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A bibliometric analysis of 16,826 triple-negative breast cancer publications using multiple machine learning algorithms: Progress in the past 17 years

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Background: Triple-negative breast cancer (TNBC) is proposed at the beginning of this century, which is still the most challenging breast cancer subtype due to its aggressive behavior, including early relapse, metastatic spread, and poor survival. This study uses machine learning methods to explore the current research status and deficiencies from a macro perspective on TNBC publications.

Methods: PubMed publications under "triple-negative breast cancer" were searched and downloaded between January 2005 and 2022. R and Python extracted MeSH terms, geographic information, and other abstracts from metadata. The Latent Dirichlet Allocation (LDA) algorithm was applied to identify specific research topics. The Louvain algorithm established a topic network, identifying the topic's relationship.

Results: A total of 16,826 publications were identified, with an average annual growth rate of 74.7%. Ninety-eight countries and regions in the world participated in TNBC research. Molecular pathogenesis and medication are most studied in TNBC research. The publications mainly focused on three aspects: Therapeutic target research, Prognostic research, and Mechanism research. The algorithm and citation suggested that TNBC research is based on technology that advances TNBC subtyping, new drug development, and clinical trials.

Conclusion: This study quantitatively analyzes the current status of TNBC research from a macro perspective and will aid in redirecting basic and clinical research toward a better outcome for TNBC. Therapeutic target research and Nanoparticle research are the present research focus. There may be a lack of research on TNBC from a patient perspective, health economics, and end-of-life care perspectives. The research direction of TNBC may require the intervention of new technologies.

KEYWORDS

machine learning, bibliometric analysis, Latent Dirichlet Allocation, triple-negative breast cancer, Nanoparticle research

Highlights

- All Triple-negative breast cancer (TNBC) publications in the PubMed database from 2005 to 2021 were included in the analysis.
- Triple-negative breast cancer research mainly focused on three aspects: Therapeutic target research, Prognostic research, and Mechanism research.
- Therapeutic target research and Nanoparticle research are the present research focus.
- The Latent Dirichlet Allocation (LDA) algorithm we built is a convenient tool that can help researchers discover changes in research focus from medical text big data.

1. Background

Breast cancer currently accounts for 30% of newly diagnosed malignant tumors in women and causes 15% of women to die from cancer (1). For the first time, Perou described the intrinsic molecular subtypes of breast cancer and described Triple-negative breast cancer (TNBC) in 2000 using complementary DNA microarray technology (2). Furthermore, TNBC is the most aggressive subtype of breast cancer, accounting for about 10–20% of breast cancer cases (3, 4). TNBC is still unsatisfactory in diagnosis and treatment.

Bibliometrics is a quantitative analysis method of academic publications, which can discover the progress of discipline research from a macro perspective and provide support for future research directions (5). TNBC-related literature information analysis is scarce. Teles et al. (6) conducted a bibliometric study of 1,932 publications in 2018 to study nanomedicine research's global trend on TNBC. However, the inclusion criteria of this study are too broad, and the analysis methods are insufficient to analyze the *status quo* of the TNBC study. Unfortunately, bibliometric studies on TNBC remain insufficient due to the lack of practical language analysis tools to integrate metatext data.

Natural Language Processing (NLP) is a computing technology used to analyze human language, a part of machine learning (7). Various algorithms have been successfully applied to deal with medical information (8). Latent Dirichlet Allocation (LDA) is bibliometrics's most classical topic modeling method to present many unstructured texts and information (9, 10). LDA can perform topic analysis on texts (5). We recently constructed LDA and NLP methods to analyze more than 23,000 rectal cancer-related publications between 1994 and 2018. We have found the research deficiencies in the last 25 years and predicted the future research focus (11). Therefore, through the use of mature LDA methods and machine learning techniques to discover the current research from a macro perspective, at the same time discover the missing research topics in the past, and predict potential research breakthroughs in the future.

We analyzed all past TNBC publications indexed by PubMed under Triple-negative breast cancer in the present study. We improved our algorithm based on previous research and conducted a more detailed analysis of all TNBC publications with more visual expression to highlight current research focus in TNBC, research deficiencies, and specific areas with future opportunities.

2. Materials and methods

2.1. Research design

The study design was based on the basic rules of bibliometrics, as shown in **Figure 1** for a flowchart (12, 13). The study used a two-stage structured approach to bibliometric analysis and visual assessment of published scientific literature. Provide an understanding based on the data and the researcher's professional background. The PubMed database¹ is a biomedical specialty database that provides multiple search strategies and is a free, publicly available database. For this research, the PubMed database, which contains an application programming interface (API) that can export abstracts, was used, and publications containing abstracts were downloaded for analysis.

2.2. Inclusive and exclusive criteria

Table 1 shows the steps to obtain full TNBC-related publications in the PubMed database. All publications under Triple Negative Breast Cancer were downloaded between January 1, 2005, and January 1, 2022. There are 17,562 publications. Missing data, conference abstracts, conference proceedings, book reviews, and news items were excluded, and 17,338 publications were ultimately included in the bibliometric analysis (Figure 1A). Details of inclusion and exclusion are shown in Table 2. After excluding non-English publications and incomplete abstracts, the final 16,826 publications were analyzed by the LDA algorithm to obtain the focus changes and their relevance of research topics in publications in this field. The whole record of search results is downloaded in XML format *via* R's easyPubMed package. Data extracted from R² and Python³, including publication year, abstract, study types, geographic information, and Medical Subject Headings (MeSH) terms, were obtained.

2.3. LDA and algorithms and analytical methods

Latent Dirichlet Allocation was used to identify more specific research topics in each article. Python was used to model the topics by analyzing the abstracts of all indexed articles in the record. Topics were set at 50. The criteria for selecting the number of topics were perplexity, redundancy, and legibility. Based on the algorithmic calculation of topic probability, we finally determined the topic to which each article belongs. Next, we manually checked the names of each glossary based on the abstract. Finally, we used the Louvain algorithm and Gephi to perform cluster analysis to establish a topic network to determine the relationship between topics (14). We identified the two topics with the highest attribution probability in each publication, counted the number of simultaneous occurrences in each document, and established links between topics.

All the original data were uploaded and publicly available, including all retrieval methods, algorithm codes, and raw literature data in this article (Figure 1A). The literature search and download

2 https://www.r-project.org/, version:4.1.1

Abbreviations: TNBC, triple-negative breast cancer; NLP, natural language processing; LDA, Latent Dirichlet Allocation.

¹ https://pubmed.ncbi.nlm.nih.gov/

³ https://www.python.org/, version 3.7.1



The number of publications on triple-negative breast cancer (TNBC) has increased rapidly in recent 17 years. (A) Using the search terms "triple-negative breast cancer" in the PubMed database, download publications through the R pubquery package. Missing data or when the publication was a meeting abstract, proceedings paper, a correction, a book review, or a news item were manually excluded, and finally, 17,338 publications were included in the general analysis. Latent Dirichlet Allocation (LDA) analyzed 16,826 publications. (B) Publications analyzed by LDA, Python. Data were visualized using Excel. The number of publications is shown yearly, and $\gamma = 3.8931x^{2.3677}$ (R² = 0.9906) is the fitted function.

code can be obtained on R by easyPubMed package⁴. The R code is publicly available on GitHub⁵. We have uploaded relevant Python code on GitHub⁶, Zenodo⁷ and LDA code (Supplementary LDA coding-updated). The network visualization in this article is carried out using the software package Gephi⁸. This study used publicly published data and did not need approval by the relevant institutional review board or ethics committee. A stepby-step instruction is provided in the **Supplementary material** to facilitate the reader to understand further the research details (**Supplementary information 1**).

- 7 https://doi.org/10.5281/zenodo.7461925
- 8 https://gephi.org/, version 0.9.2

3. Results

3.1. The number of publications in TNBC research increases every year

We identified and analyzed 16,826 publications from January 2005 to 2022 (Figure 1B). The annual growth trend aligns with the fitting curve $y = 3.8931x^{2.3677}$ ($R^2 = 0.9906$). An average of 1,019 publications are published each year, with an average annual growth rate of 74.7%. It is expected that 3,650 publications will be published in 2022. Among all publications, 1,646 journals have publications on TNBC. We identified the ten most popular journals that published 3,118 publications, accounting for 18.0% of all publications (Supplementary Table 1). Therefore, emphasizing posts from these key journals helps us keep up with the latest trends. *Breast*

⁴ https://cran.r-project.org/web/packages/easyPubMed/index.html

⁵ https://github.com/christopherBelter/pubmedXML

⁶ https://github.com/mxdwangdali11/guid-to-Bibliometric-LDA-Analysis

Cancer Research and Treatment, PLoS One, and *Scientific Reports* are the top three journals with 690, 427, and 331 publications.

3.2. The proportion of clinical trials in TNBC publications has increased every year

To explore the research fields of TNBC, we first divided the publications into nine categories according to the fields provided by the database from 2010 in cancer research and set them as 100 per cent (Figure 2). We found that clinical trials and multicenter studies accounted for 25% of publications. The proportions of reviews and meta-analyses increased from 35% in 2011 to 50% in 2021.

Since high-quality meta-analysis is generally considered a clinically guiding study, it is reasonable to expect that the publication of TNBC meta-analysis will increase. Many clinical trials of TNBC have been improved and will continue to improve its clinical practice.

3.3. The United States and China have the highest number of publications in the field of TNBC

To further understand the global TNBC research situation, we analyzed the geographic information by research institutions. We found that 98 countries or regions worldwide have publications on TNBC (Figure 3A). The top 10 countries' publications accounted

TABLE 1 Triple-negative breast cancer (TNBC) publications assortment steps.

TABLE 2 Inclusive and exclusive criteria

Exploration steps	Query on PubMed	Description
1	Triple negative breast cancer	("triple negative breast neoplasms"[MeSH Terms] OR ("triple"[All Fields] AND "negative"[All Fields] AND "breast"[All Fields] AND "neoplasms"[All Fields]) OR "triple negative breast neoplasms"[All Fields])
2	Data duration	(2005:2021[pdat])

Parameter of selection of a publication	Inclusion criterion Exclusion criterion		Rationale for inclusion-exclusion		
Language	English	Other languages	The working language of the LDA algorithm is English. Other languages are not recognized		
Publication date	2005-2021	Publications before 2005 and after 2021	Not included in the 2022 publication as it has not been fully published		
Publication type	All	Missing data, meeting abstract, proceeding paper, book review, news item	As the LDA algorithm is unsupervised machine learning, the analysis must include abstract as the text editor. In addition to incomplete content, try to include research articles and reviews.		
Funding sponsor	All	No exclusion	This parameter does not affect the selection criterion		
Affiliation/organization	All	No exclusion	This parameter does not affect the selection criterion		
Funding	All	No exclusion	This parameter does not affect the selection criterion		
Country	All	No exclusion	Publication from each country has its significance		

100% 90% 80% Clinical Trials Proportion of Publications 70% Multicenter Study 60% Meta-Analysis Case Reports 50% Comment 40% Letter Systematic Review 30% Review 20% 10% 0% 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 Year

FIGURE 2

Clinical trials and multicenter studies have a large proportion of research. We divide publications into eight categories according to the types provided in the database. Data were shown by percentage.

for 78.2%, indicating a pronounced head effect. Moreover, more than half of the publications were derived from the United States, China, Korea, and Italy, accounting for 25.0%, 21.8%, 5.4%, and 4.9% of all publications, respectively (Figure 3B). This phenomenon reminds us that the vast majority of the global population has participated in TNBC research, especially in the northern hemisphere.

3.4. Molecular pathogenesis and medication are most studied in TNBC research

MeSH terms can represent the research content of the publications. A total of 6,288 MeSH terms appeared 248,250 times in all 16,826 publications, indicating that the studies covered multiple

aspects (Supplementary Table 2). The top 10 cited MeSH terms are listed in Figure 4. Both pathology and metabolism have appeared more than 7,000 times, suggesting that the research on TNBC focused on exploring its molecular pathogenesis. In addition, 5 of the top 10 cited MeSH terms are directly related to medication research. Therefore, we infer that pathogenic mechanism and medication research will continue to focus on TNBC research in the foreseeable future.

3.5. LDA results: TNBC research focus on therapeutic target research, prognostic research, and mechanism research

The topic network analyzed by LDA and Louvain algorithm highlights the areas where interrelated topic clusters appear



Global triple-negative breast cancer (TNBC) research differs significantly between regions. (A) The global distribution of TNBC publications in the recent 17 years is shown. We extracted the country information based on the first publication's affiliation. (B) Top 10 countries with the highest publication numbers in TNBC research.



simultaneously and provides remarkable insights into the relationships between the essential topics of interest. We divided publications into 50 topics. The results of the LDA analysis suggest that all TNBC-related studies are mainly focused on three clusters, i.e., Therapeutic target research, Prognostic research, and Mechanism research (Figure 5). However, few studies on hospice care, patient perspective, surgical treatment of metastasis, and economics are available.

The Therapeutic target research cluster contains 3,465 publications. The research focuses on Therapeutic target research, Protein expression, and Chemotherapy research. This cluster is particularly close to the other two clusters, indicating that the relationship between essential clinical integration and TNBC basic research is very close. We also found that clinical trials can quickly transform basic research into clinical practice to improve patient prognosis.

In the Prognostic research cluster, Survival related research and Demography research are the most studied topics. There are 1,275 publications on Prognostic research, which account for the most significant proportion and are closely related to the other two topics, indicating that prognostic research is the research focus. Interestingly, we found that Demography research and Methylation research are highly connected, weighing 359. We further analyzed and found that TNBC methylation differs significantly among races with different genetic backgrounds, and long-term survival studies are lacking.

In the Mechanism research cluster, we found that Apoptosis research, Growth factors study, and Nanoparticle research are the three most researched topics. In addition, The research cluster contains 21 topics, accounting for up to 42%, covering everything from basic medical research to clinical research.

3.6. LDA results: Therapeutic target research and Nanoparticle research are the research focus

To understand the changes in research focus, we visualized the LDA results and generated a heat map showing the changes in all 50 research topics of TNBC obtained by the LDA algorithm (Figure 6). The number of publications on therapeutic target research and nanoparticle research has increased dramatically, with 15.4% and 15.7%. These results indicate these two are research focus in the future.

3.7. LDA and citation analysis results: TNBC research is based on technology that advances TNBC subtyping, new drug development, and clinical trials

Highly cited publications often represent the emergence of outstanding contributions, leading knowledge, or examples in the field. Attention was paid to the citations of publications within the TNBC field. All publications with a total of 490,599 citations, among which the top ten publications with the highest internal citations are listed in Table 3, the publication with the highest internal citations, 1,293, and the total citations of these 10 publications are 21,550. These publications focus on three categories, clinical characteristics of extensive population studies (15–17), clinical trials of new medications (18–21), and subtyping studies of TNBC (22–24). They represent researchers focused on discovering new molecular targets and developing multiple therapies such as Atezolizumab and



Nab-Paclitaxel for treatment. Therefore, under the guidance of this research model, similar studies in the future can get more citations. On the other hand, combined with the steady increase of MeSH terms year by year, the lack of drastic changes suggests that TNBC research presents a stable and mature research model, that is, new drug development based on TNBC typing, target drug development, and clinical trials.

4. Discussion

We analyzed 16,826 publications in the field of TNBC from 2005 to 2022 using machine learning and NLP. Furthermore, we visualize and analyze the results from a macro perspective. Over the past 17 years, we found that TNBC-related publications have increased from none to 16,826 in 2021, with more extensive research content. TNBC research focuses on Therapeutic target research, Prognostic research, and Mechanism research. Research topics have changed over the years, and the current research focus is expected to be Therapeutic target research and Nanoparticle research, according to our LDA results.

Bibliometrics is a compelling analysis method to obtain information from massive texts quantitatively, and there are very few

bibliometrics analyses on TNBC such as VOSviewer, Bibliographic Items Co-occurrence Matrix Builder (BICOMB), and CiteSpace. However, with the development of the publishing industry, these tools have difficulty applying to massive publication analysis due to their architecture, insufficient computer memory, and sharing protocols. Therefore, our research uses the LDA algorithm based on Python, an unsupervised topic model. Furthermore, our topic model is based on the publication's abstract, not on the keywords. It is easy to use with negligible memory consumption and can analyze massive publications.

We found that Therapeutic target research has always been research-focused because TNBC lacks effective therapeutic targets and has high heterogeneity (24, 25). Our research found that this part contains a variety of attempts, DNA repair research, immune checkpoint research, and protein expression. We only found 137 publications related to immune checkpoint research, and immunotherapy research is not closely related to the prognosis and mechanism research of TNBC. Several clinical studies are being carried out, including IMpassion130, KEYNOTE-355, and Impassion 131 (26–28). Some positive results can reduce the risk of death by up to 35%. However, more important is the research on the underlying mechanism and the exploration of various influencing factors, especially



cancer (TNBC). Latent Dirichlet Allocation (LDA) generated all data. The topics marked in red are the research focus. The lighter the color in the figure, the more publications.

the extracellular matrix, hypoxia, and immune cell infiltration (29). In addition, immune checkpoint research has just started for five years, according to our results, and several medications have already been applied in the clinic. This research trend will continue, and immunotherapy will become a safe and effective treatment option.

The research scope of the TNBC mechanism is pervasive, covering the immune microenvironment and subtypes of TNBC. The successful subtyping provides a solid theoretical basis for the precision therapy of TNBC (30). Gene sequencing technology allows us to fully understand the mutation rate of TNBC, which is about 1.68 bp/Mb (31). Mutations occur in genes in multiple key signaling pathways such as PI3K/Akt/mTOR pathway, RAS/RAF/MEK pathway, JAK/STAT pathway, DNA repair pathway, and cell cycle checkpoint (32–34). Therefore, various treatments targeting the signal pathways are currently undergoing clinical trials. Some inhibitors have been used as potential medications for TNBC treatment, including PI3K, MEK, PARP, EGFR, VEGF, and AR inhibitors (32).

Triple-negative breast cancer subtyping has always been the focus of research. There is no unified standard based on the TNBC genome and cell heterogeneity. The first classification was based on Lehmann's gene expression analysis of breast cancer and constructed a "triple negative classification" and six subclassifications (24). In 2016, Lehmann's further research found that immunomodulatory (IM) patients are more likely to benefit from checkpoint inhibitor therapy (35). With the advancement of technology, such as the emergence of single-cell RNA sequencing, spatial transcriptomics, and radionics, and the further expansion of data volume, new technologies have provided new insights into the typing of TNBC and proposed guidance for treatment. Xie's research established a new prognostic model through the comprehensive analysis of multiple cell death patterns on more than 1,000 breast cancer patients, which can predict the clinical prognosis and drug sensitivity after TNBC surgery (36). In addition to technological progress, an in-depth understanding of the oncological course, mechanism of occurrence and development, and algorithm advances will provide a more detailed classification of TNBC.

Reference title DOI	References	Internal citation	Total citation	LDA results
J Clin Invest. 2011 Jul; 121 (7): 2750-67 https://doi.org/10.1172/jci45014	Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies (24)	1,293	3,205	Protein expression
Clin Cancer Res. 2007 Aug 1; 13 (15 Pt 1): 4429-34 https://doi.org/10.1158/1078-0432.ccr-06-3045	Triple-negative breast cancer: clinical features and patterns of recurrence (23)	1,220	3,025	Subtype research
N Engl J Med. 2010 Nov 11; 363 (20): 1938-48 https://doi.org/10.1056/nejmra1001389	Triple-negative breast cancer (21)	1,062	2,501	Therapeutic target research
J Clin Oncol. 2008 Mar 10; 26 (8): 1275-81 https://doi.org/10.1200/jco.2007.14.4147	Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer (20)	700 1,909 Prognostic research		Prognostic research
Cancer. 2007 May 1; 109 (9): 1721-8 https://doi.org/10.1002/cncr.22618	Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry (17)	550	1,483	Demography research
Clin Cancer Res. 2007 Apr 15; 13 (8): 2329-34 https://doi.org/10.1158/1078-0432.ccr-06-1109	The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes (16)	515	1,472	Subtype research
Nat Rev Clin Oncol. 2016 Nov; 13 (11): 674-690 https://doi.org/10.1038/nrclinonc.2016.66	Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease (15)	485	1,280	Therapeutic target research
N Engl J Med. 2018 Nov 29; 379 (22): 2108-2121 https://doi.org/10.1056/nejmoa1809615	Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer (19)	358	2,064	Immune checkpoint research
Lancet. 2014 Jul 12;384 (9938): 164-72 https://doi.org/10.1016/s0140-6736(13)62422-8	Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis (18)	335	2,113	Neoadjuvant chemotherapy
Ann Oncol. 2011 Aug; 22 (8): 1736-47 https://doi.org/10.1093/annonc/mdr304	Strategies for subtypes-dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011 (22)	311	2,498	Therapeutic target research

TABLE 3 Top 10 publications of triple-negative breast cancer (TNBC) based on internal citations and Latent Dirichlet Allocation (LDA) results.

On the other hand, studies on operations and radiotherapy were rarely reported, especially for re-operations related to localregional recurrence risk or distant metastasis. Many studies suggest that surgery is essential in treating distant metastases of cancers, such as colorectal cancer (37). In addition, many studies on other cancers, including pancreatic and colorectal cancer, demonstrated that the tumor microenvironment, especially the extracellular matrix, has been found to play an essential role in cancer metastasis, local recurrence, and chemotherapeutic drug resistance (38, 39). Many potential drugs are used due to their ability to target the extracellular matrix, such as PEGPH20 (an enzyme that targets matrix hyaluronic acid), pegilodecakin (a PEGylated IL-10) (40, 41). However, the study on extracellular matrix in TNBC is insufficient so far.

Although the research on TNBC has made significant progress in many aspects, the present research also found some research deficiencies on TNBC. There is a lack of research on TNBC from patients' perspectives, health economics, and hospice care. Although, at present, the 5 years overall survival rate of most tumors has been dramatically improved, helping tumor patients with psychological issues re-enter society will become a new important research topic (42). TNBC patients are more likely to relapse and metastasize than other breast cancer subtypes, resulting in more significant mental and economic pressure on patients and their families. Studies on patients with more prolonged survival can better understand TNBC and even other long-term survival tumors (43). In the future, we will face more challenges for patients with a long survival period of 5–10 years (44). There are some limitations in the present study. Besides PubMed, several other databases, including Scopus, Web of Science, and Embase, could be used for bibliometric research. Although PubMed contains the highest quality peer-reviewed research and excludes irrelevant, non-peer-reviewed publications, the literature will provide detailed and comprehensive knowledge if other databases are explored simultaneously. Secondly, we considered that all publications publish more positive research results. Negative results and clinical participants' perspectives are naturally more difficult to be published. With the development of complete medical record texts, publication databases, and improved algorithms, it is reasonable for machine learning to play a more active auxiliary role in future clinical practice. The data presented in this study will hopefully help scientists understand the current status of TNBC research and design more relevant basic and clinical research projects.

5. Conclusion

We analyzed 16,826 TNBC publications through the NLP Method. TNBC research shows insufficiencies, especially in longterm survival-related research, and a lack of research from patients' perspectives. The publications mainly focused on three aspects: Therapeutic target research, Prognostic research, and Mechanism research. The research direction of TNBC may require the intervention of new technologies.

Data availability statement

The original contributions presented in this study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

KW initiated the project, analyzed the data, constructed analytical methods, and wrote the primary manuscript draft. XD initiated and supervised all aspects of the project and wrote the primary manuscript draft. CZ performed statistical analyses and contributed to the manuscript writing. DD helped interpret results and contributed to the statistical analyses. LZ contributed to the manuscript's revision in terms of writing and interpretation. ML contributed to the interpreting results and supervising statistical analyses. All authors contributed to the manuscript writing and read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023. 999312/full#supplementary-material

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