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A bibliometric analysis of Barrett's esophagus

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Abstract. – OBJECTIVE: Esophageal adenocarcinoma is known to have a high incidence and poor prognosis in the population and is a serious threat to public health. As a precancerous lesion of esophageal adenocarcinoma, early intervention of Barrett's esophagus is key to the prevention and treatment of esophageal adenocarcinoma.

MATERIALS AND METHODS: Research publications on Barrett's esophagus (BE) were searched in the Web of Science Core Collection, and the extracted publications were screened to obtain relevant data. The included articles were analyzed bibliometrically using Microsoft Excel 2019, Citespace V, and VOSviewer 1.6.18. The keywords used for the search can be categorized into 4 clusters: endoscopic therapy, clinical screening, risk factors, and drug therapy.

RESULTS: A total of 3,497 publications from 83 countries and 3,319 research institutions were retrieved. Since 1983, there has been a rapid increase in publications in this field. The United States (n = 1,941) and Mayo Clinic (n = 218) were the most productive countries and institutions, respectively, and the most prominent author was Kenneth K. Wang, who published 89 papers.

CONCLUSIONS: In this study, we were able to perform a comprehensive and systematic analysis of literature related to BE. Endoscopic resection and radiofrequency ablation may emerge as research hotspots for BE in the future. Our findings provide insight into the current trends in the management of BE and facilitate the choice of appropriate measures to improve the prognosis of patients.

Key Words:
Barrett's Esophagus, Bibliometric, Research hotspots, VOSviewer, Citespace.

Abbreviations

BE: Barrett's esophagus; CPP: number of citations per publication; D: doubling time; EAC: esophageal adenocarcinoma; EMR: endoscopic mucosal resection; FBs: forceps biopsies; FICE: transnasal flexible spectral imaging color enhancement; GERD: gastroesophageal reflux disease; HGD: high grade dysplasia; h-index: hirsch index; IF: impact factor; JCR: journal citation report; LGD: low grade dysplasia; LS: link strength; LSBE: long-segment BE; NDBE: non-dysplastic BE; PaI: participation index; PDT: photodynamic therapy; PI: productivity index; RFA: radiofrequency ablation; SCIE: science citation index-expanded; SGA: small for gestational age; SSBE: short-segment BE; TC: total citations; TI: transience index; TLS: total link strength; TP: total publications; UK: the united kingdom; VFI: vital-dye en-hanced gluorescence imaging; WOS: web of science; WOSCC: WOS core collection.

Introduction

Barrett's esophagus (BE) is a disease characterized by the replacement of the squamous epithelium of the distal esophagus by metaplastic columnar epithelium[1]. The pathological hallmarks of BE are cupped cells[2]. Approximately 5.6% of adults in the US are estimated to have BE[3]. Gastroscopy and histopathology are the diagnostic gold standard for BE[4], and depending on the length of the lesion, BE is classified into long-segment BE (LSBE) and short-segment BE (SSBE)[5]. In actual clinical practice, misdiagnosis[6] and omission[7] of BE patients occur frequently, although the advent of a range of advanced detection technologies[8,9] has minimized such lapses. The pathogenesis of BE is thought to be associated with chronic inflammation due to esophageal reflux and the resulting oxidative stress causing DNA damage[10]. Esophageal hiatal hernia and gastroesophageal reflux disease (GERD) have been shown to be the most important risk factors for BE[11]. Male sex, tobacco, and centripetal obesity are also risk factors for BE[12]. In addition, aging and LSBE have emerged as independent predic-

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tors of BE disease progression[13]. BE is a relatively clear major risk factor for esophageal adenocarcinoma (EAC)[14] and precancerous lesions[15]. Compared to the general population, patients with BE are at a greater risk of developing EAC[16], with approximately 0.2-0.5% of patients[17] progressing to EAC through a multi-step sequence of changes – non-dysplastic BE to low-grade dysplasia (LGD) to high-grade dysplasia (HGD) to EAC[18,19]. As the major type of esophageal cancer, EAC is characterized by higher incidence[20] and lower survival[21] than other GI tumors, and it has become a major public health problem worldwide[22]. Consequently, effective long-term monitoring and early intervention for BE are key to reducing the risk of malignant progression[23]. For example, BE screening in high-risk populations is recommended according to the Seattle protocol[24], and the UK Gastroenterology guidelines[25] specify screening intervals of every 2-3 years for patients with LSBE and every 3-5 years for patients with SSBE.

Modern bibliometrics originated in 1955[26], but it was not until 1969 that Alan Pritchard first introduced the term "bibliometrics" to define "the application of mathematical and statistical methods to books and other media of communication"[27]. Unlike traditional literature reviews[28], bibliometrics is an approach that allows for an objective assessment of the impact of scholarly publications based on measurements extracted from the knowledge available in publications and subjected to statistical analysis[29]. Since its introduction, bibliometric analysis has been widely used in medical fields[30], such as hematology[31], oncology[32], and neurology[33].

After decades of development, substantial progress has been made in the field of BE in terms of basic theory, diagnostic techniques, and prevention and control concepts, and a wealth of research experience has been accumulated. Although literature reviews[34,35] and systematic reviews[36,37] of BE studies have been conducted in the past, these analyses only examine some results in the field of BE research from different perspectives and do not provide a more comprehensive picture of the current state of research and changes in hotspots in the field of BE. This study, therefore, attempts to provide an overall overview of the advances in BE research by comprehensively collecting research data using bibliometric methods and thereby helping specialists quickly understand the research hotspots and cutting-edge trends in the field of BE in recent years. Briefly, this study will focus on the following three research questions:

(1) What is the basic distribution of the BE field, such as the annual volume of publications, authors, countries, and institutions?

(2) What are the hot directions in the field of BE?

(3) What are the research trends in the field of BE?

Materials and Methods

Search Strategies

Web of Science (WOS) is the pioneering, most comprehensive, and most detailed database worldwide[38], having a significant influence in the biomedical field[39]. The data were retrieved using the Science Citation Index-Expanded (SCIE) in the WOS Core Collection (WOSCC), combining clinical experience, medical subject terms (MeSH), and published articles to determine the search terms[40,41]. To improve accuracy and minimize false-positive search results[42], we opted for title search over other search methods. Although some publications may be missed (false negative) with title search, the errors obtained by title/abstract search[43] or topic search (false positive) would be much larger[44]. In addition, the title search method used in the present study has been well-validated and used in previous studies[45-47]. The search formula was finally set as follows: TI = (Barrett* Esophagus) OR TI = (Barrett Metaplasia*) OR TI = (Barrett* Syndrome) OR TI = (Barrett Epithelium), where the asterisk * is a wildcard used to retrieve publications containing different forms of this keyword, such as Barrett or Barrett's. The screening criteria were as follows: (i) The time span was set between database inception and October 22, 2022. (ii) The publication language was English. (iii) The publication type was research article or review. The data retrieval strategy and screening process are shown in Figure 1.

Quality Control

The literature search was independently conducted by two researchers (ML and NG), and the results of both searches were then compared. Discrepancies in opinion were resolved by discussion with the third researcher (YD) and the optimal outcome chosen. The data were retrieved and exported on the same day (October 22, 2022) to avoid potential bias caused by database updating. This study did not include any animals or laboratory experiments and, therefore, did not involve ethical consent. 3,497 publications in the field of BE were identified and included in the final analysis.

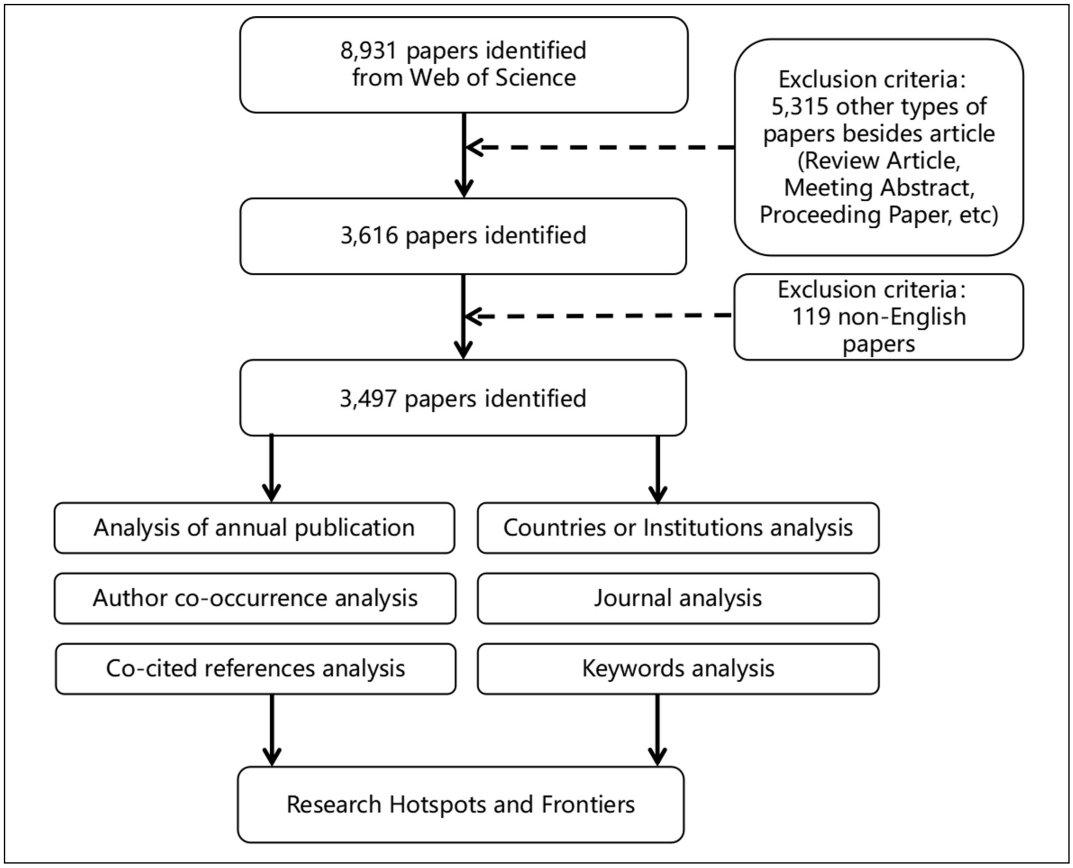

Figure 1. Flow chart of literature screening.

Bibliometric Indicators

The following biometric indicators were considered in this study:

(1) Price's law: a common indicator reflecting the laws of scientific production[48] with the formula ; where x represents the year, b is the literature growth rate, and a is the number of documents at the initial moment.

(2) Doubling time (D): the time required to double the output in a given field, with the formula $D = \frac{Ln2}{b}$.

(3) Bradford's law: according to Bradford, if journals are sorted in decreasing order according to the number of documents they contain, they can be classified into core regions and several other regions containing an equal number of documents[49]. The following patterns exist in the number of journals in each region: , where "a" is also known as the Bradford constant.

(4) Lotka's law: Lotka proposed a theoretical formula for the distribution of authors in literature: $A(n) = \frac{A(1)}{n^2}$, where "n" represents the number of publications and "A" represents the number of authors. According to Lotka's law, authors can be assigned to three categories, depending on the number of publications they produce: "small producers" (PI = 0), "medium-sized producers" (0 < PI < 1) and "large-scale producers" (PI > 1), where the productivity index (PI) is equal to the logarithm of the number of author publications.

(5) Hirsch index (*h*-index): this value indicates that at least h publications have been cited h times, and it is a criterion to simultaneously assess the quantity and quality of publications[50].

(6) Impact factor (IF): IF is a key indicator reflecting the impact of publications[51]; it is available through the online journal search platform (https://www.medsci.cn/sci/index.do).

(7) $$\frac{\text{Number of authors with a publication}}{\text{Total number of authors}} \times 100$$

(8) $$\frac{\text{Number of publications in a country}}{\text{Total number of publications}} \times 100$$

(9) $$= \frac{\text{Total publications (TP)}}{\text{Total citations (TC)}}.$$

Bibliometric Software

The software used for data analysis in this study were Microsoft Excel 2019, Citespace V, and VOSviewer 1.6.18. Both Citespace and VOSviewer allow for data visualization[52], but they have slightly different features. Citespace is a JAVA platform-based application designed by Prof. Chaomei Chen[53] to quickly organize the growth history of research topics[54]. VOSviewer, which was developed by Dr. Ness Jan van Eck and Dr. Ness Jan van Eck of Leiden University in the Netherlands, has a simple operator interface[55] and is a web application used for building knowledge maps[56].

Data Analysis

Price's law for the determination of the coefficient of determination (R2) was used to analyze the annual distribution of publications and assess whether they were in the exponential growth phase. Bradford's law and Lotka's law were used to identify the most prolific core journals and authors in the field of BE research, respectively. Microsoft Excel was used to analyze the descriptive statistics on the number of publications and citations by country, institution, and author[57]. VOSviewer software was used to build a collaborative network of countries, institutions, and authors, while forming a visual analysis of keyword clusters. In a cooperative network, the size of the nodes is determined by the volume of the articles published, whereas the connection between the nodes indicates the cooperative relationship and the thickness of the connection reflects the strength of the cooperation[58]. Keyword burst detection was achieved using Citespace software, which analyzes research hotspots and trends in a given time dimension[59]. The parameters were set as follows: time span (2000-2022), years per slice (1), node types (keyword), g-index (k = 25), and pruning (pathfinder).

Results

Publication Outputs and Citation Trend

A total of 3,497 publications, including 3,042 articles and 455 reviews, were extracted from the database using the defined search formula and selection criteria[60]. The publications were classified into 3 phases according to the changes in the annual publications: (1) the first phase of 1960-1983, with no more than 10 annual publications; (2) the second phase of 1983-2011, with an overall upward trend in the number of annual publications, which peaked at 164 in 2011; and (3) the third phase of 2012-2022, with a small decline in the number of annual publications (Figure 2A-C). The period of 2003-2012 was the decade with the most published articles, accounting for 36.76% of the total literature (Figure 2C). In parallel to the annual publications, the number of annual citations also showed an upward trend since 1960, with two peaks in 2000 and 2011 reflecting the growing research interest in BE.

To determine whether the growth in research output was in accordance with Price's law, we exponentially adjusted the data using the equation $y = 1E\text{-}78e^{0.0915x}$, where a variance of 10.43% did not explain by the model fit ($R^2 = 0.8957$). Then, we linearly adjusted the data again using the equation $y = 3.0495x - 6018.9$, which had a variance of 15.60% ($R^2 = 0.844$) (Figure 2B). We found that our data better matched the exponential fit than the linear fit and therefore complies with the assumptions of Price's law. Furthermore, on calculating the D-value, we found that the number of publications doubles approximately every 7.58 years.

Contributions of Countries

In terms of regional contributions, 66 countries were involved in publishing BE-related studies, with the majority (3,638) of publications coming from the top 10 countries (Table I). USA had the highest number of publications (PaI = 55.50), followed by England (PaI = 10.64), Netherlands (PaI = 8.49), and Germany (PaI = 6.55). In terms of citations, the country with the highest CPP was Sweden (CPP = 59.03), followed by the Netherlands (CPP = 51.19) and Germany (CPP = 48.71). Figure 3A shows the data on the worldwide distribution of publications, which indicates that there are regional variations in the distribution of BE research worldwide, with publications concentrated in the economically developed countries of Europe and the United States.

The U.S. has the highest total link strength (TLS = 689) in co-authorship between institutions, having co-authorship with 42 countries. The closest cooperation was with the UK (TLS = 104), followed by the Netherlands (TLS = 87) and Australia (TLS = 68). Additionally, the node colors indicate that European countries such as France, Chile, and Switzerland started to focus on BE around 2006, while China, Singapore, and Poland started later, but developed at a more rapid pace and emerged as prominent research countries in the field (Figure 3B).

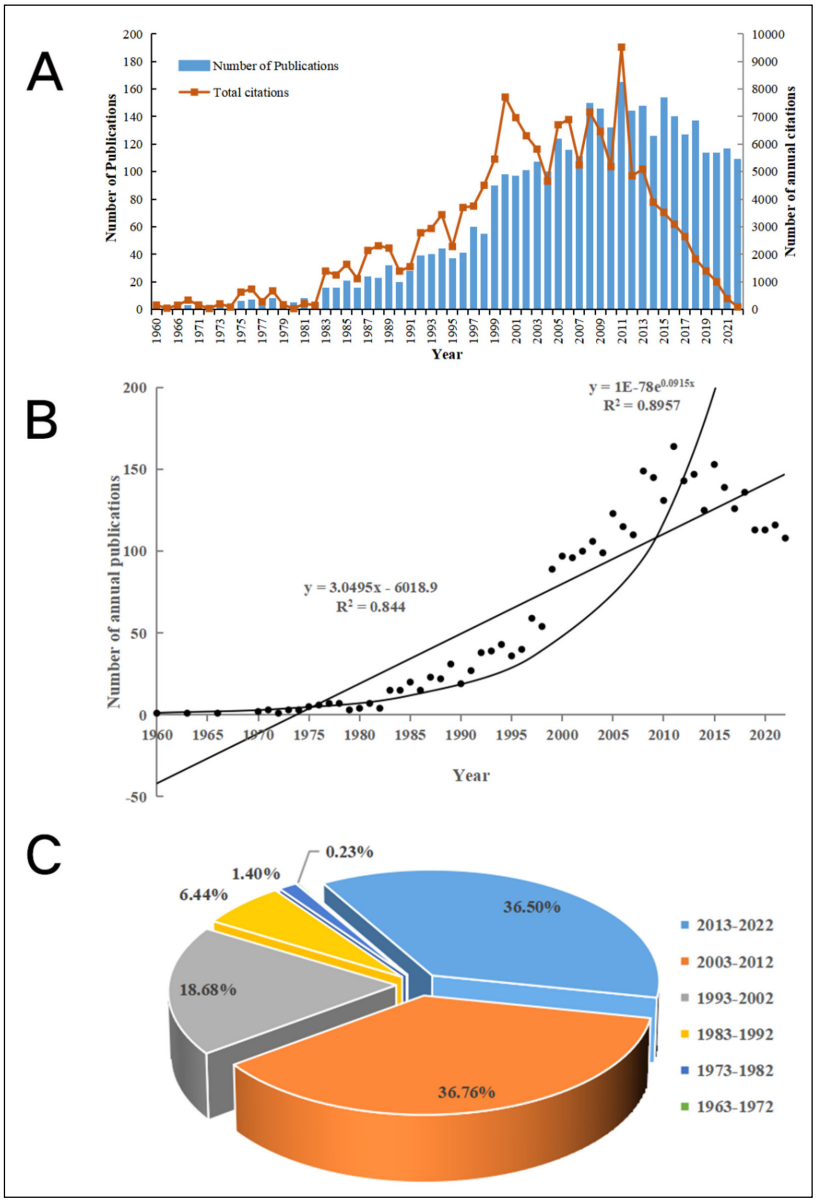

Figure 2. Analysis of the number and trends of publications. **A**, Annual number of the publications and citations in BE research. **B**, Fitted curves for annual number of publications. **C**, Evolution of the number of documents every 10-year periods.

Table I. The top 10 countries contributing to publications in BE research.

Rank	Country	TP	PaI	TC	CPP
1	USA	1,941	55.50	93,263	48.05
2	UK	372	10.64	16,476	44.29
3	Netherlands	297	8.49	15,204	51.19
4	Germany	229	6.55	11,154	48.71
5	Japan	203	5.80	5,293	26.07
6	Australia	156	4.46	6,409	41.08
7	China	153	4.38	2,509	16.40
8	Italy	131	3.75	3,471	26.50
9	Canada	118	3.37	5,071	42.97
10	Sweden	64	1.83	3,778	59.03

TP, total publications; PaI, participation index; TC, total citations; CPP, number of citations per publication.

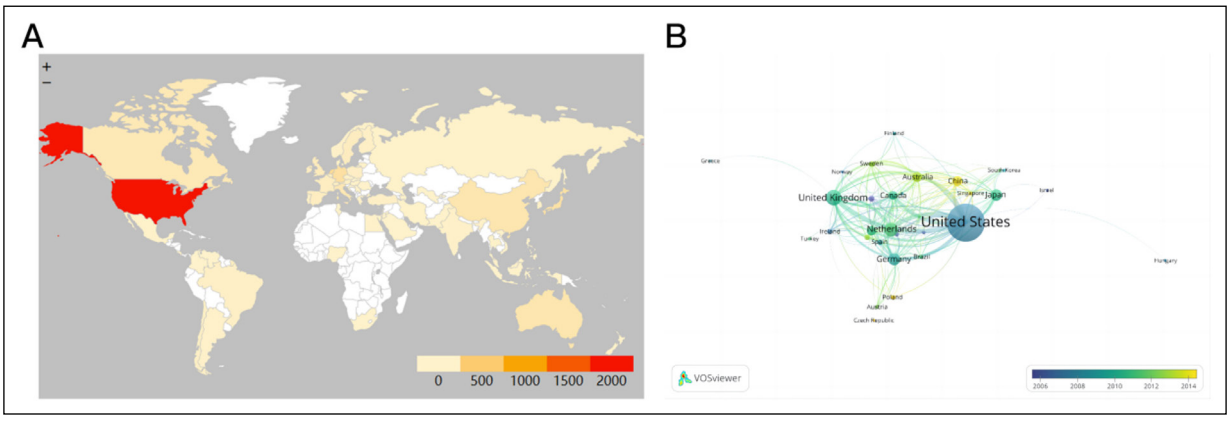

Figure 3. The distribution of countries in BE research. **A**, Distribution of BE publications in the world map. According to the color gradient in the lower right corner, the color of each country or region represents the amount of literature published. **B**, Co-authorship network visualization map of countries.

Contributions of Institutions

A total of 2,641 institutions have participated in BE-related research, and the top 10 publishers have published 1,230 articles (Table II). Mayo Clinic is the research institution contributing the most publications (TP = 218), followed by Washington State University (TP = 159), Kansas State University (TP = 131), and Harvard University (TP = 122). Figure 4 shows the inter-institutional collaborations, with Mayo Clinic having the highest TLS (TLS = 799), having collaborated with 288 institutions. The closest collaboration was with North Carolina State University (link strength, LS = 30), with 43 publications coming from both institutions.

Contributions of Authors

Applying Lotka's law, we classified authors in the field of BE research according to productivity, and the results are shown in Table III. The total number of authors was 12,730, with an average number of 3.64 authors per article. The TI index of 75.17 indicates that the majority of authors contributed only one paper, making them "small producers". The number of "large producers" with more than 10 articles to their credit was 193, which accounts for 1.52% of the total number of authors. Table IV shows the top 10 large producers: Prateek Sharma (TP = 95, TC = 6,335, CPP = 66.68) was the most prolific author, followed by Nicholas J. Shaheen (TP = 91, TC = 4,816, CPP = 52.92) and Kenneth K Wang (TP = 89, TC = 4,784, CPP = 53.75); all the top three authors were from the USA. The author collaboration network was constructed for "large producers" (Figure 5), and the highest total link strength (TLS = 169) was found for Nicholas J. Shaheen, who has successively collaborated with 75 authors; Evan S Dellon, David C Whiteman, and Charles J. Light-

Table II. The top 10 most productive institutions in BE research.

Rank	Institution	Country	TP	Percentage
1	Mayo Clinic	USA	218	6.23%
2	Washington State University	USA	159	4.55%
3	Kansas State University	USA	131	3.75%
4	Harvard University	USA	122	3.49%
5	North Carolina State University	USA	121	3.46%
6	Vrije Universiteit Amsterdam	The Netherlands	110	3.15%
7	Fred Hutchinson Cancer Research Center	USA	103	2.95%
8	Baylor College of Medicine	USA	97	2.77%
9	Columbia University in the City of New York	USA	85	2.43%
10	University of Arizona	USA	84	2.40%

TP, total publications.

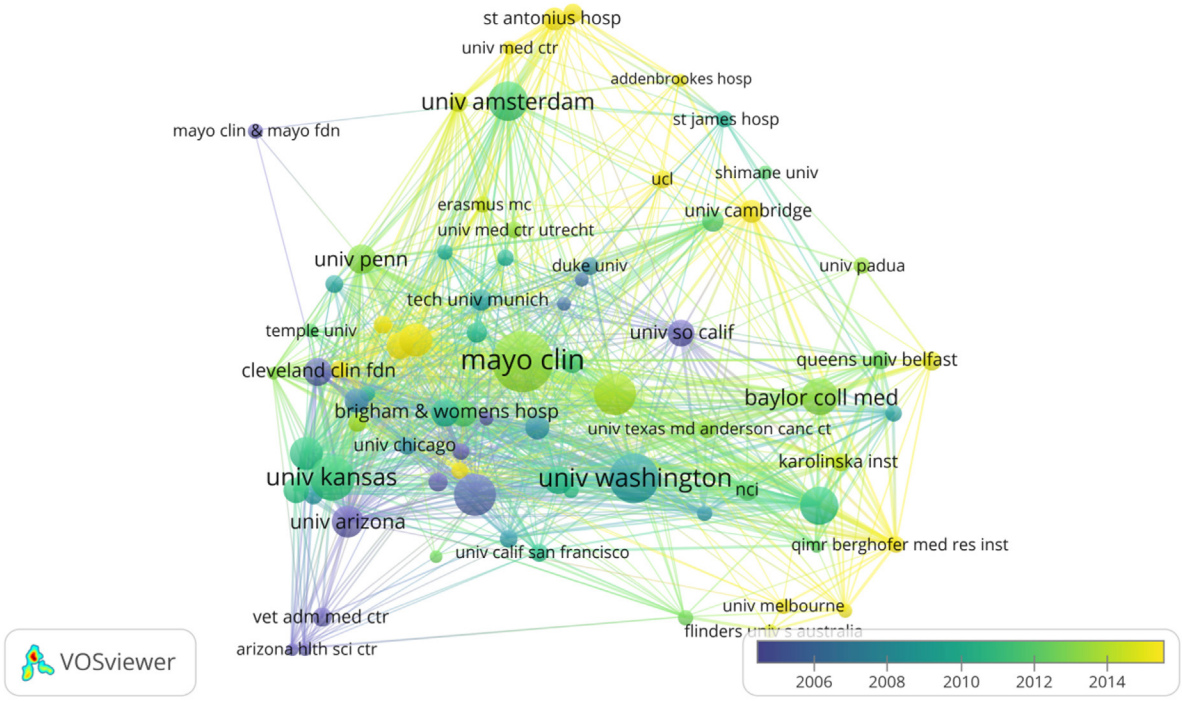

Figure 4. Co-authorship overlay visualization map of institutions.

Table III. Classification of authors based on productivity.

	PI ≥ 1 (10 or more articles)	0 < PI < 1 (2-9 articles)	PI = 0 (1 article)	Total
Number of authors	193	2,965	9,564	12,722
% authors	1.52	23.31	75.17	100

PI = 0 (small producers); 0 < PI < 1 (medium-sized producers); PI ≥ 1 (large producers). PI, productivity index.

dale were the other authors with the high number of collaborations. In addition, as can be seen by the node colors in Figure 5, numerous tight-knit research teams have formed within the BE field, with the main participants being Robert D. Odze, Brian J. Reid, and Patricia L. Blount.

Table IV. The top 10 most productive authors in BE research.

Rank	Author	TP	Percentage	TC	CCP	h-index
1	Prateek Sharma	95	2.55%	6,335	66.68	40
2	Nicholas J. Shaheen	91	2.43%	4,816	52.92	39
3	Kenneth K. Wang	89	2.32%	4,784	53.75	43
4	Jacques J.G.H.M. Bergman	64	1.66%	3,853	60.20	28
5	Prasad G. Iyer	58	1.49%	2,230	38.45	26
6	Gary W. Falk	45	1.43%	2,504	55.64	29
7	Robert D. Odze	44	1.29%	2,116	48.09	31
8	Hashem B. El-serag	43	1.26%	1,432	33.30	20
9	Rebecca C. Fitzgerald	43	1.23%	1,510	35.12	26
10	Charles J. Lightdale	43	1.23%	2,670	62.09	29

TP, total publications; TC, total citations; CPP, number of citations per publication; h-index, hirsch index.

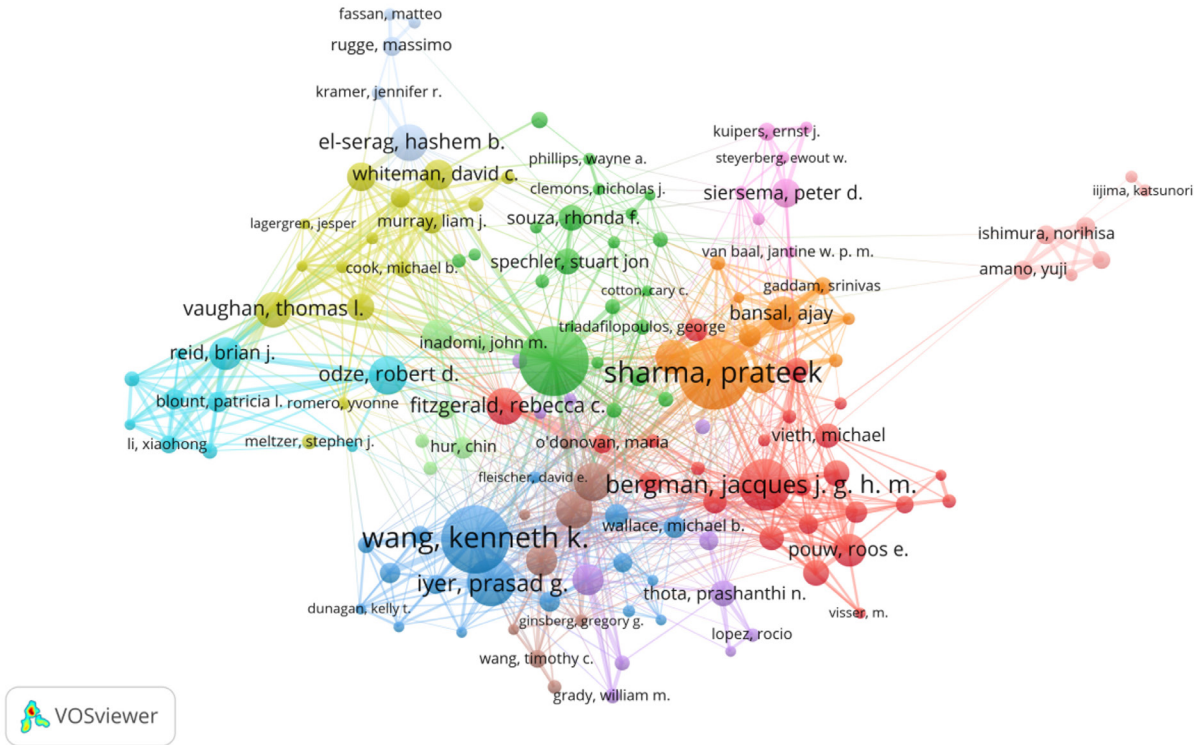

Figure 5. Co-authorship network visualization map of authors.

Journal Analysis

We evaluated the journals in the field of BE research by applying Bradford's model. As seen in Table V, a total of 502 journals have published articles on BE. The journals were grouped into five Bradford's zones according to the number of articles published; an average of 699 articles were noted per zone. Although the core region and Zone 1 contained only 9 journals (1.80%), they published close to 40% of the literature. In addition, we found that Core:Zone 1:Zone 2:Zone $3 \approx 1:3:3^2:3^3$, which fit Bradford's law.

Table VI presents the details of these nine journals. "Gastrointestinal Endoscopy" was ranked first in terms of TP, TC, and CPP, followed by "The American Journal of Gastroenterology" (TP = 250, CPP = 75.47), "Digestive Diseases and Sciences" (TP = 169, CPP = 23.83). In addition, the journal with the highest IF was "Gastroenterology" (IF = 33.883), with four journals belonging to the Q1 division.

Co-cited References Analysis

Highly cited papers indicate that they have a significant impact on a field[61], reflecting the hotness and depth of research in that field[62]. Table VII lists the ten most cited papers in BE field. Four of these articles were published in "Gastroenterology" and three in "The New England Journal of Medicine". An article by Sato et al[63], "Long-term expansion of epithelial organoids from human colon, adenoma, adenocarcinoma, and Barrett's epithelium" published in "Gastroenterology", was the most cited article, with 2,003 citations.

Table V. Distribution of the journals in Bradford's zones.

	No. of journals	% of journals	No. of articles	% of articles	Bradford multiplier
Core	3	0.60	673	19.25	
Zone 1	6	1.20	691	19.76	2.00
Zone 2	22	4.38	736	21.05	3.67
Zone 3	67	13.34	696	19.90	3.05
Zone 4	404	80.48	701	20.04	6.03
Total	502	100	3,497	100	3.69

Table VI. The top 9 journals with the most publications in BE research.

Rank	Journal	Country	TP	TC	h-index	JCR	IF
1	Gastrointestinal Endoscopy	USA	254	15,402	74	Q1	10.396
2	American Journal of Gastroenterology	USA	250	18,867	81	Q1	12.045
3	Digestive Diseases and Sciences	USA	169	4,028	36	Q3	3.487
4	Diseases of the Esophagus	USA	164	2,305	25	Q3	2.822
5	Gastroenterology	UK	161	25,608	86	Q1	33.883
6	Endoscopy	Switzerland	147	5,504	45	Q1	9.776
7	Clinical Gastroenterology and Hepatology	UK	88	5,028	38	Q1	13.576
8	World Journal of Gastroenterology	China	69	1,038	20	Q2	5.374
9	Journal of Clinical Gastroenterology	USA	62	1,177	21	Q3	3.174

TP, total publications; TC, total citations; h-index, hirsch index; IF, impact factor; JCR, journal citation report.

Table VII. The top 10 high-cited papers in BE research.

Rank	First author	Journal	Title	TC
1	Toshiro Sato	Gastroenterology	Long-term expansion of epithelial organoids from human colon, adenoma, adenocarcinoma, and Barrett's epithelium	2,003
2	Nicholas Shaheen	The New England Journal of Medicine	Radiofrequency ablation in Barrett's esophagus with dysplasia	973
3	Frederik Hvid-Jensen	The New England Journal of Medicine	Incidence of adenocarcinoma among patients with Barrett's esophagus	921
4	Kenneth K. Wang	The American Journal of Gastroenterology	Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus	854
5	W. Hameeteman	Gastroenterology	Barrett's esophagus: development of dysplasia	790
6	Stuart J. Spechler	Gastroenterology	American Gastroenterological Association medical position statement on the management of Barrett's esophagus	758
7	Stuart J. Spechler	The New England Journal of Medicine	Barrett's esophagus	752
8	Prateek Sharma	Gastroenterology	The development and validation of an endoscopic grading system for Barrett's esophagus: The Prague C and M criteria	725
9	Nicholas J. Shaheen	The American Journal of Gastroenterology	ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus	690
10	Hitoshi Satodate	Gastrointestinal Endoscopy	Circumferential EMR of carcinoma arising in Barrett's esophagus: case report	676

TC, total citations.

Co-occurrence Analysis of Keywords

High-frequency keywords are indicative of the hot topics in a given research field[64]. A total of 5,786 keywords were extracted and analyzed in this study, and the top 20 keywords in terms of frequency of occurrence are displayed in Table VIII. In addition to the search terms, "dysplasia" (n = 1,492), "adenocarcinoma" (n = 1,484), and "gastroesophageal-reflux disease" (n = 1,381) had the highest frequency of occurrence. The co-occurrence density visualization map (Figure 6) was plotted to identify the core keywords of this domain. In the keyword concurrent network (Figure 6), the keywords were assigned to 5 clusters according to the color: Cluster 1 (red) included keywords related to BE canceration, such as "adenocarcinoma," "breast-cancer," "cancer," "colorectal-cancer," "esophageal cancer," "neoplastic progression," etc. Cluster 2 (green) included keywords related to reflux, such as "acid reflux," "omeprazole," and "gastroesophageal reflux disease". Cluster 3 (blue) included keywords pertain-

Table VIII. The top 20 keywords in BE research.

Rank	Keyword	TP	Rank	Keyword	TP
1	dysplasia	1,492	11	prevalence	385
2	adenocarcinoma	1,484	12	management	379
3	Barrett's esophagus	1,381	13	radiofrequency ablation	315
4	gastroesophageal-reflux disease	1,079	14	endoscopic mucosal resection	279
5	cancer	1,038	15	esophagogastric junction	277
6	intestinal metaplasia	937	16	photodynamic therapy	251
7	diagnosis	593	17	columnar-lined esophagus	247
8	esophageal cancer	592	18	progression	245
9	surveillance	489	19	acid	244
10	risk	413	20	early cancer	234

TP, total publications.

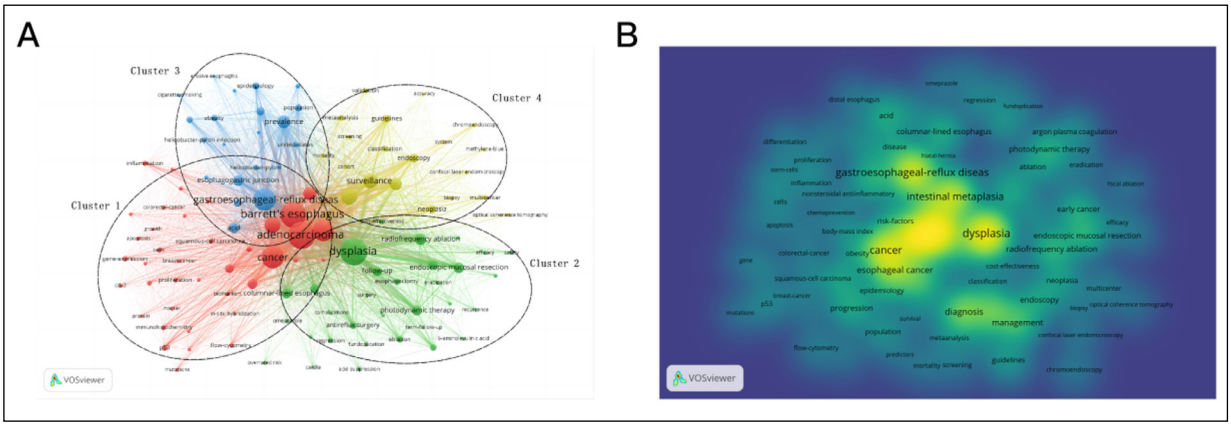

Figure 6. Analysis of keywords. **A**, Co-occurrence network visualization map of keyword. **B**, Co-occurrence density visualization map of keyword.

ing to endoscopic therapy, such as "argon plasma coagulation", "endoscopic mucosal resection," "photodynamic therapy," etc. Cluster 4 (yellow) included keywords related to risk factors, such as "obesity", "body-mass index", "helicobacter-pylori", etc. Cluster 5 (purple) included keywords pertaining to other areas of research, including "classification", "diagnosis", "guidelines", and 14 other keywords.

Keyword Burst Analysis

Keyword bursts conducted through Citespace are used to assess changes in research hotspots over time, thereby identifying the evolution of hotspots in the research field[65]. The stronger the burst, the more attention the research topic has received, which in turn reflects the research frontier for that period. We performed burst detection using Citespace for 3,497 keywords in the BE literature published between 2010 and 2022 and identified the top 20 keywords with the strongest burst intensity (Figure 7). The studies were classified into two main phases: the first phase lasting from 2000 to 2011 and the second phase from 2012 to 2022. For the first phase, the most important keywords were as follows: endoscopic surveillance, omeprazole, acid suppression, acid, 5-aminolevulinic acid, flow cytometry, photodynamic therapy, argon plasma coagulation, and chromoendoscopy. Keywords for the second phase include intramucosal carcinoma, meta-analysis, adenocarcinoma incidence, endoscopic resection, guideline, recurrence, and radiofrequency ablation. These results suggest that there is a gradual shift in the direction of research on BE. The strongest keyword was meta-analysis (13.83), while the longest outbreak was adenocarcinoma incidence (2014 - 2022). Notably, the keywords that continued the outbreak to 2022 were endoscopic resection (2015 - 2022), and radiofrequency ablation (2017 - 2022), which are the current frontline research areas in the field of BE.

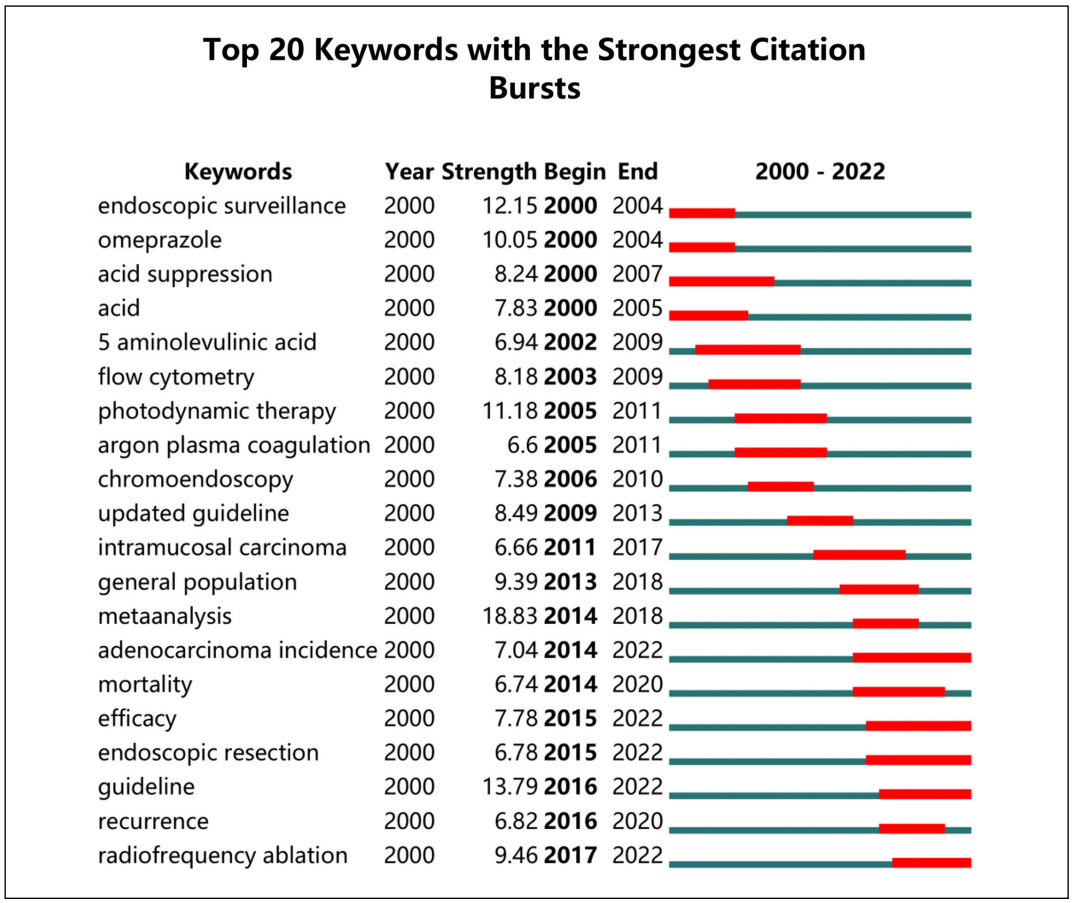

Figure 7. Top 20 keywords with the strongest citation bursts. Begin and End represent the beginning and end years of keyword emergence respectively. Strength indicates the intensity of the cited change. Each red or blue bar represents the time interval, and a single bar is equal to one year. The red bar especially represents citation burst.

Discussion

General Information

In this study, we analyzed extracted from WoSCC database 3,497 articles and 455 reviews in the field of BE. A total of 12,730 researchers from 83 countries and 3,319 institutions have conducted research on this topic, and the relevant findings have been published in 502 journals. "Gastrointestinal Endoscopy" is the journal with the highest number of publications in this field. Figure 2 illustrates the growth pattern of the number of publications since 1960 when M. C. Goldman and R. C. Beckman published the first research paper in the field of BE in "Gastroenterology"[66]. Until 2011, the annual number of publications showed exponential growth and doubled every 7.58 years. As these data demonstrate, recent years have witnessed the emergence of many interesting subfields in this topic.

Table I and Figure 3A show that the main countries leading research on VE are North America (USA and Canada), East Asia (China and Japan), and Western Europe (Netherlands, Germany, Italy, and Sweden) are the main countries leading BE research. Among them, the USA not only features as the country contributing the most articles but also has a significant influence in the field, acting as a strong driver for research in other countries. Although Sweden ranks 10th in the number of publications, its CPP is higher than that of other countries, which indicates that Sweden's publications are of higher quality and have some reference value. In contrast, China's CPP is the lowest among the top 10 countries, reflecting a need for further improvement in the quality of research.

Table II shows that the major contributors to BE research are from the United States, with the only exception being the Vrije Universiteit Am-

sterdam in the Netherlands. The Mayo Clinic is the highest contributor, collaborating most closely with North Carolina State University. The two institutions published a total of 43 papers, mainly on endoscopic radiofrequency ablation (RFA) for BE, analyzing in detail the durability[67] of RFA in the treatment of BE, the incidence of postoperative esophageal adenocarcinoma[68], the biopsy depth after RFA[69]. Another observation is that the timing of BE research varies among institutions; for example, Harvard University, the University of Arizona, and the University of Texas were the first institutions to conduct research in this area, while Columbia University and the University of Colorado focused on this area until 2014.

Tables III and IV show the variability of author involvement, with "small producers" still accounting for a large proportion; this indicates that the collaborative relationship between authors remains weak. However, as seen in Figure 5, there are several tightly knit research teams[71-74], such as the Kenneth K. Wang, Prasad G. Iyer, and David A. Katzka team from Mayo Clinic, whose studies[72-74] are mainly concerned with the economic analysis of BE screening[70,71] and systematic reviews of BE risk evaluation; the Dutch Jacques JGHM Bergman, Roos E. Pouw, and Sybren L. Meijer team, which has mainly focused on clinical validation studies of RFA for BE, such as radiofrequency vapor ablation[75], novel cryoballoon 180 degrees ablation system[76], and circumferential balloon-based RFA[77].

Research Hotspots and Fronts

Based on the analysis of co-cited references, high-frequency keywords, keyword clusters, and keyword bursts, we identified the following research hotspots in BE field: (1) endoscopic therapy; (2) clinical screening, (3) risk factors, and (4) drug therapy. The important research topics in these hotspots were RFA, endoscopy, *Helicobacter pylori* infection, and proton-pump inhibitors, respectively, as identified on the basis of the top five keywords according to the frequency of research in each hotspot (Table IX).

(1) Endoscopic therapy

Endoscopic therapy is currently the first-line treatment modality for BE-associated atypical hyperplasia and mucosal malignant adenoma[78]. It includes different techniques such as endoscopic mucosal resection (EMR), RFA, photodynamic therapy (PDT), and cryotherapy[79]. Each of these techniques has different indications; for example, EMR can provide curative interventions for lesions smaller than 2 cm by whole-block resection

Table IX. The top 5 keywords in four research hotspots.

Research Hotspots	Keyword	Frequency	Total Frequency
Endoscopic therapy	Radiofrequency ablation	315	955
	Photodynamic therapy	251	
	Endoscopic mucosal resection	138	
	Antireflux surgery	137	
	Argon plasma coagulation	114	
Clinical screening	Endoscopy	210	403
	Chromoendoscopy	59	
	Biomarkers	52	
	Confocal laser endomicroscopy	49	
	Magnification endoscopy	33	
Risk-factors	Helicobacter-pylori infection	172	553
	Body-mass index	111	
	p53	94	
	Obesity	90	
	Smoking	86	
Drug therapy	Proton pump inhibitors	78	220
	Nonsteroidal antiinflammatory drugs	55	
	Omeprazole	54	
	Aspirin	22	
	Cimetidine	11	

when the lesion size is less than 2 cm, as determined by endoscopy[80]. Based on the results of our analysis, RFA appears to be the most important and promising modality for endoscopic therapy currently. We further examined the efficacy, complications, and controversies of RFA and another similar ablation modality, cryotherapy.

RFA is a widely accepted treatment for BE[81]. A systematic review[82] conducted on 20 clinical studies showed that RFA afforded eradication rates of 70-86% for intestinal metaplasia and 87-95% for dysplasia, although a recurrence rate of 9-18% for intestinal metaplasia still exists. The eradication rate of RFA has been shown to reach 90.5% for LGD and 81.0% for HGD[83]. One study[84] showed that timely RFA intervention can reduce the risk of BE progression to adenocarcinoma by 7.4%. However, patients with BE are also known to be at risk of adverse effects after RFA treatment, with approximately 5.6% of patients experiencing esophageal stricture and the risk of bleeding and perforation being 1% and 0.6%, respectively[85]. Therefore, the risks and benefits of RFA treatment for patients with LGD are still debatable, and decisions should be made jointly between physicians and patients on a deliberative basis[86].

Cryotherapy is a form of thermal ablation that involves the use of rapid cooling and thawing cycles to induce tissue destruction. The refrigerant used is usually a liquefied gas[87], such as nitrogen, carbon dioxide, and other compressed gases. However, by far, the most commonly used cryogenic gas is liquid nitrogen[88]. Cryotherapy has been used in cancer treatment since the mid-19th century[89]. In 1985, Rodgers et al[90] first validated cryotherapy for superficial esophageal lesions through experiments on felines. Cryotherapy is a relatively targeted treatment modality due to the non-contact technique of targeted spraying of cryogens[91], while minimizing damage to the normal mucosa and effectively reducing the risk of esophageal stricture[92]. Cryotherapy causes cellular damage, death, and tissue necrosis primarily through direct and indirect mechanisms that lead to changes in the cellular microenvironment and impair tissue viability[93]. The TruFreeze system is the first cryotherapy system developed for endoscopic accompaniment and was first used in clinic practice in 2005[94].

(2) Clinical screening

Early detection and intervention in patients with BE can be effective in preventing the development of EAC[95]. Currently, the most common screening tool is the examination of the esophagus by high-definition white light endoscopy with four-quadrant forceps biopsies (FBs) targeting the lesion site[24]. However, there is currently an ongoing debate among American and European gastroenterology experts regarding whether the diagnosis of BE requires the involvement of intestinal epithelial chemosis[96]. Unfortunately, there exists the possibility of missing the diagnosis because of the difficulty in detecting flat or subtle lesions by white light endoscopy[97]. A number of studies[95] have focused on the development of new and more advanced imaging modalities to address this problem. For example, Vital-dye-enhanced fluorescence imaging (VFI) can help highlight the glandular morphology and detect early lesions by using an exogenous local fluorescent contrast agent in combination with high-resolution epithelial imaging[98]. Furthermore, transnasal flexible spectral imaging color enhancement (FICE) clearly shows the fenestrated vessels and the boundaries of normal and diseased mucosa[99]. The above-mentioned diagnostic modalities have all contributed to improving the diagnosis of endoscopic BE. Studies[100] that combine expert knowledge with existing clinical decision-making pathways through a deep learning framework also provide information to improve the efficiency of pathologic diagnosis and thus reduce the workload of pathologists. In addition, minimally invasive esophageal sampling methods offer alternative diagnostic options for BE screening in the general population[101].

Conventional endoscopic screening for BE in the general population is controversial because of its cost[102]. The search for appropriate serologic biomarkers for BE and EAC is a major challenge that has attracted the interest of investigators[103]. One study[104] found elevated plasma levels of BMP2, BMP4, and BMP5 in BE patients, with the elevations of BMP2 and BMP5 being significantly high; however, the utility of these biomarkers as a non-invasive assay in screening needs further validation. COX-2, PPARγ, HGF, gastrin, and their receptors are significantly upregulated in mucosa involved in BE when compared to normal esophageal squamous mucosa, and these factors may play a role in carcinogenesis associated with BE[105]. One study[106] targeting a high-risk population for EAC analyzed the value of predictive markers of carcinogenesis associated with BE, such as a heterozygous deletion of 17p11.1-p13 on chromosome 17p, in identifying BE patients at risk for tumor development. A sep-

arate meta-analysis[107] of clinical studies of BE patients who underwent baseline biopsy using p53 immunostaining showed a significant correlation between abnormal p53 immunostaining and progression to highly dysplastic or malignant adenoma of the esophagus. In another study[108], investigators analyzed the expression of CAS/CSE1L protein in esophageal sections by immunohistochemistry and found that it was less abundant in BE patients, significantly upregulated in 60% of LGD cases, and overexpressed in HGD and EAC, thus suggesting that CAS/CSE1L may be a potential marker of dysplasia/cancer.

(3) Risk factors

The latest guidelines[109] from the American College of Gastroenterology state that the screening of the general population for BE is not recommended as extensive screening is impractical; this makes it particularly necessary to identify high-risk patients[110]. Aging, male sex, and esophageal hiatal hernia are typical risk factors for BE, and the development of BE is also associated with race[111] and smoking history[112]. In addition, recent studies[113] have found that small-for-gestational-age (SGA) infants have a 3-fold greater risk of developing BE in adulthood compared to infants born with normal weight. A cohort study[114] of 120,852 subjects found that meat consumption and N-nitrosation-related factors were not associated with BE risk. Currently, there is growing interest in developing risk prediction models to help practitioners identify which patients are likely to benefit most from investigations and interventions[115].

(4) Drug therapy

Anti-reflux therapy, i.e., the use of acid-suppressing drugs, can relieve symptoms and reduce the extent of esophagitis and severity of Barrett's ulcer lesions, thereby preventing the formation of esophageal strictures. Since their approval in the United States in the late 1980s, proton-pump inhibitors have become a major therapeutic agent for BE[116,117]. Esomeprazole has been shown to significantly reduce intragastric acidity and lower esophageal acid exposure to mean normal values in patients with BE[118]. This effect is related to the fact that proton-pump inhibitors target the H^+, K^+-ATPase by covalently binding to the sulfhydryl group (-SH) of the protein. However, their efficacy in inhibiting acidity in the esophagus may decrease over time[119]. The benefit of proton-pump inhibitors in reducing the risk of EAC in patients with BE remains controversial. Nevertheless, one meta-analysis[120] has shown that proton-pump inhibitors are not associated with the risk of EAC and/or HGD in patients with BE, and another study[121] has shown that proton-pump inhibitors reduce the risk of conversion from BE to EAC. Although these drugs are not currently recommended in clinical guidelines as a means of reducing cancer risk in patients with BE, they are frequently used in clinical practice.

Limitations

This study also has a few limitations. First, only the literature published in English was taken into consideration in this study, and therefore, the possibility of excluding relevant research published in other languages cannot be ruled out. Secondly, we only searched the WOS database in this study, and it is possible that some of the relevant literature available in other databases may have been overlooked.

Conclusions

The number of publications in the field of BE has steadily increased over the last 60 years. The contributions made by authors and institutions from the US to the field of BE research have been remarkable and have motivated collaborations in other countries. The emergence of core research teams has accelerated the advancement in this field, and a large number of BE patients may benefit from the understanding gained from these studies in the future. Current research hotspots include endoscopic therapy, clinical screening, risk factors, and drug therapy. The available research shows that endoscopic resection and radiofrequency ablation are becoming popular therapeutic options. Nevertheless, it is necessary to acknowledge the inadequacies of the field, as regional disparities persist and are difficult to overcome in the short term.

Conflict of Interest

The authors declare that they have no competing interests.

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Authors' Contributions

YFG and ZL contributed to the conception and design of the study. SLW is responsible for literature searching, data collection. YD is responsible for statistical analysis and charting. This manuscript was drafted by ML and revised by NG. All authors read and approved the final manuscript.

Ethics Approval

The data for this study were downloaded directly from the database and it was not applicable for ethical approval.

Availability of Data and Materials

Data is available upon reasonable request.

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