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REVIEW ARTICLE

Trends of early-onset colorectal cancer biomarkers from 1985 to 2024 : a bibliometric analysis

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ABSTRACT

Early-onset colorectal cancer (EOCRC) is increasingly recognized as a global public health concern. Biomarker research in EOCRC has expanded across hereditary, molecular, epigenetic, liquid biopsy, microbiome, and multi-omics domains, but the overall research landscape remains fragmented. This study aimed to map global research trends and identify prominent and underdeveloped topics in EOCRC biomarker research. A bibliometric analysis was conducted using publications on EOCRC biomarkers retrieved on October 27, 2024. Eligible documents were limited to English-language articles, reviews, and conference proceedings, with a final publication stage and no restriction on publication year. After screening, 134 relevant documents published between 1985 and 2024 were included. Bibliometric indicators, including publication trends, leading contributors, influential publications, topic evolution, and keyword co-occurrence patterns, were analyzed using Biblioshiny (Bibliometrix R package v4.1.3) and VOS viewer (v1.6.18). Early-onset colorectal cancer biomarker research showed steady growth, with an annual growth rate of 7.54% and a publication peak in 2023. The dataset included 134 documents from 92 sources and involved 1,121 authors, with international collaboration observed in 20.9% of publications. Earlier studies focused mainly on hereditary predisposition, Lynch syndrome, mismatch repair genes, and microsatellite instability. More recent research shifted toward molecular profiling, epigenetic alterations, liquid biopsy, gut microbiota, tumor microenvironment, and multi-omics approaches. Underdeveloped areas included diagnostic biomarker validation, screening implementation, gut microbiota, risk factors, and machine learning-based biomarker discovery. Overall, EOCRC biomarker research has evolved from a hereditary-centered focus toward a broader precision oncology framework, but further work is needed to strengthen validation, translational relevance, and clinical applicability across diverse populations.

Keywords: Early-onset colorectal cancer, biomarkers, bibliometric analysis, digestive surgery

INTRODUCTION

Due to its rising incidence worldwide, particularly in developed countries, early-onset colorectal cancer (EOCRC), diagnosed in individuals under 50, has become a critical public health issue.[1] In the United States, EOCRC is one of the leading causes of cancer-related deaths among young adults, ranking as the first and second leading causes, respectively, for men and women.[2] Unlike late-onset colorectal cancer (LOCRC), EOCRC often presents at more advanced stages, with distinct molecular characteristics and poor prognostic factors, which may contribute to its more aggressive clinical course.[3,4] Environmental, genetic, and biological factors involving a complex regulatory mechanism of a living organism play a role in the progression of EOCRC.[5] There are genetic predispositions to some diseases, such as Lynch syndrome [6] and familial adenomatous polyposis,[7,8] but the majority of cancers are sporadic and unexplained by known hereditary causes.[9] This implies the possibility of non-traditional risk factors involvement—including diet, sedentary behavior, obesity, and gut microbiome alterations, which require further study.[10,11]

Biomarkers are essential for improving the early detection, prognosis, and personalized treatment of EOCRC.[12] Globally, the incidence of EOCRC is on the rise, underlining the importance of effective biomarkers that can support prompt diagnosis and guide personalized treatment.[13] Biomarkers, whether histological, molecular, or circulating, help understand the biology of EOCRC, distinguishing it from LOCRC, and highlighting the need for personalized treatment approaches.[14] The translation of biomarker findings into clinical practice faces challenges due to variability in biomarker expression and the need for large-scale validation. Further research efforts are focused on improving these biomarkers and overcoming these obstacles, with the ultimate goal of integrating them into routine clinical procedures.[15,16]

Bibliometrics is an interdisciplinary science that analyzes documents statistically in a particular research domain, using mathematical and statistical methodologies to reveal cutting-edge knowledge development and research trends.[17] A bibliometric analysis is crucial for understanding the main trends, influential topics, and leading contributors within a research area.[18] Previous bibliometric work has described the broader landscape of EOCRC research, but the specific development of biomarker-focused research has not been clearly characterized.[19] Therefore, this study aimed to offer a detailed overview of EOCRC biomarker research by identifying widely referenced biomarkers, evaluating their significance, and highlighting the contributions of leading authors, journals, and countries. This study not only adds to the existing knowledge on EOCRC biomarkers but also provides valuable insights to guide future research and clinical practices. By mapping research trends, this study is expected to support the advancement of less-invasive diagnostic tools and improve risk assessment and monitoring methods, ultimately leading to more precise and personalized treatment for EOCRC patients.

METHODS

The data in this bibliometric study were acquired from the Scopus database due to its comprehensive coverage of scientific literature. Using a combination of Boolean logic and MeSH terms, a keyword-based search was conducted on October 27, 2024, to capture relevant publications on EOCRC biomarkers. The eligibility criteria limited the language to English and the document types to articles, reviews, and conference proceedings with a final publication stage. There was no publication time limit. Studies that did not specifically mention biomarkers related to early-onset colorectal cancer were excluded. The initial search retrieved 173 articles, which were further refined to 134 based on the relevance of titles and abstracts. We collected information about the articles' author, journal, institution, country, and keywords. The detailed search strategy is depicted in Figure 1.

Data analysis

The extracted data from Scopus were downloaded in CSV format for detailed analysis. Two primary software tools were used: VOSviewer (version 1.6.18) for network visualization and clustering,[20] and the R package Bibliometrix (using the Biblioshiny interface) for quantitative scientometric and informetric analysis.[21] This analysis examined various indicators, such as publication trends, top journals, top authors, top countries, top articles, trend topics, as well as prominent/key and underdeveloped topics. Using Biblioshiny, quantitative analyses were performed to examine publication patterns and outputs of all indicators, while VOS viewer was used to construct a visual bibliometric network that highlighted connections between authors and topic indicators. In this study, VOS viewer was employed to analyze by country/institution/journal/author/keyword. The resulting visualizations showcase nodes representing a variety of items, including countries, institutions, journals, and others. The size of the nodes reflects the frequency of occurrence, while node color indicates different clusters or years. Lines between nodes symbolize cooperation or co-citation relationships among these items. Additionally, a keyword co-occurrence network analysis was carried out to identify major research themes. The visualization settings were configured with a minimum total link strength of one and a minimum occurrence threshold of two to emphasize the most significant research clusters. The bibliometric analysis followed a structured approach based on the method used by Ilyas.[22]

RESULTS

Main information

This bibliometric study analyzes research output from 1985 to 2024, focusing on 134 documents across 92 sources. The annual growth rate of publications was 7.54%, reflecting steady expansion in this field. The study involved 1,121 authors, with only three single-author publications, reflecting a predominantly collaborative environment with an average of 9.32 co-authors per document. Notably, international collaboration was prominent, as 20.9% of the publications included authors from multiple countries. The average document age was 6.83 years, indicating a balance between foundational and recent research in the dataset. Collectively, authors contributed 328 unique keywords, and the total number of references cited across the studies reached 6,343, resulting in an average citation count of 40.1 per document.

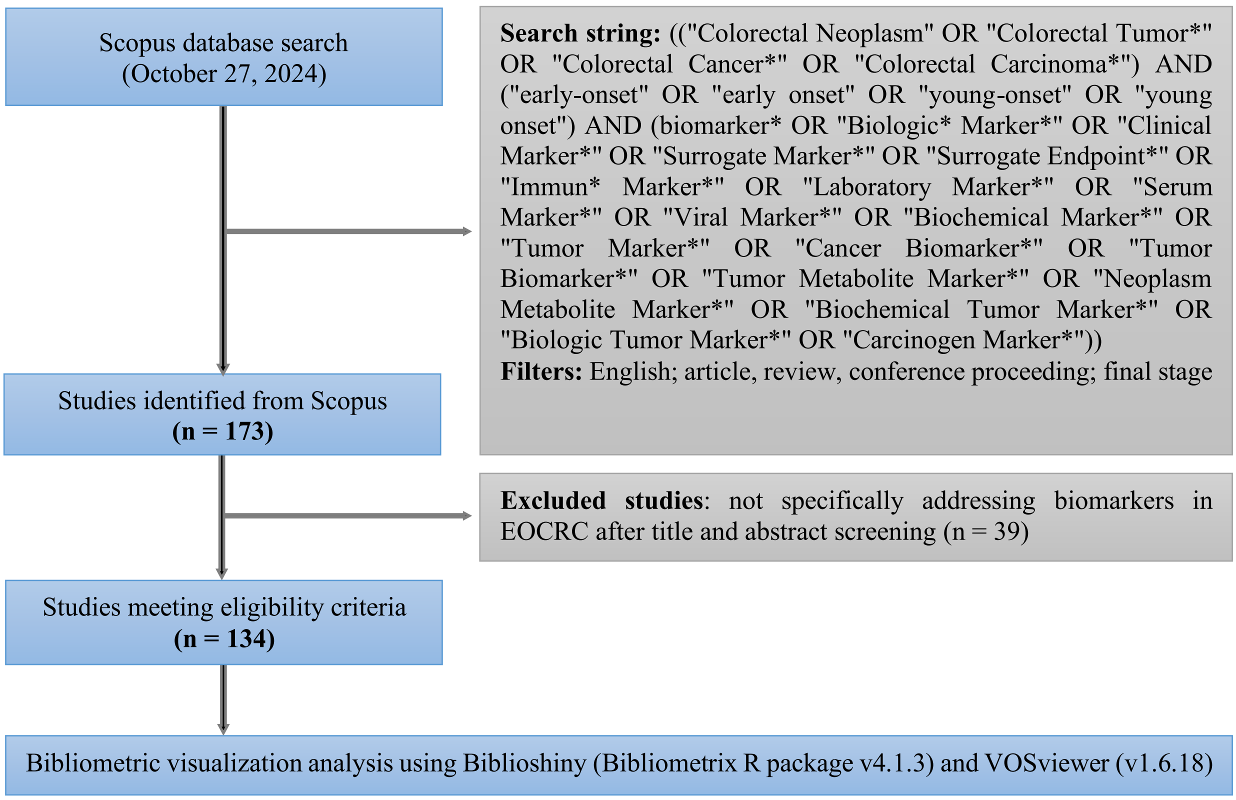

Figure 1. Flow diagram of data retrieval, screening, and study inclusion for the bibliometric analysis

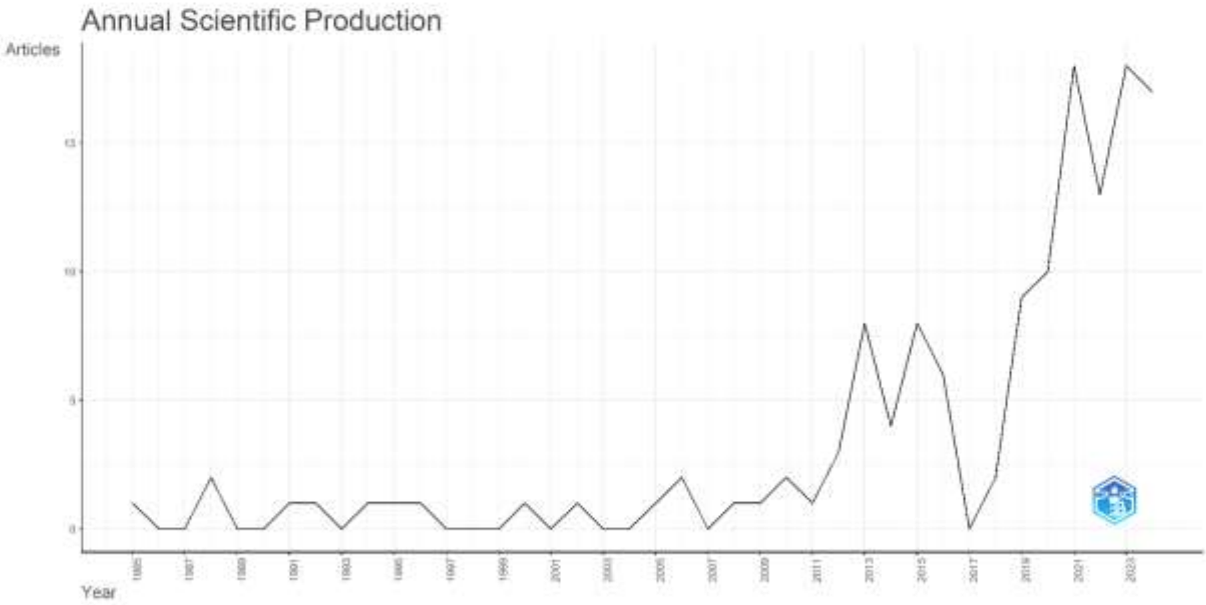

Figure 2. Annual publication trend in EOCRC biomarker research. Annual number of publications on EOCRC biomarkers from 1985 to 2024

The annual growth trend of publications

The temporal distribution of publications from 1985 to 2024 in Figure 2 demonstrates a progressive rise in research output, particularly following the year 2011. Before this period, the annual number of publications remained relatively low with limited variability. A significant increase in research activity was observed in 2013 and 2015, producing 8 publications each year, indicating an initial phase of increased interest in the research. The publication rate reached its peak in 2023, with a total of 18 articles, making it the most productive year within the examined period. As of October 2024, the publication count remained steady, with the potential for additional contributions before the end of the year. This trend corresponded with the annual growth rate of 7.54%, as derived from our bibliometric analysis, and suggested an escalating scholarly interest in the field. The prominent surge of publications after 2015 indicated an increased recognition, emphasizing its expanding significance within the scientific community.

Most relevant authors, affiliations, and countries

This bibliometric analysis assessed main contributors in the study of EOCRC biomarkers at the author, institutional, and country levels. At the author level, Lynch HT and Perea J stood out as leading scholars, each contributing six publications to the field. They were closely followed by Hopper JL, Jenkins MA, Lynch JF, and Young JP, who published five articles each. This pattern highlights the importance of well-established collaborative networks for the advancement of EOCRC biomarkers research. Institutional contributions showed rising activity, displaying their pivotal roles in the field. Uludağ University led with 27 publications, followed by The University of Texas MD Anderson Cancer Center with 23 publications and the University of Ulsan College of Medicine with 20 publications. Furthermore, the Memorial Sloan Kettering Cancer Center and the University of Melbourne made equally notable contributions, with 18 publications each, further highlighting the expansion of international engagement. In terms of geographical distribution, the United States dominated the field with 39 publications, followed by China (23), Australia (9), and Korea (7), demonstrating a significant research output in North America and East Asia. These findings highlight the global and multidisciplinary approach of EOCRC biomarker research, highlighting the vital contributions from leading academic institutions and the importance of international collaboration. Figure 3 shows the most relevant authors, affiliations, and countries.

Journal and co-cited journal

Cancer Epidemiology Biomarkers and Prevention and World Journal of Gastroenterology were the most productive sources in EOCRC biomarker research, each publishing 6 articles. They were followed by

Cancer, Frontiers in Oncology, and Gastroenterology, with 4 articles each. Several other journals, including Annals of Surgical Oncology, Cancer Medicine, Cancers, Clinical Epigenetics, and Human Pathology, each contributed 3 articles. As shown in Table 1, this distribution indicates that EOCRC biomarker research is mainly disseminated through journals in oncology, gastroenterology, pathology, and translational cancer research.

In terms of source impact, Table 1 shows that cancer had the highest total citation count among the top 10 most relevant sources, with 605 citations from 4 publications, followed by World Journal of Gastroenterology with 327 citations and Gastroenterology with 306 citations. World Journal of Gastroenterology showed the highest h-index (Hirsch index) at 6, whereas Cancer Epidemiology Biomarkers and Prevention combined high productivity with a g-index (Egghe index) of 6. Frontiers in Oncology was among the most productive sources by publication count, although its citation impact remained relatively low in this dataset.

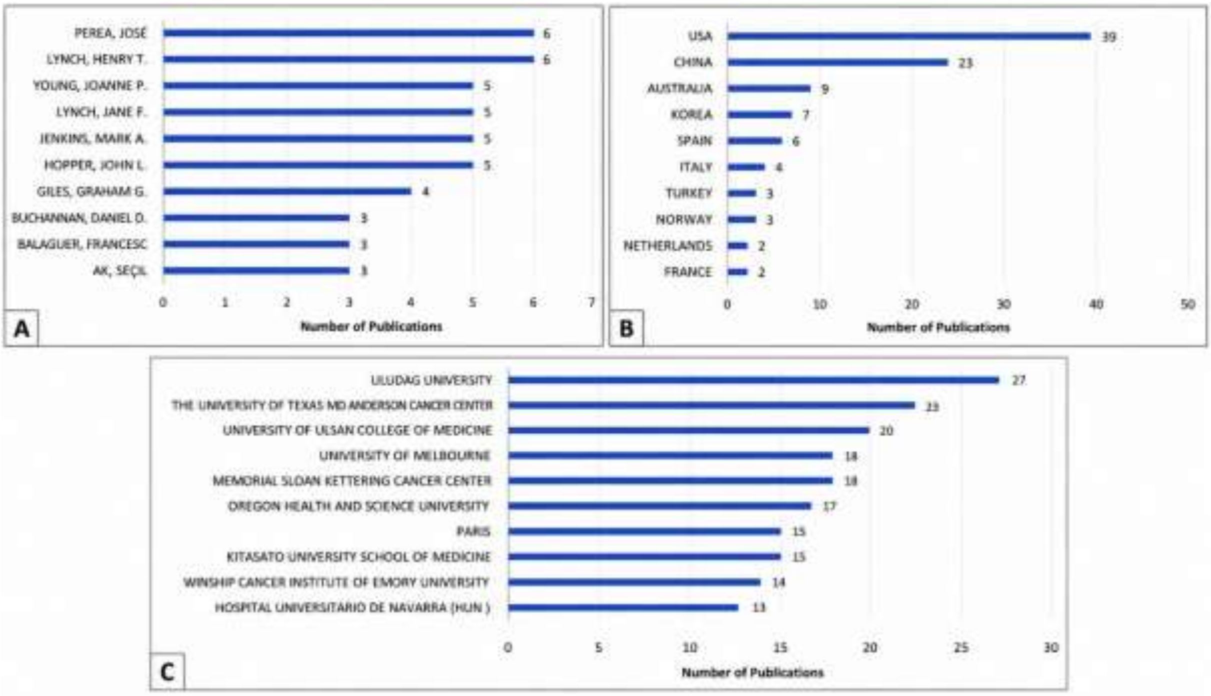

Figure 3. Most relevant authors, affiliations, and countries in EOCRC biomarker research. (A) Top ten authors with most publications; (B) Top ten countries with most publications; (C) Top ten affiliations with most publications

Table 1. Top 10 most relevant sources and source impact in EOCRC biomarker research

Source	Articles	h-index	g-index	m-index	TC	NP
Cancer Epidemiology Biomarkers and Prevention	6	4	6	0.286	167	6
World Journal of Gastroenterology	6	6	6	0.353	327	6
Cancer	4	4	4	0.095	605	4
Frontiers in Oncology	4	1	1	0.167	4	4
Gastroenterology	4	4	4	0.333	306	4
Annals of Surgical Oncology	3	3	3	0.120	33	3
Cancer Medicine	3	3	3	0.333	48	3
Cancers	3	3	3	0.600	9	3
Clinical Epigenetics	3	3	3	0.250	108	3
Human Pathology	3	3	3	0.214	43	3

Note : h-index : Hirsch index; g-index : Egghe index; m-index, m quotient; TC, total citations; NP, number of publications; PY_start, publication year start

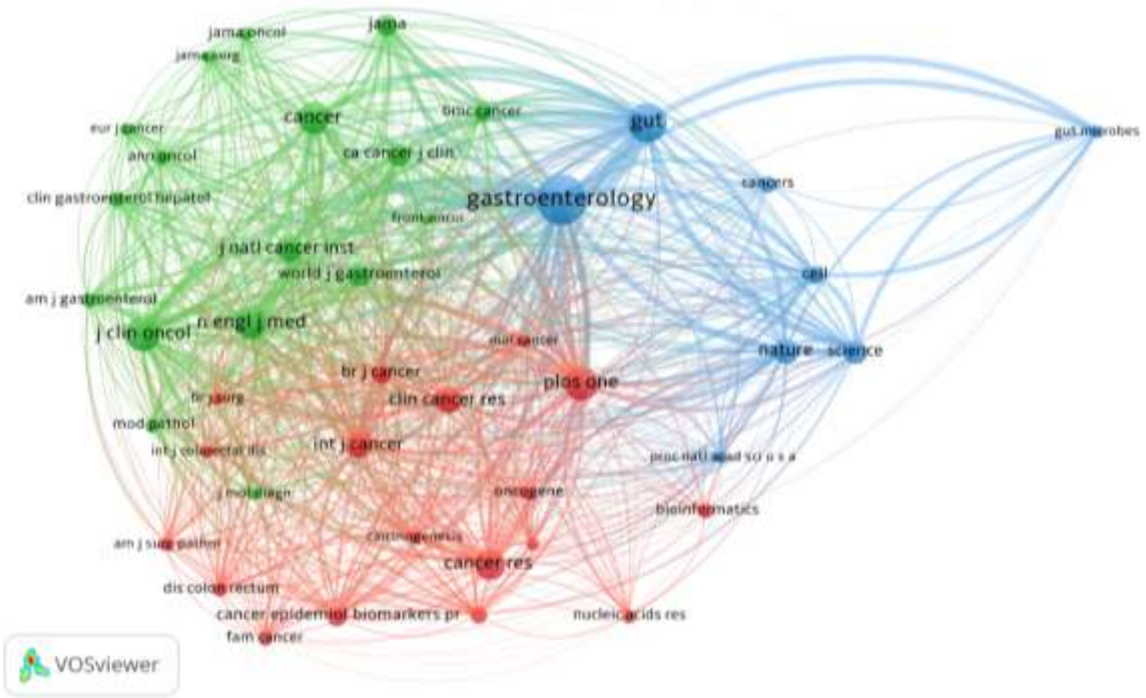

Figure 4. Source co-citation network of journals in EOCRC biomarker research. Source co-citation network generated using VOSviewer with a minimum citation threshold of 25. Node size represents co-citation frequency, line thickness represents link strength, and colors indicate clusters

Source co-citation analysis further highlighted the intellectual structure of the field. As shown in Figure 4, the co-citation network generated using a minimum citation threshold of 25 identified Gastroenterology, Gut, Cancer, Journal of Clinical Oncology, World Journal of Gastroenterology, Nature, Science, and PLoS ONE as the most prominent co-cited journals. The network formed 3 major clusters, reflecting the close relationship between gastroenterology, oncology, and molecular or translational bioscience. In particular, Gastroenterology and Gut occupied central positions in the network, suggesting that they serve as major intellectual anchors linking clinical gastrointestinal research with broader biomarker and cancer research.

Most influential publications

Table 2 shows the most Influential publications in early-onset colorectal cancer and biomarker study. Citation per year represents the average frequency at which a publication is cited each year since its publication. In contrast, normalized citations adjust this figure by comparing it to the average citation rates within the same subject area and publication year, providing a more context-sensitive measure of the article's impact. Early studies, such as Liu B, 1996 and Lynch HT, 1985, were pivotal in uncovering the genetic predispositions of colorectal cancer, particularly Lynch syndrome. These studies helped establish a basis for understanding genetic risk and hereditary patterns in colorectal cancer, which later informed diagnostic and screening strategies targeting high-risk individuals. Recent studies reflect an increasing urgency in EOCRC research, particularly as the incidence of colorectal cancer rises in younger populations. Mauri G, 2019 and Akimoto N, 2021 emphasized EOCRC as a distinct pathogen with unique clinical features and called for changes in screening protocols and public health policies to address this growing concern. These studies, with high citation rates, highlight the importance of recognizing EOCRC's specific needs compared to traditional colorectal cancer in older adults. In addition to genetic factors, molecular and epigenetic characteristics of EOCRC are becoming significant research areas. Antelo M, 2012 identified LINE-1 hypomethylation as a unique epigenetic feature in EOCRC, while Willauer AN, 2019 focused on molecular profiling to better characterize EOCRC's distinct biological markers.

Table 2. Most influential publications in early-onset colorectal cancer and biomarkers study

Authors	Title	Citations	Citations per year	Normalized citations
Liu et al. [53]	Analysis of mismatch repair genes in hereditary non-polyposis colorectal cancer patients	867	29.90	1.00
Mauri et al. [54]	Early-onset colorectal cancer in young individuals	389	64.83	4.00
Akimoto et al., [55]	Rising incidence of early-onset colorectal cancer - a call to action	330	82.50	8.10
Lynch et al. [56]	Hereditary nonpolyposis colorectal cancer (lynch syndromes I and II). I. Clinical description of resource	221	5.53	1.00
Willauer et al. [38]	Clinical and molecular characterization of early-onset colorectal cancer	215	35.83	2.21
Southey, et al. [58]	Use of molecular tumor characteristics to prioritize mismatch repair gene testing in early-onset colorectal cancer	189	9.45	1.00
Abdel-Rahman et al. [59]	Inheritance of the 194Trp and the 399Gln variant alleles of the DNA repair gene XRCC1 are associated with increased risk of early-onset colorectal carcinoma in Egypt	183	7.32	1.00
Antelo et al. [60]	A high degree of LINE-1 hypomethylation is a unique feature of early-onset colorectal cancer	166	12.77	2.31
Burnett-Hartman et al. [61]	An update on epidemiology, molecular characterization, diagnosis, and Screening Strategies for Early-Onset Colorectal Cancer	152	38.00	3.73
Yantiss et al. [62]	Clinical, pathological, and molecular features of Early-Onset Colorectal Carcinoma	147	9.19	1.00

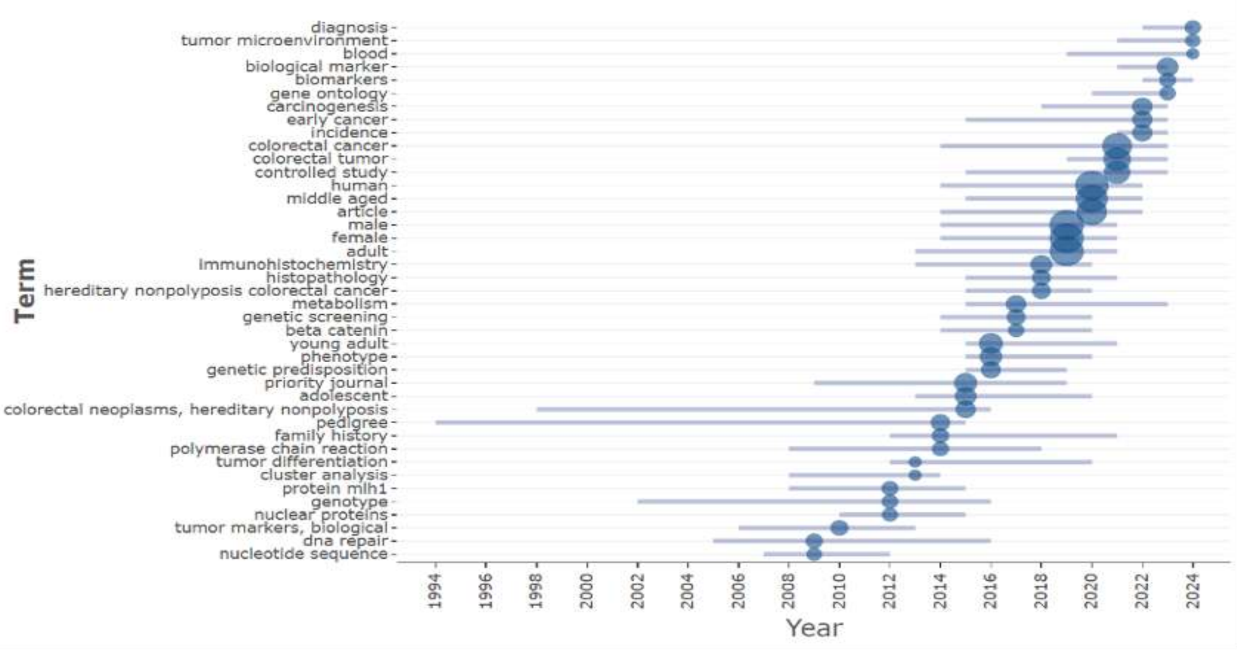

Figure 5. Trend topics in EOCRC biomarker research. Temporal distribution of frequently occurring terms in EOCRC biomarker research from 1994 to 2024. Bubble size represents term frequency

Trend topics

Figure 5 illustrates the shifting landscape of research topics related to colorectal cancer biomarkers from 1994 to 2024 (Figure 5). The temporal evolution of EOCRC biomarker research reveals distinct thematic shifts across decades. In the earliest period (1994 to mid-2000s), studies largely focused on genetic and hereditary factors, with keywords such as “hereditary nonpolyposis colorectal cancer” and “pedigree” appearing sporadically. This suggests an emerging but still limited focus on familial risk. The introduction of molecular tools such as “polymerase chain reaction” and “genotype” marked the early exploration of genetic screening techniques to identify high-risk individuals. However, the small size and low frequency of bubbles during this era reflect a relatively low volume of research activity, suggesting that the field was still in its early stages of development.

From the mid-2000s through 2015, the scope of research expanded considerably, with new keywords such as "immunohistochemistry," "histopathology," and "beta-catenin" starting to emerge. During this time, the trends shifted to identifying diagnostic biomarkers, and the term “biological markers” became more common. Additionally, demographic terms such as "middle-aged," "male," and "female" became more noticeable, suggesting that the studies began to include more diverse populations. More recently, from 2016 to 2024, research prioritized early detection and personalized medicine, proven by the terms such as “early cancer,” “tumor microenvironment,” and “gene ontology”. In the current period, keywords such as "young adult," "adolescent," "biomarkers," and "diagnosis" have become much more common, reflecting a deeper understanding of the unique aspects of early onset colorectal cancer (EOCRC). This shift indicates a pressing need for improved precision diagnostics and customized treatment options. The growing importance of this area is also evident in the larger and more frequent clusters of related research topics, highlighting a significant increase in scientific interest and activity.

Prominent/key and underdeveloped topics

Figure 6 shows a keyword co-occurrence network that illustrates the evolution of colorectal cancer research in recent years. The size of the nodes in the network represents their prominence in the literature, indicating “colorectal cancer,” “early-onset colorectal cancer,” and “biomarkers” as the focus of EOCRC biomarker research. The color gradient from purple to yellow illustrates the chronological development of research trends. There was a heavy focus on genetic and hereditary predispositions in early studies (2014–2017), with keywords such as “prevention,” “age of onset,” “PCR,” “microsatellite status,” “EGFR,” “CK20,” “BRAF,” “MAP3K8,” “PIK3CA,” and “Lynch syndrome.” This period was particularly important in understanding Lynch syndrome, a genetic condition that significantly increases the risk of colorectal cancer.

In the 2018–2019 period, the research focus shifted towards molecular diagnostics and the principles of personalized medicine, marked with emerging keywords such as “ctDNA,” “DNA methylation,” “CpG island methylator phenotype,” “single nucleotide polymorphism,” and “sporadic”. These advancements reflected a growing interest in non-hereditary colorectal cancer and the development of less invasive diagnostic tools, aiming for more personalized risk assessment and treatment planning.

From 2020 to 2022, a more integrative and systems-level approach in EOCRC biomarker research is portrayed in yellow-colored nodes. The terms “diagnostic biomarker,” “prognostic biomarker,” “screening,” “gut microbiota,” “microbial dysbiosis,” “miRNA panel,” “NGS,” “IHC,” “PI3K/AKT signaling,” and “multi-omics” imply an increasing focus on combining genomic, transcriptomic, proteomic, and microbiome data to gain a better understanding in EOCRC biology. This phase signals a mature, holistic research direction that embraces complexity and promotes personalized screening and treatment approaches for younger patients.

Figure 6 presents a density visualization that maps the current research of EOCRC biomarkers. Areas of high intensity indicate well-explored topics, revolving around colorectal cancer (n=49), early-onset colorectal cancer (n=49), biomarkers (n=14), and microsatellite status (n=12), suggesting interest in genetic and molecular mechanisms. Frequently occurring terms such as DNA methylation, prognostic biomarkers, and mismatch repair further highlight the focus on epigenetic modifications and genetic instability in EOCRC. Additionally, emerging terms such as liquid biopsy and multi-omics approaches suggest ongoing efforts to better understand non-invasive diagnostic methods. However, additional keywords such as gut microbiota, sporadic cases, and screening strategies show relatively lower density, indicating that while these topics are emerging, they remain underdeveloped in the context of EOCRC biomarker research.

The visualization also shows several underexplored areas yet potentially impactful in EOCRC pathogenesis and early detection, including gut microbiota (n=2), diagnostic biomarkers (n=2), and risk factors (n=2). The limited discussion of socioeconomic and environmental risk factors suggests a lack of understanding in the non-genetic contributors to EOCRC. Additionally, the integration of machine learning for biomarker discovery and predictive modeling remains overlooked, despite its potential to enhance personalized medicine approaches. A comprehensive systematic review covering genetics, epigenetics, and microbiome research is also required considering the absence of thorough meta-analyses. Future studies should focus on these unexplored areas, particularly in gut microbiota interactions, advanced imaging techniques for biomarker validation, and personalized diagnostic strategies to improve early detection and treatment of EOCRC in younger populations.

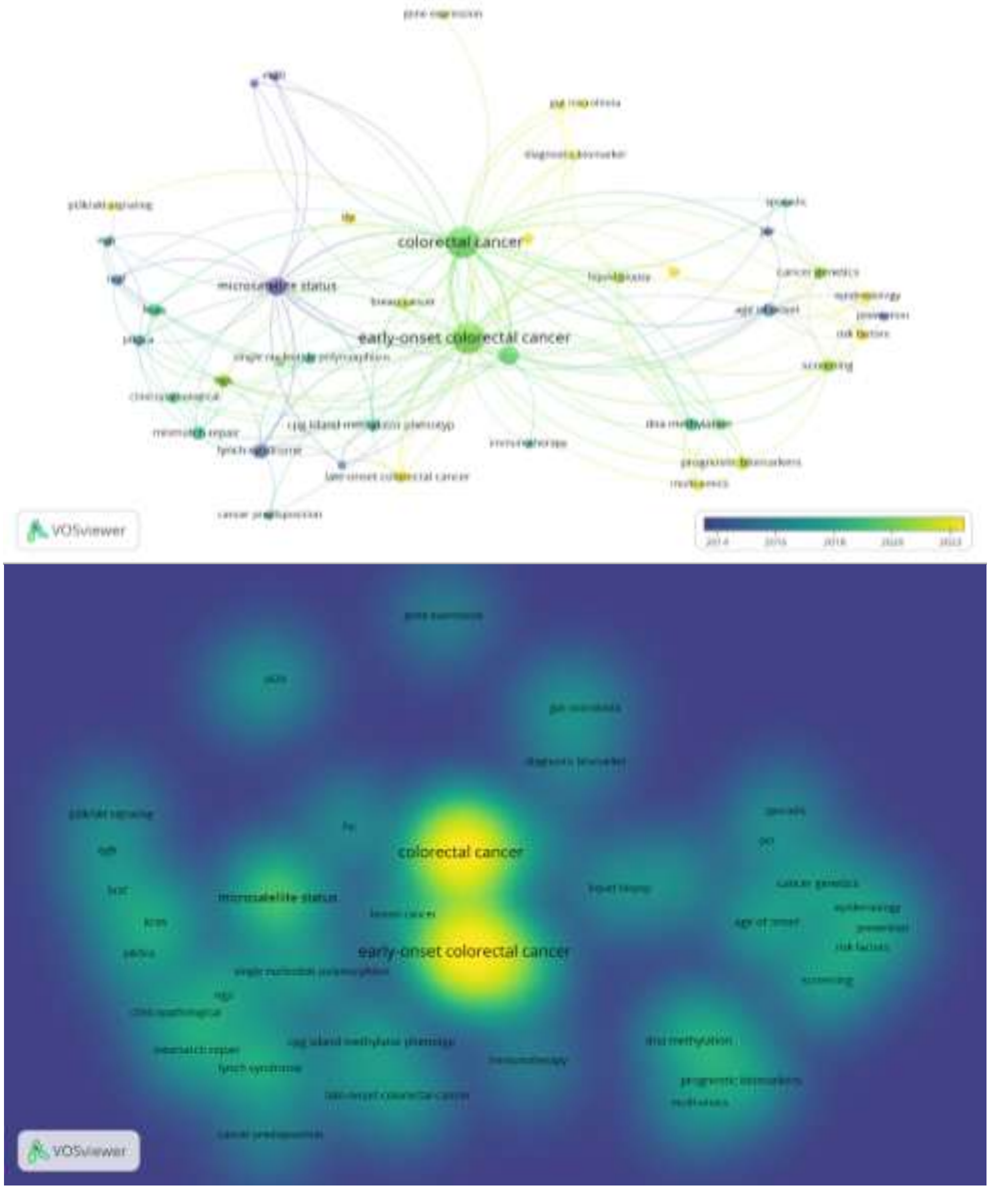

Figure 6. Co-occurrence analysis of keywords in EOCRC biomarker research. (A) Network visualization of keyword co-occurrence. Node size represents the frequency of keyword occurrence, line thickness indicates the strength of co-occurrence links, and colors represent thematic clusters. (B) Density visualization of keyword co-occurrence. Areas with warmer colors indicate higher keyword density and stronger concentration of research activity, whereas cooler colors indicate lower density

DISCUSSION

General information

The rising focus on EOCRC reflects its growing clinical importance, particularly in light of its increasing incidence and distinct molecular features compared to LOCRC. Nevertheless, the literature on EOCRC remains limited, with only 134 publications identified from 1985 to 2024. However, the publication trend has shown steady growth, particularly since 2011, with an annual growth rate of 7.54%, indicating a progressive interest in the scholarly area. Despite this, substantial gaps remain in understanding its etiology, improving early detection methods, and planning personalized treatments. To address these gaps, interdisciplinary collaboration and large-scale studies are necessary to ensure early diagnosis and prompt treatment of younger populations at risk.

The etiology of EOCRC remains unclear. Although hereditary factors, such as Lynch syndrome, contribute to some cases, a significant number of cases in younger populations have no genetic predispositions. The current colorectal cancer screening guidelines are inadequate in diagnosing younger populations at risk of EOCRC. Therefore, developing cost-effective, non-invasive screening tools specifically designed for individuals under 50 years of age is critical. The focus of current research is the development of a non-invasive diagnostic procedure for EOCRC. For instance, studies have identified circulating miRNA panels as promising biomarkers for early detection due to their high accuracy (e.g., AUC values ranging from 0.88 to 0.92) and tumor-specific character. These biomarkers hold potential use in clinical application, offering a less invasive technique than does colonoscopy.[23]

Diagnostic challenges and advancements in EOCRC screening

The diagnosis of EOCRC poses distinct challenges and requires a comprehensive approach due to its distinct characteristics and clinical presentation, especially in younger populations. As the incidence of EOCRC rises, understanding the diagnostic procedure becomes increasingly critical. Patients with EOCRC often exhibit symptoms that differ from those seen in the older population. Current guidelines recommend beginning colorectal cancer screening at age 45 for average-risk individuals. However, individuals with a family history of colorectal cancer or polyps may require screening at an earlier age.[24,25] These high-risk individuals can benefit from personalized screening based on family history. Approximately 16–25% of early-onset colorectal cancer (EOCRC) cases are linked to genetic predispositions, suggesting the importance of genetic counseling and testing for younger patients presenting with a family history of colorectal cancer. [26] Common symptoms of EOCRC, such as rectal bleeding (hematochezia), abdominal pain, changes in bowel habits, and iron-deficiency anemia, are prevalent indicators of EOCRC.[27,28] The presence of these symptoms should invoke further investigation, especially in younger adults who may not typically be screened for colorectal cancer.

As the gold standard diagnostic procedure for EOCRC, colonoscopy enables direct visualization and removal of polyps and suspicious lesions in the colon and rectum. Several studies have found that patients with EOCRC often present with a more advanced stage of the disease, requiring an early colonoscopy to detect the disease.[25,27,29] Furthermore, current biomarkers for EOCRC detection, such as non-invasive stool-based tests, one of which is the fecal immunochemical test (FIT), have gained increasing recognition as valuable tools for early detection in younger populations, particularly in individuals who may be hesitant to undergo colonoscopy. The fecal immunochemical test has shown promise in detecting CRC and advanced precancerous lesions. [30] It was reported in a study that the combination of aberrantly methylated BMP3 and NDRG4, along with mutant KRAS and f-Hb, could detect CRC with a sensitivity of 92.3%. However, the sensitivity varies significantly based on the detected lesion size and type.[31,32]

One of the most widely used biomarkers to detect colorectal cancer is the immunochemical fecal occult blood test (iFOBT). This biomarker is effective in the general population, but scores low in sensitivity and specificity, particularly in young patients with different types of tumors. For instance, studies indicate that iFOBT's sensitivity for EOCRC is significantly lower compared to other biomarkers. Recent research has identified several promising biomarkers that could improve early detection of EOCRC, such as circulating microRNAs (miRNAs), methylated Septin9 (mSEPT9), microsatellite instability (MSI), and gut microbiota analysis.[31,33]

There was a study [23] that developed a signature consisting of four circulating microRNAs (miRNAs) (miR-193a-5p, miR-210, miR-513a-5p, and miR-628-3p) that had high diagnostic accuracy for EOCRC with an area under the curve (AUC) of 0.92 in initial cohorts and 0.88 in validation cohorts. Therefore, these biomarkers have a strong potential as promising biomarkers for CRC detection as a less invasive procedure. A systematic review reported several miRNAs with potential diagnostic applications.(34) Among these, miR-21 has been extensively studied; however, its diagnostic performance varies across studies, with AUC values ranging from 0.55 to 0.973, presumably resulting from various study populations and methodologies. Other miRNAs, such as miR-210 and miR-1246, have also shown potential, with miR-1246 achieving an AUC of 0.924, 100% sensitivity, and 80% specificity. In addition, compared to individual miRNAs, miRNA panels have shown higher diagnostic performance. For instance, a panel consisting of miR-211, miR-25, and TGF-β1 achieved an AUC of 0.99, with 100% specificity and 97% sensitivity in CRC patients under 50 years old.

Methylated Septin9 (mSEPT9), a blood-based biomarker, has shown promise as a screening tool specifically for EOCRC. The mSEPT9 biomarker demonstrated high sensitivity and specificity in studies, suggesting its potential applicability in clinical diagnosis.[35] Aberrant DNA methylation is a recognized diagnostic marker of cancer, including CRC. Markers such as methylated SEPT9 (mSEPT9) have been evaluated for their potential as diagnostic tools in early detection. The mSEPT9 assay, a blood-based test, has shown promise with a sensitivity of approximately 68-72% and specificity of about 80-82% for detecting CRC.[36]

Studies have indicated that EOCRC patients exhibit a higher prevalence of microsatellite instability (MSI) compared to older patients.(37,38) For instance, a retrospective review of over 36,000 CRC patients revealed that early-onset cases were more likely to present with MSI, which is associated with mismatch repair (MMR) deficiency. Tumors with high prevalence of MSI (MSI-H) are associated with better survival outcomes, making MSI testing critical for both.[37]

Emerging biomarkers in EOCRC

In order to enhance early detection capabilities, researchers are investigating novel biomarkers originating from gut microbiota analysis. The gut microbiome is a complex ecosystem that plays an important role in human health. There is evidence that dysbiosis, or an imbalance in this microbial community, plays a role in the pathogenesis of EOCRC.[39]

Studies indicate that specific bacterial populations may be enriched or depleted in individuals with EOCRC compared to healthy controls. For instance, studies have shown that the presence of certain bacteria, such as *Fusobacterium nucleatum* and enterotoxigenic *Bacteroides fragilis*, is associated with increased risk of EOCRC.[40,41] Recent systematic reviews and meta-analyses have highlighted the potential of gut microbiota-derived biomarkers for CRC screening. A systematic review identified 28 studies demonstrating varying diagnostic performances of fecal bacteria-derived biomarkers, with areas under the curve (AUC) ranging from 0.28 to 0.98 for advanced adenomas and from 0.54 to 0.89 for early CRC.[40] Another study using Bayesian methods found that incorporating microbiome data significantly improved the probability of detecting adenomas, increasing pretest probabilities from 0.17% to over 10%. [42] Moreover, specific microbial markers have been identified that can differentiate between healthy individuals and those with adenomas or carcinomas. For example, a study analyzing fecal samples found that specific microbial signatures could effectively distinguish between these groups, with AUC values indicating good diagnostic performance. [43] Despite promising findings, challenges remain in standardizing microbiome analysis for clinical application. Variability in study designs, methodologies, and populations complicates the interpretation and validation of microbiome-derived biomarkers. Future research should focus on large-scale cross-sectional studies that incorporate diverse populations and link microbiome data with other clinical markers to enhance the research validity.

Future directions

There is a growing consensus that a combination of biomarkers may yield better diagnostic performance than single markers alone. For example, combining methylated gene assays with traditional fecal testing could enhance sensitivity for detecting both CRC and advanced precancerous lesions.[31] The integration of various biomarkers might also address the diversity of CRC, which varies by molecular subtype and anatomical location. The heterogeneity of EOCRC complicates biomarker development, as different individuals may respond differently to various biomarkers based on genetic background and the stage of disease. Therefore, a multi-faceted approach that combines several biomarkers may be necessary to improve sensitivity and specificity in detecting EOCRC effectively, as the understanding of CRC biology improves. Integrating multiple biomarkers into comprehensive screening procedures could enhance detection rates while reducing unnecessary colonoscopies. Ongoing research aims to standardize these tests for broader clinical application, potentially improving early detection rates and outcomes for patients diagnosed with EOCRC.

Future directions in research should focus on targeted biomarker identification and validation within various patient populations. The considerable heterogeneity observed in EOCRC, including genetic mutations such as those associated with the POLE P286R mutation, emphasizes the need for stratified biomarker exploration. [44] Specifically, markers associated with unique molecular profiles, such as microsatellite instability (MSI) and biomarkers linked to immune responses, can lead to better patient-specific treatment modalities and contribute to the optimization of immunotherapy strategies, which have shown efficacy in dMMR-MSI-H tumors.[45] Continuing advancements in multi-omics methodologies will allow for a comprehensive understanding of tumor biology, thereby facilitating the identification of novel biomarkers from complex biological data.[44,46]

Moreover, the implementation of integrative approaches combining proteomics and metabolomics can reveal new insights into the tumor microenvironment of EOCRC, potentially discovering novel biomarkers that could be applied in clinical settings. Proteomic studies have already underscored the utility of certain proteins as biomarkers of aggressive disease and treatment responses.[47,48] Utilizing quantitative mass spectrometry, researchers can identify differential protein expressions and their pathways, thereby enhancing the early detection accuracy of EOCRC.[49] Integrating metabolomics into these studies can provide metabolic profiles that correlate with disease phenotypes, ultimately contributing to the establishment of reliable biomarkers for prognostic assessments and early diagnosis.[50]

Researchers must also prioritize the practical application of identified biomarkers through rigorous clinical validation processes. Biomarker studies should follow clearly defined guidelines that evaluate risk assessment, screening efficacy, and clinical utility before being integrated into standard practice.[13] For biomarkers such as circulating microRNAs and neutrophil-lymphocyte ratios, which display potential for prognostic and predictive capabilities in advanced-stage disease,[34,51] clinical trials should assess their effectiveness in various populations, particularly in young patients presenting with atypical symptoms.[52] The emphasis on clinical applicability and regulatory approval will ensure that successful biomarkers become integral to the management of EOCRC, aligning with a growing demand for personalized medicine in oncology.

CONCLUSION

The increasing focus on EOCRC highlights its clinical significance and the urgent need for enhanced research efforts to fill existing research gaps. The diagnosis of EOCRC requires a comprehensive understanding of its unique clinical presentation, risk factors, and appropriate screening modalities. While colonoscopy remains the diagnostic gold standard, non-invasive tests and imaging studies play essential roles in early detection. It is important for healthcare systems to develop more effective screening tools and personalized approaches to ensure that young people at risk of EOCRC are diagnosed earlier and receive better care. As the EOCRC incidence continues to rise, the advancement of screening strategies will be crucial in detecting the population at risk.

Conflict of Interest

All authors declare that there are no conflicts of interest.

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Authors' Contributions

HHP, AS, NR elaborated the concept and design of the study; HHP and AS data retrieval and analysis; HHP, AS, NR drafted the manuscript; NR critically revised the manuscript. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

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The data that support the findings of this study were obtained from the Scopus database. Because Scopus is a subscription-based database, the raw data are not publicly deposited. The bibliometric dataset generated and analyzed during the current study is available from the corresponding author upon reasonable request.

Declaration of AI Usage in Scientific Writing

During the preparation of this work, the authors utilized ChatGPT (OpenAI) to support editorial refinement, including language polishing, sentence clarity, manuscript flow, presentation of table and figure descriptions, and consistency with the journal's formatting requirements. The validity of the outputs was evaluated through author review, cross-checking with the original manuscript draft, bibliometric data, tables, figures, and journal instructions, followed by manual revision where necessary. After carefully reviewing and editing the content as necessary, full responsibility for the publication's content is taken by the authors. This incorporation of AI tool usage primarily impacted language clarity, manuscript presentation, table and figure description clarity, and formatting consistency.

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