagnostic accuracy of a fluorescence imaging device in diabetic wounds: a pilot study. *Wounds.* 2023;35(7):E218-E223. doi:10.25270/wnds/23002
33. Schmidt BM, Kaye KS, Armstrong DG, Pop-Busui R. Empirical antibiotic therapy in diabetic foot ulcer infection increases hospitalization. *Open Forum Infect Dis.* 2023;10(10):ofad495. doi:10.1093/ofid/ofad495
34. Ruke MG, Savai J. Diabetic foot infection, biofilm and new management strategy. *Diabetes Res Open Access.* 2019;2019(1):7.
35. Afonso AC, Oliveira D, Saavedra MJ, Borges A, Simoes M. Biofilms in diabetic foot ulcers: impact, risk factors and control strategies. *Int J Mol Sci.* 2021;22(15):8278. doi:10.3390/ijms22158278
36. Bowen G, Richardson N. Biofilm management in chronic wounds and diabetic foot ulcers. *Diabetic Foot J.* 2016;19(4):198-204.
37. Ghanaim AM, Foaad MA, Gomaa EZ, et al. Bacteriophage therapy as an alternative technique for treatment of multidrug-resistant bacteria causing diabetic foot infection. *Int Microbiol.* 2023;26(2):343-359. doi:10.1007/s10123-022-00293-2
38. Young MJ, Hall LM, Merabishvili M, Pirnay JP, Clark JR, Jones JD. Phage therapy for diabetic foot infection: a case series. *Clin Ther.* 2023;45(8):797-801. doi:10.1016/j.clinthera.2023.06.009
39. Miranda E, Bramono K, Yunir E, et al. Efficacy of LL-37 cream in enhancing healing of diabetic foot ulcer: a randomised double-blind controlled trial. *Arch Dermatol Res.* 2023;315(9):2623-2633. doi:10.1007/s00403-023-02657-8
40. Pfalzgraff A, Brandenburg K, Weindl G. Antimicrobial peptides and their therapeutic potential for bacterial skin infections and wounds. *Front Pharmacol.* 2018;9:281. doi:10.3389/fphar.2018.00281
41. Yang CC, Wu MS, Hsu H. Management of diabetic foot ulcers using topical probiotics in a soybean-based concentrate: a multicentre study. *J Wound Care.* 2023;32(Suppl 12):S16-S21. doi:10.12968/jowc.2023.32.Sup12.S16
42. Hung SY, Yeh YM, Chiu CH, et al. Microbiome of limb-threatening diabetic foot ulcers indicates the association of fastidious Stenotrophomonas and major amputation. *J Microbiol Immunol Infect.* 2024;57(1):156-163. doi:10.1016/j.jmii.2023.10.007
43. Mudrik-Zohar H, Carasso S, Gefen T, et al. Microbiome characterization of infected diabetic foot ulcers in association with clinical outcomes: traditional cultures versus molecular sequencing methods. *Front Cell Infect Microbiol.* 2022;12:836699. doi:10.3389/fcimb.2022.836699
44. Pouget C, Dunyach-Remy C, Pantel A, Schuldiner S, Sotto A, Lavigne JP. Biofilms in diabetic foot ulcers: significance and clinical relevance. *Microorganisms.* 2020;8(10):1580. doi:10.3390/microorganisms8101580

45. Henig O, Pogue JM, Cha R. Epidemiology of diabetic foot infection in the Metro-Detroit area with a focus on independent predictors for pathogens resistant to recommended empiric antimicrobial therapy. *Open Forum Infect Dis*. 2018;5(11):ofy245. doi:10.1093/ofid/ofy245
46. Perim MC, Borges JC, Celeste SRC, et al. Aerobic bacterial profile and antibiotic resistance in patients with diabetic foot infections. *Rev Soc Bras Med Trop*. 2015;48(5):546-554. doi:10.1590/0037-8682-0146-2015
47. Park JU, Oh B, Lee JH, et al. Influence of microbiota on diabetic foot wound in comparison with adjacent normal skin based on clinical features. *BioMed Res Int*. 2019;2019:7459236. doi:10.1155/2019/7459236
48. Zloch M, Maslak E, Kupczyk W, Pomastowski P. Multi-instrumental analysis toward exploring the diabetic foot infection microbiota. *Curr Microbiol*. 2023;80(8):271. doi:10.1007/s00284-023-03384-z
49. Kalan L, Loesche M, Hodkinson BP, et al. Redefining the chronic-wound microbiome: fungal communities are prevalent, dynamic, and associated with delayed healing. *mBio*. 2016;7(5):e01289-16. doi:10.1128/mBio.01058-16
50. Van Netten JJ, Woodburn J, Bus SA. The future for diabetic foot ulcer prevention: a paradigm shift from stratified healthcare towards personalized medicine. *Diabetes Metab Res Rev*. 2020;36(Suppl 1):e3244. doi:10.1002/dmrr.3234
51. Dowd SE, Sun Y, Secor PR, et al. Survey of bacterial diversity in chronic wounds using pyrosequencing, DGGE, and full ribosome shotgun sequencing. *BMC Microbiol*. 2008;8:43. doi:10.1186/1471-2180-8-43
52. Gieron M, Zarnowiec P, Zegadlo K, et al. Loop-mediated isothermal amplification of DNA (LAMP) as an alternative method for determining bacteria in wound infections. *Int J Mol Sci*. 2023;25(1):411. doi:10.3390/ijms25010411
53. Gardner SE, Hillis SL, Heilmann K, Segre JA, Grice EA. The neuropathic diabetic foot ulcer microbiome is associated with clinical factors. *Diabetes*. 2013;62(3):923-930. doi:10.2337/db12-0771
54. Wolcott R, Dowd S. The role of biofilms: are we hitting the right target? *Plast Reconstr Surg*. 2011;127(Suppl 1):28S-35S. doi:10.1097/PRS.0b013e3181fca244

Ankyra Medical Journal

Case Report

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Incidental benign Brenner tumor and symptomatic uterine leiomyomas: a clinicopathological correlation

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ABSTRACT

Brenner tumor is a rare epithelial-stromal tumor of the ovary. It is mostly asymptomatic and benign. It often accompanies other gynecological pathologies such as uterine fibroids and is incidentally detected during pathological examination after surgery. This case report presents a 47-year-old female patient who presented with complaints of dysmenorrhea and menorrhagia. Evaluation revealed multiple uterine fibroids and simple endometrial hyperplasia without atypia. Preoperative ultrasonography showed a well-defined, 22 mm hypoechoic cystic lesion in the right ovary. The patient underwent laparoscopic hysterectomy and bilateral salpingo-oophorectomy. While uterine pathology was reported as leiomyoma, pathological examination of the right ovary revealed epithelial cell nests with clear cytoplasm and nuclear grooves embedded in fibromatous stroma. Due to the tumor's rarity and to definitively rule out malignant mimics, the specimen was referred for expert consultation at a tertiary pathology center, which confirmed the diagnosis of a benign Brenner tumor. This case aims to contribute to the literature by highlighting the frequent association of benign Brenner tumor with symptomatic uterine pathologies, its asymptomatic course, and the fact that the diagnosis was made through histopathological examination.

Keywords: Brenner tumor, ovary, benign, incidental diagnosis, uterine myoma

INTRODUCTION

Brenner tumor is one of the rare epithelial-stromal tumors of the ovary. It constitutes approximately 1-2% of all neoplasms of ovarian origin.[1,2] Histologically, these tumors are characterized by urothelium-like epithelial cell nests embedded within a fibrous stromal structure.[3]

The vast majority of Brenner tumors (more than 98%) are benign. They are usually between 2-5 cm in size and are mostly asymptomatic.[4] Therefore, they are diagnosed incidentally during surgical procedures performed for other gynecological indications such as uterine pathologies or during subsequent pathological examinations.[5] Although it can occur in female of reproductive age, it is typically seen in middle age and postmenopausal period (especially 50-60 years old).[6]

Benign Brenner tumor has a characteristic ultrasonographic appearance. It is often seen as a solid, hypocoic or isoechoic, well-defined mass. The presence of mucinous cystadenoma, which may also be accompanied by internal calcifications, is also among its typical features.[5,7] The prognosis after surgical resection is very good and no further treatment is required.

This case report presents a 47-year-old female patient who presented with complaints of dysmenorrhea and menorrhagia and was diagnosed with multiple uterine fibroids and simple endometrial hyperplasia without atypia. An asymptomatic benign Brenner tumor, not suspected on preoperative imaging but discovered incidentally during pathological examination of the patient's material after elective hysterectomy and bilateral salpingo-oophorectomy, is presented. This case aims to contribute to and review the literature on this rare tumor, given its frequently asymptomatic course and its potential association with other common pelvic pathologies.

CASE

A 47-year-old female patient presented to the gynecology outpatient clinic with complaints of dysmenorrhea and menorrhagia. She had three previous vaginal deliveries. Her blood pressure was 110/75 mmHg and pulse was 88 bpm. Physical examination revealed a palpable mass in the pelvic region on deep palpation. Laboratory tests showed

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no abnormalities except for mild anemia (hemoglobin; 10.4 g/dl). Abdominal ultrasonography revealed 68 mm and 32 mm myoma nuclei originating from the anterior wall of the uterus, mostly intramural in location. Endometrial thickness was 19 mm. A well-defined 22 mm hypoechoic cystic lesion was observed in the right ovary, and Doppler ultrasound showed no increased vascularity. The left ovary was normal. Pathology materials from the patient's smear and endocervical curettage were reported as benign findings, while the endometrial biopsy was reported as simple endometrial hyperplasia without atypia.

The patient underwent elective laparoscopic hysterectomy and bilateral salpingo-oophorectomy based on the available findings. No complications arose during the procedure, and the patient, who had no problems during follow-up in the ward, was discharged on the second postoperative day.

The pathology report indicated a uterine leiomyoma. Microscopic examination of the right ovary revealed a fibromatous stroma composed of cells with spindle-shaped nuclei and spindle-shaped eosinophilic cytoplasm (**Figures 1, 2**), and randomly distributed cell clusters of epithelioid cells with oval-spindle-shaped nuclei (**Figure 3**), large clear cytoplasm, and a uniform appearance (**Figure 4**), with cystic changes in some cell clusters. Based on the available findings, it was interpreted as a Brenner tumor, but a re-examination in a tertiary pathology laboratory was recommended to confirm the diagnosis and differentiate between benign and malignant tumors. This examination at an external center confirmed that the mass in the right ovary was a benign Brenner tumor.

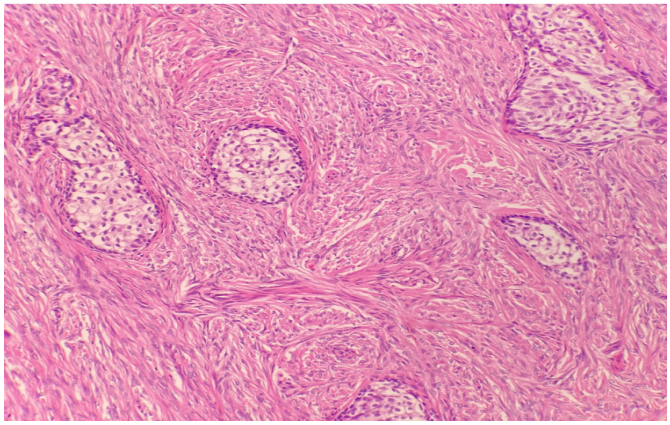

Figure 1. Well-defined, transitional epithelial nests in dense fibromatous stroma (H&E, x200)

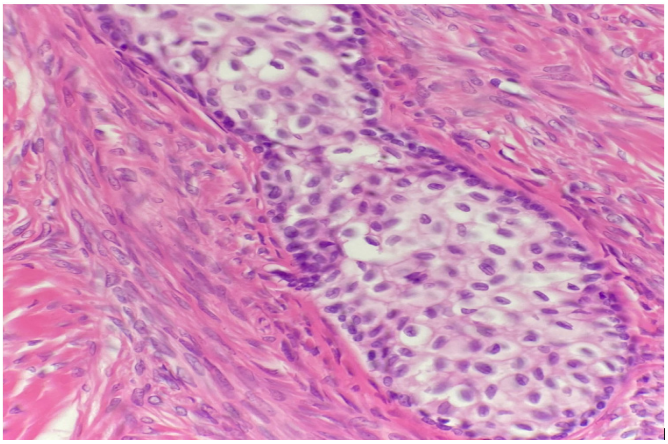

Figure 2. Oval, uniform cells with pale cytoplasm, some showing grooves (H&E, x400)

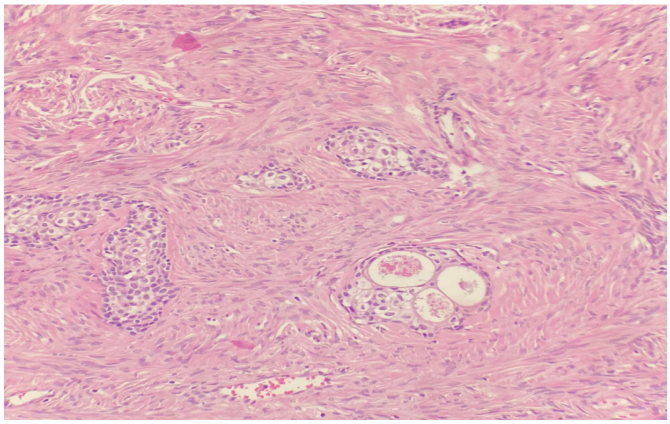

Figure 3. Microcystic changes containing eosinophilic material in some cell nests (H&E, x200)

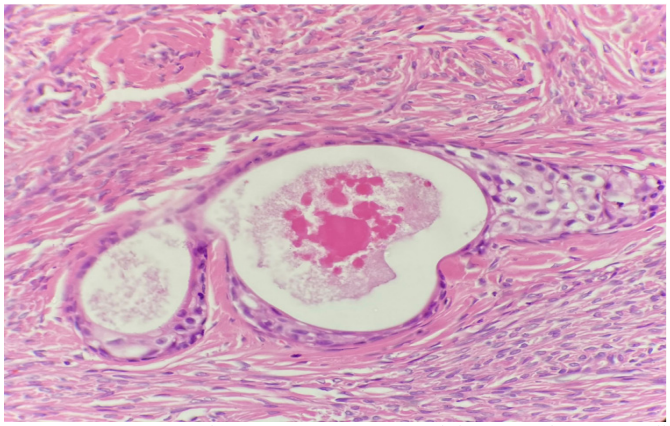

Figure 4. Microcystic changes containing eosinophilic material in some cell nests (H&E, x400)

The patient, who showed no further problems during post-operative outpatient follow-ups, was definitively diagnosed with uterine leiomyoma and benign Brenner ovarian tumor, and no further treatment was administered.

DISCUSSION

Brenner tumors originate from the epithelial/stromal region of the ovary and have a distinctive histopathological appearance. They are incidentally diagnosed and are a rare neoplasm. This presented case describes an asymptomatic benign Brenner tumor incidentally detected in a patient who underwent surgery for symptomatic uterine myoma and endometrial hyperplasia. This case, consistent with the literature, once again demonstrates that Brenner tumors are generally incidental tumors accompanying another pelvic pathology.[5,6]

This patient's age (47) is consistent with the typical diagnostic age reported in the literature (50-60), but also indicates that it can occur in the late reproductive age.[6] The tumor in this case was described on preoperative ultrasonography (USG) as a well-defined, 22 mm hypoechoic cystic lesion in the right ovary. This appearance points to a variant in which the cystic component is prominent, unlike the classic solid and hypoechoic USG pattern of benign Brenner tumors. Montoriol et al.,[7] while describing the computed tomography and magnetic resonance imaging findings of benign Brenner tumors, stated that a significant portion of these tumors may be complex (solid-cystic) in structure. The cystic lesion seen

in the present case is most likely due to cystic changes in the epithelial nests (Figures 3, 4) or to the frequently associated mucinous cystadenoma component. In addition, the absence of a significant increase in blood flow observed in the ovarian mass on Doppler examination can be interpreted as favoring a benign course.

One of the most striking features of Brenner tumors, as in our case, is their high rate of association with other ovarian or uterine pathologies. In a retrospective study covering 10 years by Alloush et al.,[4] another ovarian pathology, most frequently mucinous cystadenoma, was detected simultaneously in 54.5% of cases with Brenner tumors. This association was also emphasized in Wang's[8] classic and comprehensive study on these tumors. Similarly, in their study, Yüksel et al.[6] reported that most patients with Brenner tumors were operated on for a different gynecological indication and the tumor was identified incidentally during pathological examination. In the present case, the main accompanying pathology was symptomatic multiple uterine myomas and endometrial hyperplasia. This supports the idea that clinical complaints are usually caused by these other accompanying pathologies, due to the benign character and often asymptomatic course of Brenner tumors.

Histopathological diagnosis is the gold standard for Brenner tumor. Microscopic examination in this case revealed nests of epithelial cells with clear cytoplasm and nuclear groove embedded in fibromatous stroma (Figures 1, 2). These findings demonstrate the characteristic urothelial differentiation.[3] Confirmation of the diagnosis at a tertiary center is an important practice, especially for ruling out rare borderline or malignant forms. Malignant Brenner tumors can be confused with other malignant ovarian tumors (such as clear cell carcinoma).[3] Therefore, careful differential diagnosis is necessary. The differential diagnosis and histopathological criteria for malignant Brenner tumors have been described in detail by Koufopoulos.[9] Especially in the presence of atypical appearance or suspicious areas, confirmation of the diagnosis by an experienced pathologist and exclusion of malignancy are important for treatment planning. Our case underscores a critical practice in diagnosing rare ovarian tumors: the histopathological findings, especially in small or cystic-presenting lesions like ours, can be subtle. Therefore, expert pathological review at a specialized center is invaluable to confirm the diagnosis, exclude rare malignant or borderline variants, and guide appropriate patient management, eliminating the need for unnecessary further treatment.

CONCLUSION

As a result, benign Brenner tumor is a rare, well-prognosis neoplasm of the ovary. In clinical practice, it is often detected incidentally during surgical treatment of gynecological pathologies such as uterine fibroids. Imaging findings may vary, and the definitive diagnosis is made by histopathological examination. It has an excellent prognosis after surgical excision and does not require further treatment. This case report highlights the importance for clinicians and pathologists to keep this rare tumor in mind, especially in patients with multiple pelvic pathologies.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient included in this report. Signed consent forms are retained by the authors and are available upon request.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

This case report did not receive any financial support.

Author Contributions

Idea/Concept: EU, ZM; Design: EU, ZM; Data Collection/Processing: EU, ZM; Analysis/Interpretation: EU, ZM; Literature Review: EU; Drafting/Writing: EU; Critical Review: EU, ZM.

REFERENCES

1. Lou Z, Mei L, Wan Z, Zhang W, Gao J. A report of twenty cases of ovarian Brenner tumor and literature review: a case series study. *BMC Womens Health*. 2024;24(1):471. doi:10.1186/s12905-024-03316-4
2. Toshniwal SM, Inamdar SA, Agarwal HD, Sharma SR. Malignant Brenner tumor-a rare case of ovarian carcinoma. *Med Sci*. 2020;24:3550-3554.
3. Steinharter JA, Jansen C, Ghani H, et al. Malignant Brenner tumor with extensive clear cell features: a valuable diagnostic lesson learned from molecular tumor profiling and AI-based tumor differential tool. *Gynecol Oncol Rep*. 2025;61:101939. doi:10.1016/j.gore.2025.101939
4. Alloush F, Bahmad HF, Lutz B, et al. Brenner tumor of the ovary: a 10-year single institution experience and comprehensive review of the literature. *Med Sci (Basel)*. 2023;11(1):18. doi:10.3390/medsci11010018
5. Costeira FS, Félix A, Cunha TM. Brenner tumors. *Br J Radiol*. 2022;95(1130):20210687. doi:10.1259/bjr.20210687
6. Yüksel D, Kılıç C, Çakır C, et al. Brenner tumors of the ovary: clinical features and outcomes in a single-center cohort. *J Turk Ger Gynecol Assoc*. 2022;23(1):22-27. doi:10.4274/jtgga.galenos.2021.2021.0001
7. Montoriol PF, Hordonneau C, Boudinaud C, Molnar I, Abrial C, Kossai M. Benign Brenner tumour of the ovary: CT and MRI features. *Clin Radiol*. 2021;76(8):593-598. doi:10.1016/j.crad.2021.03.018
8. Wang S, Zhou X. Ultrasonographic and clinicopathologic features of benign Brenner tumors of the ovary. *Oncol Translational Med*. 2022;8(3):146-149.
9. Koufopoulos NI, Pouliakis A, Samaras MG, et al. Malignant Brenner tumor of the ovary: a systematic review of the literature. *Cancers (Basel)*. 2024;16(6):1106. doi:10.3390/cancers16061106

Ankyra Medical Journal

Erratum

DOI: 10.51271/ANKMJ-0074

Erratum to: "Frequency of night eating syndrome and its relationship with impulsivity in bariatric surgery candidates"

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In the original article entitled “Frequency of night eating syndrome and its relationship with impulsivity in bariatric surgery candidates”, published in Journal of Translational and Practical Medicine, 2023;2(2):64-68 with doi:10.51271/JTPM-0043, the ethics committee decision number was incorrectly reported by the authors as 2022/56. At the request of the authors, the ethics committee decision number has been corrected to 2022/55, reflecting the accurate ethics committee approval information dated 17.05.2022. This correction does not affect the study design, data, statistical analyses, results, content, or conclusions of the article. The authors apologize for this oversight.

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Ankyra Medical Journal

Erratum

DOI: 10.51271/ANKMJ-0075

Erratum to "Healthcare-associated infections: prospective rotational surveillance data of a training and research hospital"

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The authors have noticed an error in the "Author names" section of the article titled "Çekli Y, Çavuşlu Ş. Healthcare-Associated Infections; Prospective rotational surveillance data of a training and research hospital. Ankyra Medical Journal 2024; 3(1); 6-12" published in the first issue of the third volume of Ankyra Medical Journal (Date: 31.01.2024). At the request of the authors, the last name has been corrected to reflect the accurate information. This correction does not affect the content or conclusions of the article. The authors apologize for this oversight.

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