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ABOUT COVER

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

INDEXING/ABSTRACTING

The *WJGO* is now abstracted and indexed in PubMed, PubMed Central, Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJGO* as 2.5; JIF without journal self cites: 2.5; 5-year JIF: 2.8; JIF Rank: 71/143 in gastroenterology and hepatology; JIF Quartile: Q2; and 5-year JIF Quartile: Q2. The *WJGO*'s CiteScore for 2023 is 4.2 and Scopus CiteScore rank 2023: Gastroenterology is 80/167; Oncology is 196/404.

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SCIENTOMETRICS

Current trends and hotspots of depressive disorders with colorectal cancer: A bibliometric and visual study

Zi-Wei Yan, Ying-Nan Liu, Qian Xu, Yuan Yuan

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Zi-Wei Yan, Ying-Nan Liu, Qian Xu, Yuan Yuan, Tumor Etiology and Screening Department of Cancer Institute and General Surgery, The First Hospital of China Medical University, Shenyang 110001, Liaoning Province, China

Zi-Wei Yan, Ying-Nan Liu, Qian Xu, Yuan Yuan, Key Laboratory of Cancer Etiology and Prevention in Liaoning Education Department, The First Hospital of China Medical University, Shenyang 110001, Liaoning Province, China

Zi-Wei Yan, Ying-Nan Liu, Qian Xu, Yuan Yuan, Key Laboratory of GI Cancer Etiology and Prevention in Liaoning Province, The First Hospital of China Medical University, Shenyang 110001, Liaoning Province, China

Co-first authors: Zi-Wei Yan and Ying-Nan Liu.

Corresponding author: Yuan Yuan, MD, PhD, Professor, Tumor Etiology and Screening Department of Cancer Institute and General Surgery, The First Hospital of China Medical University, No. 155 NanjingBei Street, Heping District, Shenyang 110001, Liaoning Province, China. yuanyuan@cmu.edu.cn

Abstract

BACKGROUND

Depression is strongly associated with colorectal cancer (CRC). Few bibliometric analyses have systematically summarized the research focus and recent progress in this field.

AIM

To determine the research status and hotspots by bibliometric analysis of relevant publications on the relationship between CRC and depression.

METHODS

Articles on depression in CRC patients were collected from the Web of Science Core Collection. CiteSpace and VOSviewer software were used to visualize bibliometric networks.

RESULTS

From 2001 to 2022, *Supportive Care in Cancer*, the United States, Tilburg University, and Mols were the most productive and influential journal, country, institution, and author name. Co-occurrence cluster analysis of keywords placed quality of life, anxiety, and psychological stress in the center of the visual network diagram.

Further clustering was performed for the clusters with studies of the relevant mechanism of action, which showed that: (1) Cytokines have a role essential for the occurrence and development of depressive disorders in CRC; (2) MicroRNAs have a role essential for the development of depressive disorders in CRC; (3) Some anticancer drugs have pro-depressant activity; and (4) Selective serotonin reuptake inhibitors have both antitumor and antidepressant activity.

CONCLUSION
Life quality and psychological nursing of the cancer population were key topics. The roles of cytokines and microRNAs, the pro-depression activity of anticancer drugs and their antitumor properties deserve in-depth study.

Key Words: Depression; Colorectal cancer; Bibliometric analysis; Cytokines; Drugs; Mechanism

Core Tip: Colorectal cancer (CRC) is the third leading cause of cancer-related death. The impact of psychological disorders on the treatment of CRC is significant, Patients with severe psychological disorders experience reduced quality of life, poor treatment compliance, prolonged recovery time, abnormal disease behavior, damage to social relationships, and poor survival. There is no systematic summary and comparison of the status and trend of research on the impact of depression on CRC. Bibliometric analysis is known as a method of rigorous, quantitative analysis of a large volume of data contained in the scientific literature. It is necessary to investigate the relationship between CRC and depression.

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INTRODUCTION

According to the 2022 Global Cancer Statistics, colorectal cancer (CRC) is the third leading cause of cancer-related death [1]. Advances in early diagnosis, chemotherapy, surgery, and radiation therapy for CRC have significantly increased the survival rate of CRC patients[2,3]. However, as survival has improved, a new research focus has emerged. The diagnosis of CRC and somatic discomfort is likely to cause patients to develop psychological disorders such as depression and anxiety[4,5]. The impact of psychological disorders on the treatment of CRC is significant and often manifests as pessimism, disappointment, helplessness, self-blame, and delusions of guilt. Patients with severe psychological disorders can develop symptoms of physical disorders, such as sleeping and eating difficulties; which in the long run, lead to reduced quality of life, poor treatment compliance, prolonged recovery time, abnormal disease behavior, damage to social relationships, and poor survival[6-8]. It has been shown that depression and CRC are highly correlated, with depressive disorders found in 13%-25% of CRC patients[9].

This review focuses mainly on assessing the relationship between the risk and prognosis of cancer and depression. There is no existing systematic summary and comparison of the status and trend of research on CRC with depression. Bibliometrics is a scientific method based on the literature system and bibliometrics characteristics. It applies mathematics, statistics, and other measurement methods to analyze the distribution structure, quantitative relationships, and change law[7-11]. CiteSpace and VOSviewer software can be used to evaluate the research status of scientific publications and predict future research trends. The software is stable, the results are readable and rich, and both applications have essential roles in the field of scientific bibliometrics[12-16]. The Web of Science (WoS) contains more scientific publications than other databases, which makes it a source of comprehensive data for bibliometric analysis[17-19]. It is currently the most commonly used database for bibliometric research. Therefore, this review used CiteSpace and VOSviewer to analyze the annual publication volume, countries, institutions, authors, journals, disciplines, and keywords in literature published between 2000 and 2022 and included in the core WoS database. Using the results of the bibliometric analysis, the research status of CRC patients with depressive disorder was explained and research hotspots and development trends were analyzed. This provides guidance for clinical intervention to improve the quality of life of patients with CRC.

MATERIALS AND METHODS

Data collection and retrieval strategy

In this study, the collected publication data were limited to the period from January 1, 2000, to December 31, 2022, retrieved on April 5, 2023, and downloaded as plain text from the WoS Core Collection database. The data collection and

retrieval strategy are shown in Figure 1. The retrieved publications met the following criteria: (1) The search terms were TS ("topic", including title, abstract, author keywords, and keywords Plus) as TS = ("colorectal cancer" OR "cancer of the colon" OR "colorectal malignancy" OR "colorectal tumor" OR "colorectal neoplasm" OR "colon tumor" OR "colon neoplasm") AND TS = (depressions OR depression OR depressive OR depressed OR despondent); (2) The document type was "article," and the document language was English; (3) The publication period was from 2000 to 2022; and (4) The information collected from the publications included country, author names, affiliated institutions, journal of publication, references, cited references, and keywords.

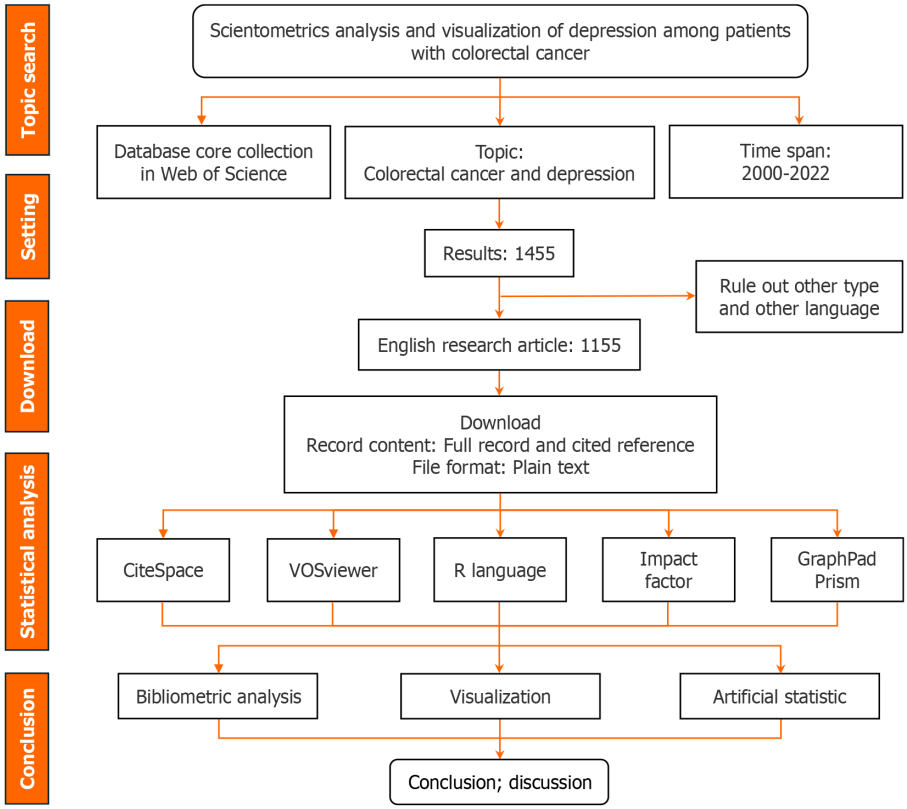


Figure 1 Flow chart of the scientometric analysis.

Data analysis

VOSviewer is a program for constructing and viewing bibliometric maps. This study used VOSviewer to analyze and visualize collaborations between institutions, journals, and authors, and keyword co-occurrence in depression disorders in CRC patients. CiteSpace is scientometric software that can generate visualizations of knowledge domains. This study used CiteSpace to analyze and visualize keyword clustering timelines, citation bursts, and journal dual map overlays. Microsoft Excel 16.63.1, GraphPad Prism 9.0, and R language 4.1.0 were used for the statistical analysis and visual graphical presentation of publication trends and the regional distribution of retrieved publications. The impact index per article values for the 10 most cited papers were obtained from Reference Citation Analysis (RCA, https://www.referencecitationanalysis.com). RCA is an open citation analysis database that spans diverse fields and is owned by Baishideng Publishing Group Inc. (Pleasanton, CA)[20-22].

RESULTS

Time trend and geographical distribution of the retrieved publications

A total of 1155 articles in the WoS Core Collection database met the search criteria. The development trend of research on depression disorders in CRC patients was reflected by the number of articles published in each period. The growth of publications on this topic was divided into two phases, a stalled stage during 2000-2008 and a rapid growth phase during 2008-2022 (Figure 2A). During 2000-2008, publication output was very low, with fewer than 30 publications per year of studies related to depression in CRC patients. During 2008-2014, the number of publications increased steadily. During 2014-2022, the number of published articles fluctuated and grew rapidly, with 102 articles published in 2020, accounting for 10% of the total publications in the previous 20 years. Overall, there has been an explosion of interest in the study of depression in CRC patients over the past two decades. Publications increased annually worldwide from 21 in 2000 to 102

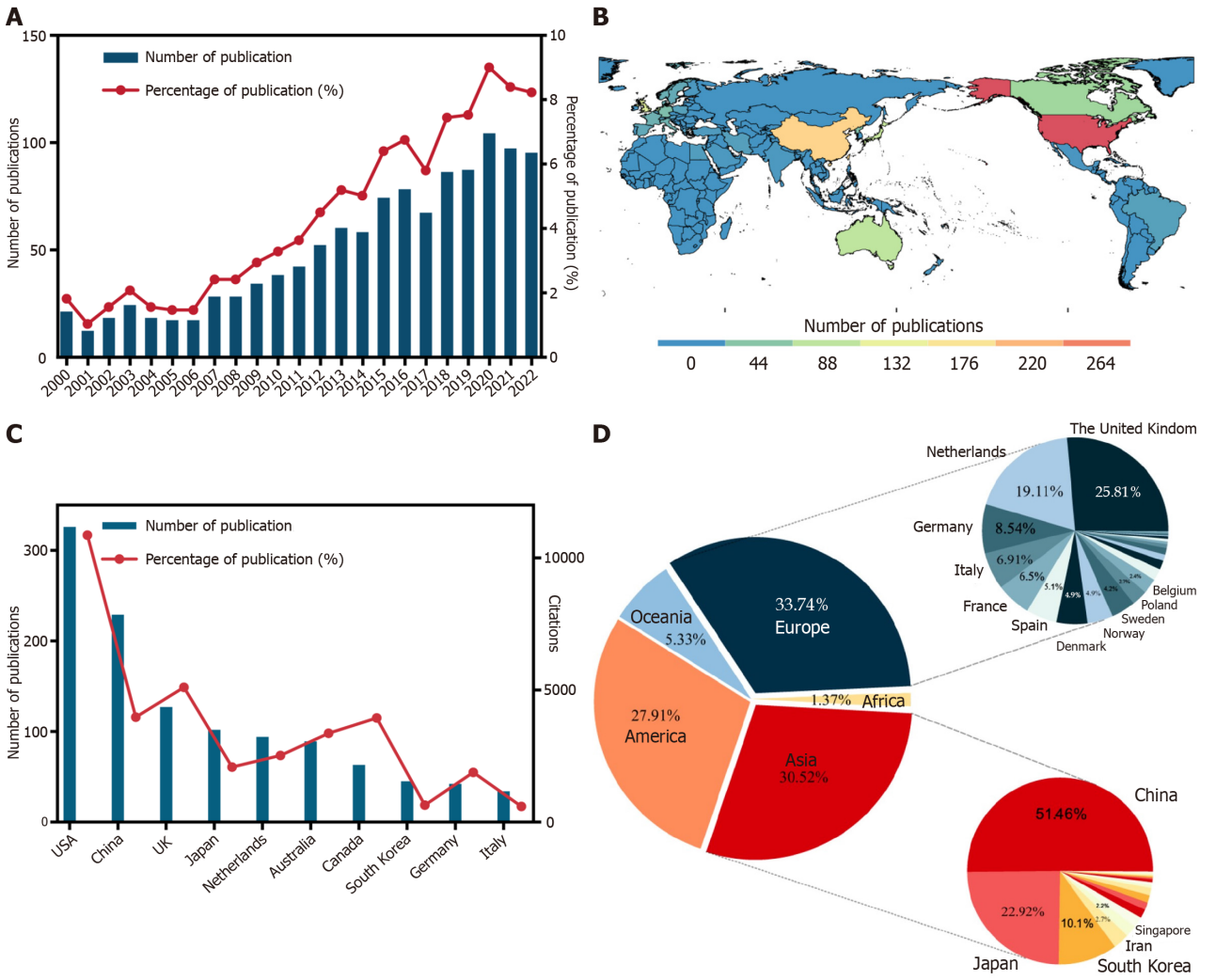


Figure 2 Global publication trend from 2000 to 2021. A: Annual publications between 2000-2021; B: Global map of publications, 2000-2021 (by country of the corresponding author); C: Continent and country distribution; D: Top 10 countries and their citations.

in 2020, an increase of 385.71%. Over half the retrieved articles were published in the last 5 years.

The overall geographical distribution of publications in this research field is shown in Figure 2B and C. Corresponding authors from European, Asian, American, and Oceanian countries published 448 (33.58%), 390 (29.24%), 384 (28.79%), and 91 (6.82%) articles, respectively. Authors from Africa published fewer studies in the field of depressive disorders in CRC patients, with 21 (1.57%) publications. The authors were from a total of 54 countries. The country with the highest number of publications (counting the number of corresponding authors) was the United States with 307 relevant articles (23.01% of the total), followed by China (196 articles, 14.69%), the United Kingdom (119 articles, 8.92%), Japan (96 articles, 7.20%), Australia (87 articles, 6.52%), and the Netherlands (85 articles, 6.37%) (Figure 2D). Twenty of the 54 countries published only one or two articles each.

Organization distribution and cooperation analysis

A total of 1700 institutions worldwide have conducted studies of CRC and the development of depression disorder. Table 1 shows the 10 most productive institutions. Tilburg University in the Netherlands ranked first, three institutions in the United States two each in China and Australia made the top 10. The analysis also listed the National Cancer Center of Japan (19) and the University of Toronto, Canada (15) in the top 10.

In terms of citations, the University of Toronto, Canada topped the list with a high citation count of 1193, followed by the University of Melbourne, Australia (1053). Duke University (United States) ranked third with 1040 citations, and was followed by Tilburg University, Netherlands (767). Combining countries and institutions showed large numbers of publications and citations in the Netherlands, Australia, and the United States, which reflects their scientific strength in this research area.

When the minimum number of articles published by the institutions met the threshold 5130, VOSviewer was used to perform a collaboration analysis of these institutions. The institutional collaboration network is shown in Figure 3A. Harvard Medical School (United States), China Medical University (China), Radboud University (Netherlands), and the Netherlands Cancer Institute have been committed to related research in the past 5 years and have made significant progress. A sudden increase in citation frequency indicated that a paper was highly cited within a specific period

Table 1 Top 10 institutions with the most published articles

Rank	Institution	Country	Publications	Citations
1	Tilburg University	Netherlands	31	767
2	The University of Hong Kong	China	24	538
3	National Cancer Center	Japan	19	360
4	The University of Melbourne	Australia	19	1053
5	University of Queensland	Australia	18	702
6	Sun Yat Sen University	China	18	437
7	University of North Carolina	United States	17	449
8	Duke University	United States	16	1040
9	Indiana University	United States	16	730
10	University of Toronto	Canada	15	1193

(Figure 3B). China Medical University, Radboud University, and Harvard Medical School were the most highly cited institutions in recent years for publications on depressive disorders associated with CRC.

Journals and co-cited journals

We used CiteSpace and VOSviewer software to visually analyze the journals and co-cited journals. The results showed that 1060 articles related to depressive disorder in CRC patients were published in 417 academic journals. When the minimum number of journal publications was set to three, 90 journals met the criteria. Figure 4A shows the collaborative analysis of these 90 journals using VOSviewer software. The cooperative network included 86 journals, and the journal *Supportive Care in Cancer* had the most partners (n = 43). *Cancer Medicine*, *Trails*, *Oncology Letters*, and *Biomed Research International* accepted more articles on related topics in the past 5 years. *Supportive Care in Cancer* (64, 6.0%) had the most publication, followed by *Psycho-Oncology* (57, 5.4%) (Table 2). Of the top 10 academic journals, the *Journal of Clinical Oncology* had the highest impact factor (*IF*, 44.544). In addition, the influence of a journal is determined by the number of times it is co-cited, which indicates whether it has a significant influence in a particular research area. Three of the top 10 academic journals had more than 1000 citations. The most cited journal was *Supportive Care in Cancer* (1856), followed by *Psycho-Oncology* (1605) (Table 2). Almost all the articles related to depression in CRC patients were published in low-impact factor (*IF* < 7) journals, indicating the need for further high-quality research in this area. According to the 2022 Journal Citation Report (JCR), there were two journals in the Q1 region, the *Journal of Clinical Oncology* and *Cancer*. The source journals of cited literature were mainly distributed in medicine, medical, clinical, and neurology (left side of Figure 4B). The cited literature in this direction were primarily in the disciplines of health, nursing, medicine, and psychology, indicating that the research on knowledge-based dynamic capabilities mainly focused on medical and health care.

Co-occurrence of authors and the top 10 most productive and cited authors

The 1060 retrieved articles were published 24310 times by 16298 authors. Each article had an average of six authors. Table 3 lists the top 10 most productive authors. Mols (23 publications, 495 citations) ranked first, followed by Van de Poll-Franse (18 publications, 460 citations), and Thong (nine publications, 307 citations). The author collaboration network is shown in Figure 5. The collaborative network of 32 authors was divided into five color-coded clusters. The green cluster consisting of 12 authors centered on Mols was the largest cluster and Mols also had the most partners (n = 12), followed by Van de Poll-Franse (n = 11), and Weijenberg (n = 7).

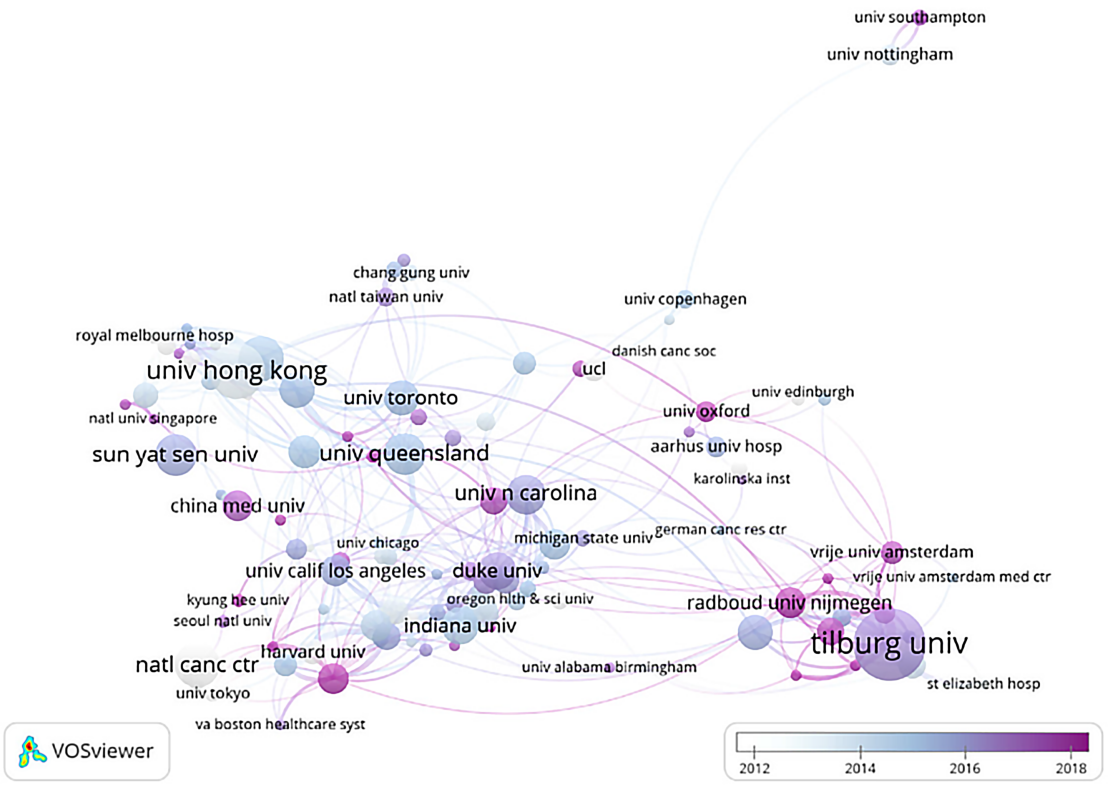
Analysis of cited literature

Co-citation is a research method used to measure the degree of relationship between articles. It involves two or more articles being cited by one or more papers simultaneously, indicating a co-citation relationship. The 1060 retrieved publications cited 33596 references. Table 4 lists the top 10 co-cited references, with citations ranging from 31 to 207. The most cited reference was "The hospital anxiety and depression scale," published in *Acta Psychiatrica Scandinavica* in 1983. Collaborative analysis of co-cited literature was performed using VOSviewer. We set the minimum number of co-citations to 25, and 16 of the 33596 co-cited articles met the criterion. In addition, according to the *RCA*, six of the 10 most cited papers had an impact index of more than 100. The collaborative network of co-cited articles was centered on the hospital anxiety and depression scale (Figure 6A), indicating that 12 of the articles with a total of more than 25 citations cited this reference. The first co-citation surge began in 2000 (Figure 6B). For over two decades, most co-cited references have been cited frequently.

Keywords analysis

Keywords indicate the main topics of publications, the co-occurrence analysis clustered the keywords in the network to reflect the basic knowledge structure of related research fields. We used VOSviewer software to cluster 4373 keywords

A



B

Top 10 institutions with the strongest citation bursts

Institutions	Year	Strength	Begin	End	2000 - 2022
National Cancer Center - Japan	2001	3.67	2001	2007	
National Institutes of Health (NIH) - USA	2005	4.46	2008	2016	
Veterans Health Administration (VHA)	2007	4.56	2010	2017	
US Department of Veterans Affairs	2007	4.56	2010	2017	
University of Texas System	2012	3.56	2012	2013	
King's College London	2013	4.25	2013	2015	
Sun Yat Sen University	2006	3.74	2014	2017	
Radboud University Nijmegen	2017	4.1	2017	2022	
University of Amsterdam	2004	3.59	2017	2022	
Institut National de la Sante et de la Recherche Medicale (Inserm)	2002	3.66	2018	2020	

Figure 3 Cooperation map of institutes. A: VOSviewer visualization map of the co-authorship network of institutions. The visualization map of publications for 121 institutions; a node represents one institution, the node size represents the number of publications, a link shows collaboration, and the distance and the thickness of the link between nodes show the relative strength of the relation. The color of each circle is determined by the year of publication, the darker the color, the more recent the publication; B: CiteSpace visualization map of top 10 institutions with strongest citation bursts. Red bars mean that some institutions are cited frequently in a certain period.

extracted from the literature. We set the minimum number of keyword occurrences to five, and a total of 414 keywords met the criteria (Figure 7A). The keywords quality of life (number of occurrences: 353), anxiety (157), psychological stress (98), hospital anxiety (97), and survival (95) are at the center of the network diagram. VOSviewer automatically divided the keywords with similarities into nine clusters, which are shown in nine different colors, each representing different research directions. Table 5 shows the top 100 keywords according to frequency. Analysis on the red cluster, which had the largest range (Figure 7B), using the connotation of the keywords and eliminating marginal words found the following categories: (1) Cytokines in CRC depressive disorder patients, including four keywords, cytokines, interleukin-2 (IL-2), IL-6, and activation; (2) The role of microRNAs in patients with depressive disorders in CRC, including five keywords, microRNA, brain, gene expression, inhibition, and cell proliferation; (3) Pro-depressant properties of anticancer drugs, including five keywords, 5-fluorouracil, fluorouracil, gut microbiota, oxaliplatin, and peripheral neuropathy; and (4) Antitumor properties of antidepressant selective serotonin reuptake inhibitors (SSRIs), including eight keywords, antidepressants, tricyclic antidepressants, serotonin reuptake inhibitors, apoptosis, toxicity, nonsteroidal anti-inflammatory drugs, neurotoxicity, and aspirin.

Figure 7C shows the top 30 keywords that had sudden increases in citation frequency. The results showed that the prognosis of cancer survivors and improving the quality of life of the diseased population may become research hotspots. The timeline viewer of CiteSpace takes into account the interaction and variation relationship between keywords in a certain field, which helps to explore the evolutionary trajectory and stage characteristics of the research field.

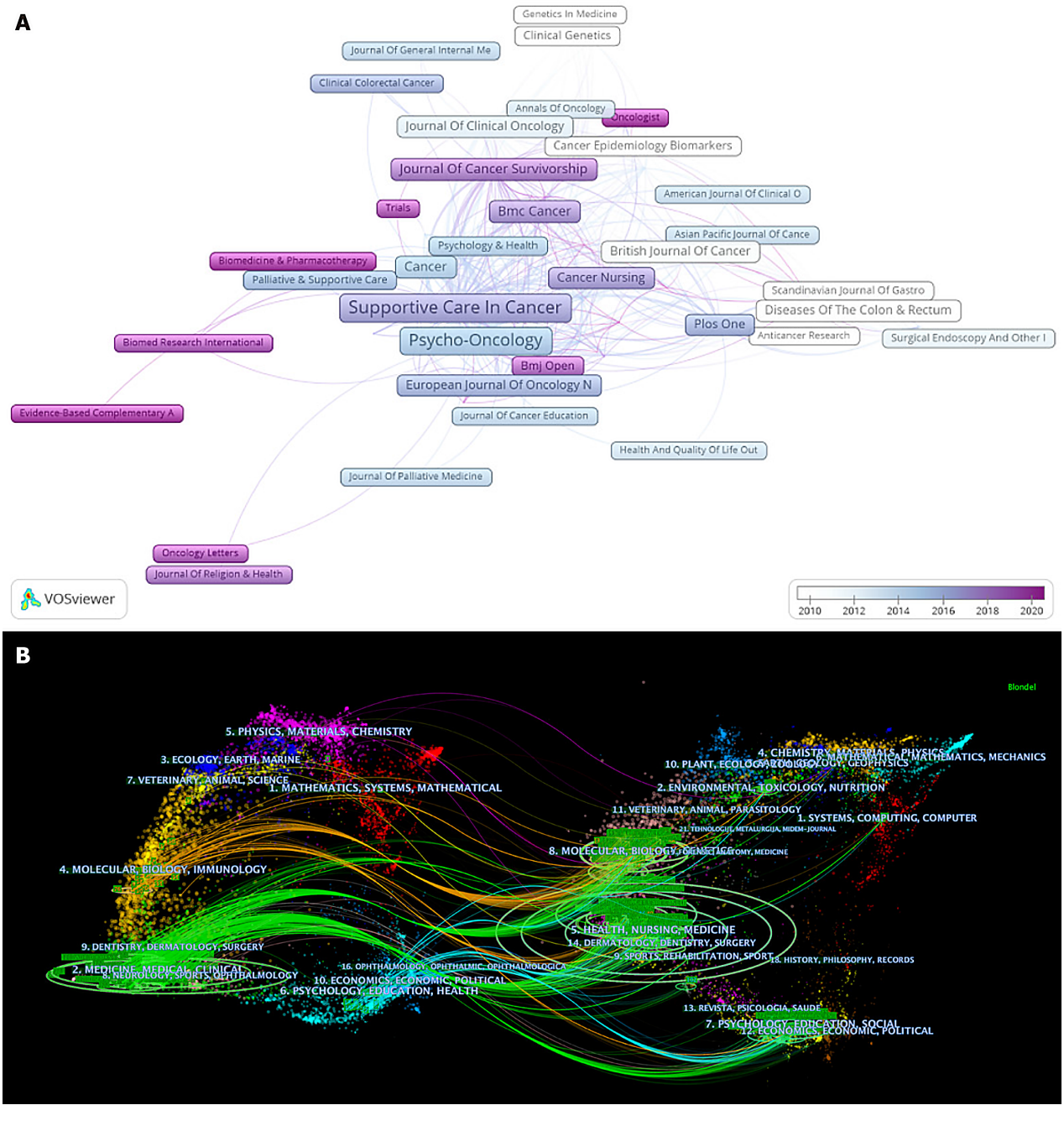


Figure 4 Cooperation map of journals. A: VOSviewer visualization map of the co-authorship network of journals. Visualization map of publications in 90 journals; a node represents one journal, the node size represents the number of publications, a link shows collaboration, and the distance and the thickness of the link between nodes show the relative strength of the relation. The color of each circle is determined by the year of publication; the darker the color, the more recent the publication; B: A dual map overlay of the science mapping literature. A dual map overlay of journals shows the distribution of relationships between journals, citing journals on the left and cited journals on the right, with colored paths connecting them indicating citation relationships and their thickness indicating co-citation strength. The color corresponds to the time when the node was first co-cited.

DISCUSSION

Depression and CRC are highly correlated[20]. Few bibliometric studies on the research focus and recent research progress in this field have been published. Bibliometric analysis can supplement traditional reviews to help researchers understand the temporal and regional trends of research on depressive disorders in patients with CRC. It reveals the quantity and quality of relevant literature and the characteristics of country/institution/author collaborations. It also helps to quickly understand the academic frontiers in the field of depressive disorders in CRC patients and find suitable collaborators. This study used CiteSpace and VOSviewer software to systematically summarize articles about depression in CRC patients in the WoS Core Collection and visualize the interactions of countries, institutions, authors, references, and keywords in this research field in network maps. We aimed to visualize depression-related CRC research hotspots and trends through bibliometric analysis and to elucidate the evolution and future directions of basic and clinical research in this field.

Table 2 Top 10 journals with the most published articles

Rank	Source	JCR	*IF* (2022)	Total publications	Total citations
1	*Supportive Care in Cancer*	Q2	3.359	64 (6.0%)	1856
2	*Psycho-Oncology*	Q4	3.955	57 (5.4%)	1608
3	*Cancer*	Q1	6.921	23 (2.2%)	677
4	*Journal of Cancer Survivorship*	Q2	4.062	22 (2.1%)	664
5	*BMC Cancer*	Q2	4.638	19 (1.8%)	439
6	*Diseases of the Colon & Rectum*	Q2	4.412	17 (1.6%)	252
7	*World Journal of Gastroenterology*	Q3	5.374	17 (1.6%)	384
8	*PLOS ONE*	Q3	3.752	16 (1.5%)	596
9	*European Journal of Oncology Nursing*	Q2	2.588	15 (1.4%)	336
10	*Journal of Clinical Oncology*	Q1	50.717	13 (1.2%)	1464

Table 3 Top 10 authors with the most published articles

Rank	Source	Total publications	Total citations
1	Mols	25	492
2	Van de Poll-Franse	18	457
3	Weijenberg	11	162
4	Thong	10	306
5	Husson	9	227
6	Hebert	8	282
7	Miaskowski	7	83
8	Bours	7	38
9	Shivappa	6	223
10	Griffin	6	220

Global trends in research on depressive disorders in patients with CRC

Psychological factors such as depression and anxiety can lead to the occurrence and development of cancer[20-23], and CRC development is a complex multifactorial process. Because of the special location of CRC, many patients cannot take care of themselves for a long time after bowel resection. That places enormous psychological pressure on patients and their families, and effectively induces depression. The 5-year survival rate and prognosis of CRC are higher than for other malignant diseases. Through effective psychotherapy, patients' negative emotions can be effectively eliminated, and confidence in treatment can be established[24,25]. There has been growing support for routine depression screening of cancer patients in primary care settings[26]. After a long period of accumulation of knowledge, research on depression in patients with CRC entered a period of rapid development. In the past two decades, the number of articles increased steadily. Although it fluctuated slightly in some years, it increased from 21 in 2000 to 102 in 2020, an increase of 385.71%. The number of articles published in the last 5 years accounted for more than half of the total published after 2000. In the past decade, research on depressive disorders in CRC patients increased significantly. The increase in the number of publications may be due to several factors. First, the overall increase in the output of academics, institutions, journals, and global scientific research in the medical field positively impacted the number of publications for depressive disorders in CRC patients. Second, some findings regarding the scientific link between depression and poor prognosis in oncology patients have triggered more research in this field. It is well documented that there is a bidirectional relationship between CRC and depression and depression as a potential risk factor for cancer[27-30].

A total of 16298 authors from 1700 research institutions in 54 countries have published on depressive disorders in CRC patients, indicating widespread global attention. The 10 institutions with most publications included three in the United States, two each in China and Australia, and the remaining three from the Netherlands, Japan, and Canada. Quantitatively, the United States was the most productive country, with the most publications on related topics and the most institutions at the forefront of research. As indicated by the institutional collaboration network, 93% of the institutions studying depressive disorders in CRC patients were in a collaborative network. Most institutions had extensive collaboration among researchers regardless of geography and language, but some institutions and countries were relatively less involved. The study of depressive disorders in CRC patients is a relatively new intersection of oncology and psychology,

Table 4 Top 10 most co-cited references

Rank	Year	Journal	Title	Citation	Impact index	Ref.
1	1983	*Acta Psychiatrica Scandinavica*	The hospital anxiety and depression scale	214	719.3	Zigmond *et al* [74], 1983
2	1993	*Journal of the National Cancer Institute*	The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology	93	339.5	Aaronson *et al* [75], 1993
3	2001	*Psycho-Oncology*	The prevalence of psychological distress by cancer site	48	69.7	Zabora *et al* [76], 2001
4	1993	*Endoscopy*	Endoscopic mucosal resection of flat and depressed types of early colorectal cancer	44	17.4	Kudo *et al*[77], 1993
5	2002	*Journal of Psychosomatic Research*	The validity of the Hospital Anxiety and Depression Scale-An updated literature review	39	305.1	Bjelland *et al* [78], 2002
6	2003	*Arthritis & Rheumatism-Arthritis Care & Research*	The self-administered comorbidity questionnaire: A new method to assess comorbidity for clinical and health services research	39	62.5	Sangha *et al* [79], 2003
7	1987	*Journal of Chronic Diseases*	A new method of classifying prognostic comorbidity in longitudinal studies: development and validation	38	949.4	Charlson *et al* [80], 1987
8	1979	*Psychosomatic Medicine*	Impact of Event Scale: a measure of subjective stress	35	104.2	Horowitz *et al* [81], 1979
9	1993	*Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*	The Functional Assessment of Cancer Therapy scale: development and validation of the general measure	33	132.4	Cella *et al*[82], 1993
10	2000	*Lancet*	Flat and depressed colonic neoplasms: a prospective study of 1000 colonoscopies in the United Kingdom	31	19.5	Rembacken *et al* [83], 2000

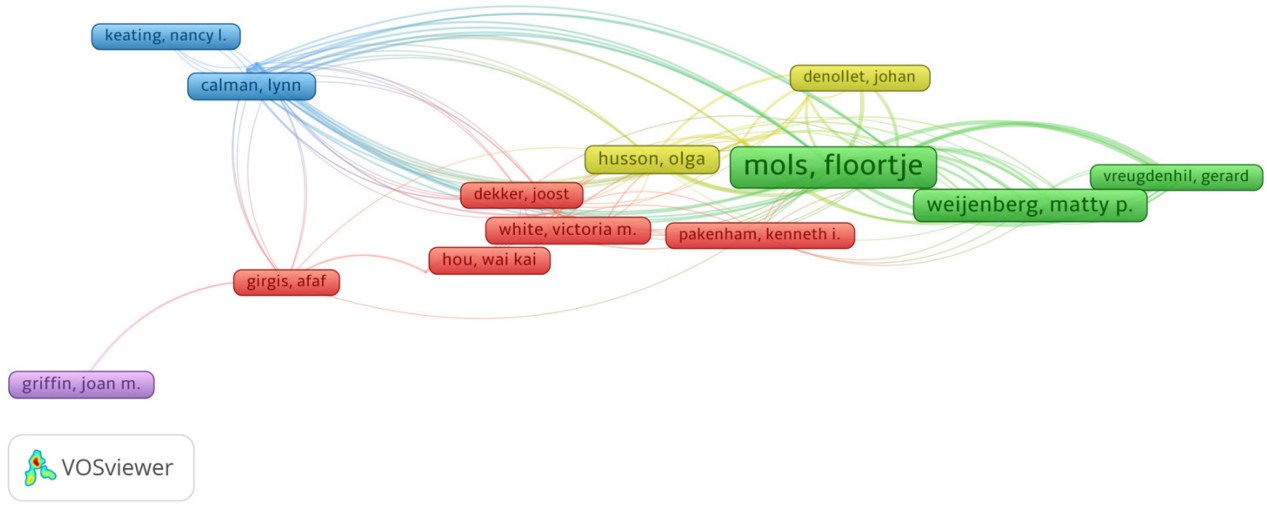


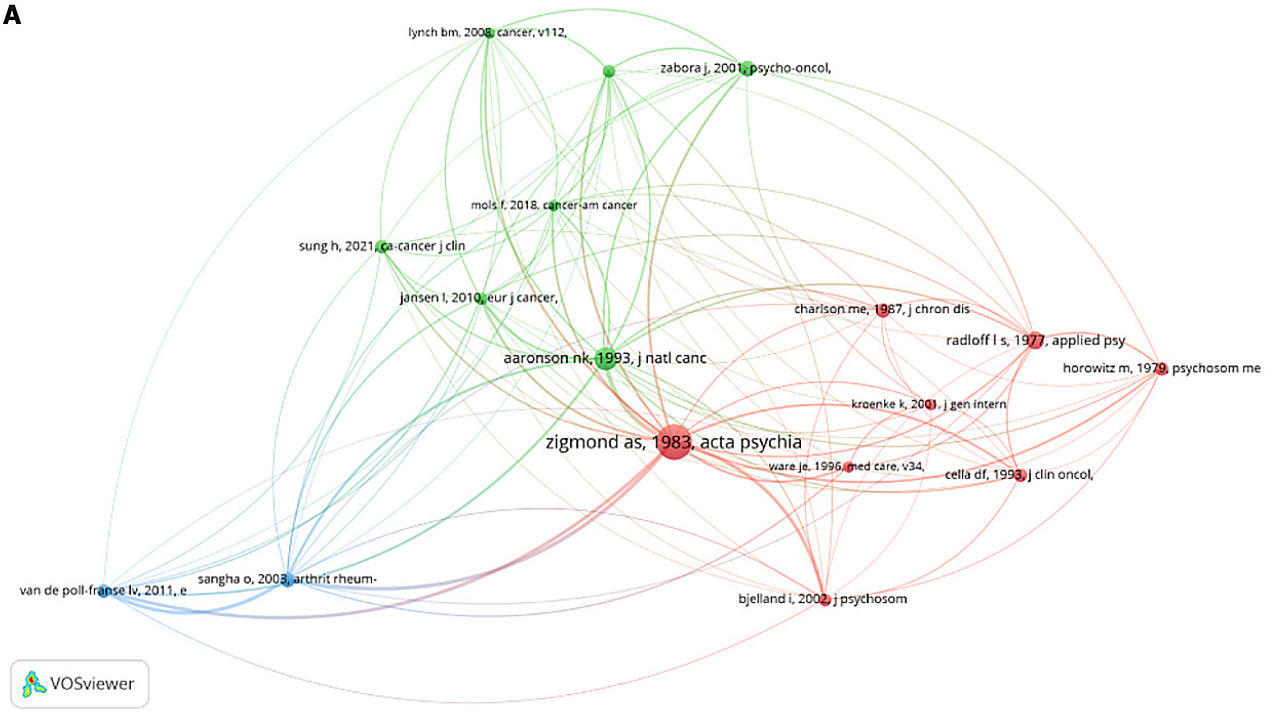
Figure 5 VOSviewer visualization map of the co-authorship network. Cluster maps of the authors who appeared at least three times. Visualization map of publications of 199 authors forming five collaborating clusters (nodes with the same color). A node represents an author, the size of the node represents the number of publications, a link shows collaboration, and the distance and the thickness of the link between nodes show the relative strength of the relation.

and almost all of the top 10 most prolific journals are affiliated with the discipline of oncology.

Research hotspots and emerging frontiers of depressive disorder in patients with CRC

Co-citation analysis of the cited literature showed that almost all of the top 10 research topics in the cited references were on the risk and assessment of depression in cancer populations; and all of the top 10 co-cited references were published before 2005. That indicates the level of research in this area was still in an early stage of development. A co-occurrence cluster analysis of the top 414 keywords revealed nine major research clusters for depressive disorders in CRC patients in 2000-2022. Only one of these clusters had a research scope related to the physiological mechanisms of the bidirectional effects of CRC and depression. The research directions of the other eight clusters focused primarily on the risk of depression in cancer patients and on palliative care and psychological interventions for psychological factors such as

A



B

Top 20 references with the strongest citation bursts

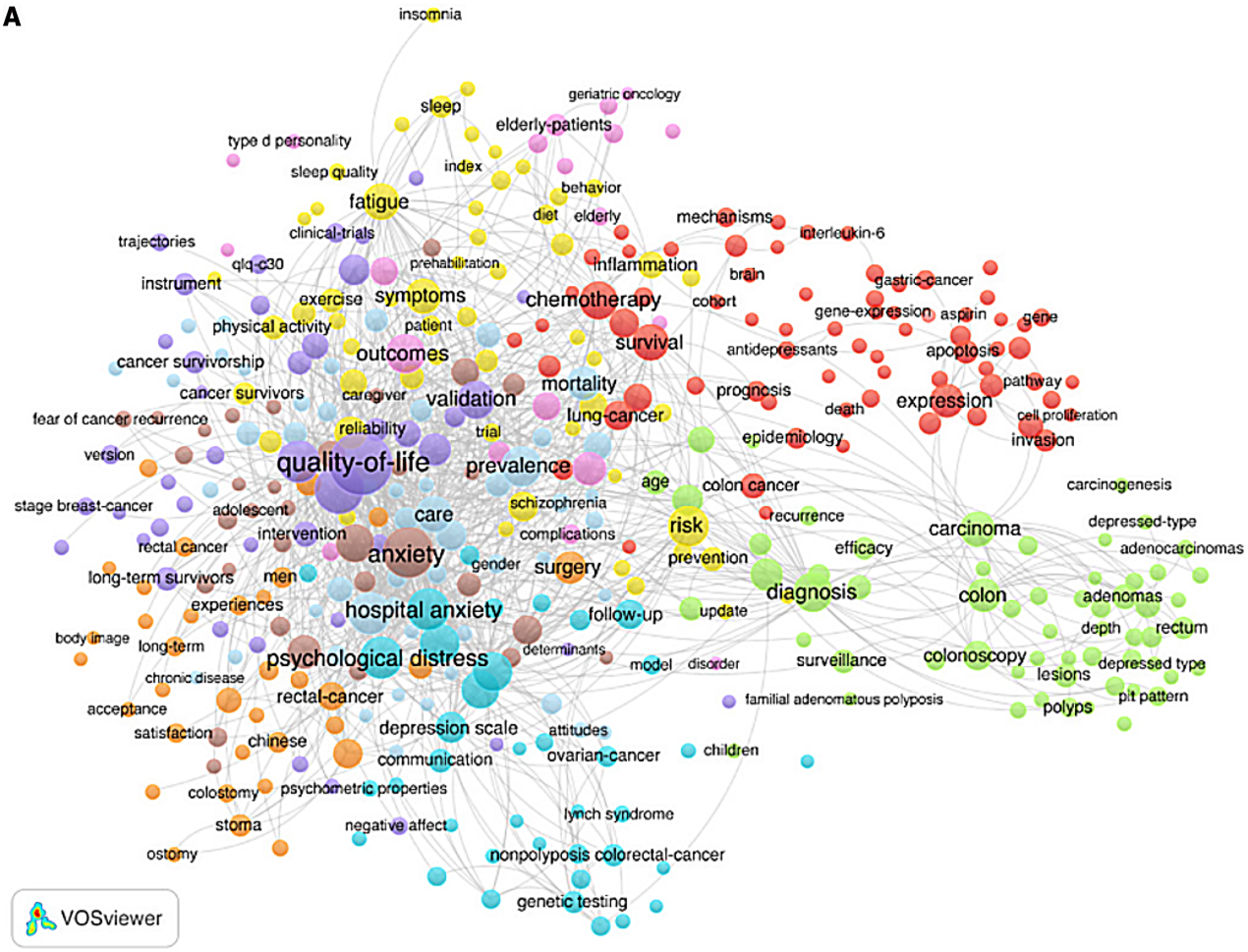
References	Year	Strength	Begin	End	2000 - 2022
Rembacken BJ, 2000, LANCET, V355, P1211, DOI 10.1016/S0140-6736(00)02086-9, DOI	2000	5.26	2003	2005	
Saitoh Y, 2001, GASTROENTEROLOGY, V120, P1657, DOI 10.1053/gast.2001.24886, DOI	2001	3.89	2003	2006	
Aktan-Collan K, 2001, INT J CANCER, V93, P608, DOI 10.1002/ijc.1372, DOI	2001	3.31	2004	2005	
Lynch BM, 2008, CANCER, V112, P1363, DOI 10.1002/cncr.23300, DOI	2008	5.21	2009	2013	
van de Poll-Franse LV, 2011, EUR J CANCER, V47, P2188, DOI 10.1016/j.ejca.2011.04.034, DOI	2011	5.61	2012	2013	
Thong MSY, 2011, INT J RADIAT ONCOL, V81, PE49, DOI 10.1016/j.ijrobp.2010.12.030, DOI	2011	4.44	2012	2013	
Jansen L, 2011, J CLIN ONCOL, V29, P3263, DOI 10.1200/JCO.2010.31.4013, DOI	2011	4.08	2013	2016	
Jemal A, 2011, CA-CANCER J CLIN, V61, P134, DOI 10.3322/caac.20115, DOI	2011	3.38	2013	2015	
Mitchell AJ, 2011, LANCET ONCOL, V12, P160, DOI 10.1016/S1470-2045(11)70002-X, DOI	2011	6.37	2014	2016	
Gray NM, 2011, BRIT J CANCER, V104, P1697, DOI 10.1038/bjc.2011.155, DOI	2011	3.9	2014	2016	
Gray NM, 2014, SUPPORT CARE CANCER, V22, P307, DOI 10.1007/s00520-013-1963-8, DOI	2014	3.77	2014	2016	
Dunn J, 2013, PSYCHO-ONCOLOGY, V22, P1759, DOI 10.1002/pon.3210, DOI	2013	5.3	2015	2018	
Siegel R, 2014, CA-CANCER J CLIN, V64, P9, DOI 10.3322/caac.21208, DOI	2014	4.43	2015	2017	
Dunn J, 2013, HEALTH QUAL LIFE OUT, V11, P0, DOI 10.1186/1477-7525-11-46, DOI	2013	3.44	2015	2017	
Torre LA, 2015, CA-CANCER J CLIN, V65, P87, DOI 10.3322/caac.21262, DOI	2015	3.43	2016	2020	
Ferlay J, 2015, INT J CANCER, V136, PE359, DOI 10.1002/ijc.29210, DOI	2015	4.24	2017	2020	
Mosher CE, 2016, PSYCHO-ONCOLOGY, V25, P1261, DOI 10.1002/pon.3954, DOI	2016	3.62	2018	2022	
Krebber AMH, 2014, PSYCHO-ONCOLOGY, V23, P121, DOI 10.1002/pon.3409, DOI	2014	3.23	2018	2019	
Sung H, 2021, CA-CANCER J CLIN, V71, P209, DOI 10.3322/caac.21492, DOI	2021	12.34	2021	2022	
Chen WQ, 2016, CA-CANCER J CLIN, V66, P115, DOI 10.3322/caac.21338, DOI	2016	5.44	2019	2022	

Figure 6 Cluster map of references. A: VOSviewer visualization map of the co-citation network of references. The cooperative network consists of 12 articles divided into four clusters represented by different colors. The node size indicates the number of citations, and the connecting line indicates a cooperative relationship between the two articles; B: CiteSpace visualization map of top 30 references with strongest citation bursts. Red bars indicate references that were cited frequently in a certain period.

depression and anxiety to improve patient quality of life and survival. In 2005, the National Academy of Medicine published a seminal report titled, "Cancer Patient to Cancer Survivor: Lost in Transition," which proposed cancer recovery as part of cancer survivor care. Although few articles examined the causal relationship between depression and CRC development, several epidemiological studies found that aggravation and progression of established malignant diseases caused by psychological factors such as depression and anxiety were almost always related to activation of the sympathetic nervous system induced by psychological factors[31-33].

Study of the mechanism of depression in patients with CRC

Despite growing evidence supporting that CRC patients were prone to depressive disorders and that the interaction between tumor and depression tended to exacerbate patients' physical and mental illnesses in a vicious cycle[34], the common mechanisms remain incompletely elucidated. Therefore, we conducted a more detailed keyword analysis of the red cluster to explore the physiological mechanisms of the bidirectional effects of CRC and depression. Using connotation


A
insomnia
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geriatric oncology
elderly-patients
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sleep quality
index
behavior
fatigue
diet
elderly
mechanisms
interleukin-6
trajectories
clinical-trials
qlq-c30
prehabilitation
inflammation
brain
gastric-cancer
instrument
exercise
symptoms
chemotherapy
cohort
gene-expression
aspirin
gene
physical activity
patient
survival
antidepressants
apoptosis
cancer survivorship
outcomes
mortality
prognosis
pathway
cancer survivors
caregiver
validation
lung-cancer
death
expression
cell proliferation
fear of cancer recurrence
reliability
trial
epidemiology
invasion
version
quality-of-life
prevalence
age
colon cancer
carcinogenesis
stage breast-cancer
adolescent
schizophrenia
care
recurrence
risk
carcinoma
depressed-type
intervention
complications
efficacy
adenocarcinomas
rectal cancer
anxiety
gender
surgery
prevention
long-term survivors
men
diagnosis
colon
adenomas
experiences
hospital anxiety
follow-up
update
depth
rectum
body image
long-term
determinants
psychological distress
model
disorder
surveillance
colonoscopy
depressed type
chronic disease
lesions
rectal-cancer
familial adenomatous polyposis
pit pattern
acceptance
polyps
satisfaction
depression scale
attitudes
chinese
communication
ovarian-cancer
children
colostomy
psychometric properties
lynch syndrome
stoma
negative affect
ostomy
nonpolyposis colorectal-cancer
genetic testing
VOSviewer
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Occurrences
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15
20
Apoptosis
Invasion
Activation
Oxaliplatin
Toxicity
Cytokines
Antidepressants
Fluorouracil
Gene-expression
Inhibition
Longitudinal study
Microrna
Neurotoxicity
Peripheral neuropathy
5-fluorouracil
Aspirin
Brain
Interleukin-6
Serotonin reuptake inhibitors
Angiogenesis
Cell proliferation
Gut microbiota
Interleukin-2
Nonsteroidal antiinflammatory drugs
Radiotherapy
Renal-cell carcinoma
Tricyclic antidepressants

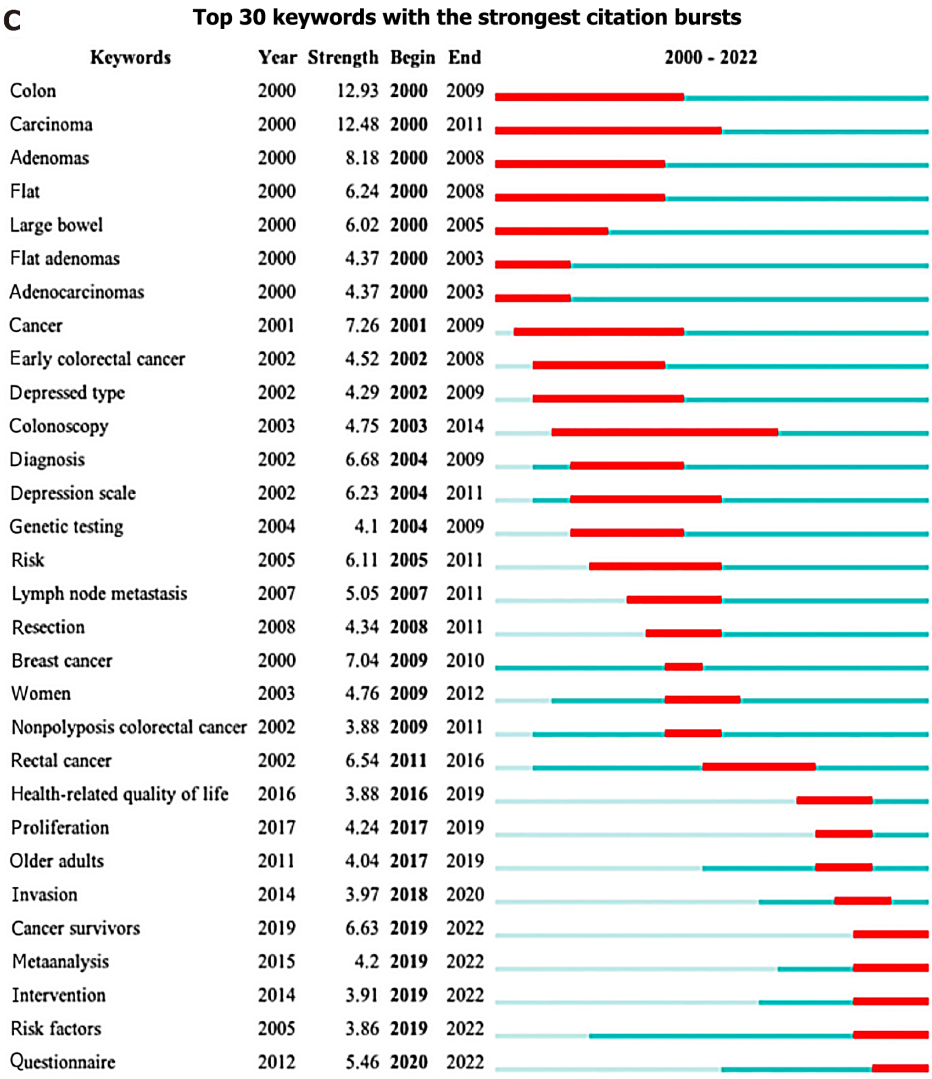

Figure 7 Cluster map of keywords. A: Co-occurrence cluster analysis of the top 414 Keywords. Cluster map of authors who appeared at least five times. Visualization map of publications by 414 authors forming nine collaborating clusters (nodes with the same color). The node labels show the keywords, and the size of each node refers to the frequency of the keywords. A link connecting two nodes represents a co-occurrence relationship between two keywords. Circles and labels form a cell, and cells of different colors form different clusters; B: The main keywords contained in the red cluster and their occurrences; C: CiteSpace visualization map of top 30 keywords with strongest citation bursts. Red bars mean that some keywords are cited frequently in a certain period.

analysis of the keywords appearing in this cluster, we classified study of the molecular and physiological mechanisms underlying the mechanism in the following directions.

Role of cytokines in development of CRC depressive disorder

Four keywords were associated with this research direction, cytokines, IL-2, IL-6, and activation. Severe psychological stress can cause not only stressful depressive symptoms but can also lead to activation of the hypothalamic-pituitary-adrenal axis, which induces an inflammatory response that leads to release of inflammatory cytokines that may result in increased cytokine levels[35]. Animal experiments have shown that cancer can induce inflammation and lead to depressive-like pathological behavior in mice[35]. The tumor microenvironment includes tumor cells and surrounding lymphocytes that can produce a variety of cytokines[36]. Tumor-cell burden, tumor-induced tissue damage, infection, and other biogenic stresses can activate inflammatory cytokines[37]. Therefore, based on the inflammatory pathogenesis hypothesis of depression described above, cytokines may be involved in the pathogenesis of cancer associated with depressive symptoms, the appearance of which is not caused only by psychological stress[38]. It has been speculated that peripheral inflammatory cytokines may reach the brain through multiple pathways[39], causing disease behavior similar to depressive symptoms[40].

Cytokines are a class of small soluble peptide proteins secreted by immune and tissue cells and have a reciprocal regulatory role between cells. They not only regulate immune responses by binding to corresponding receptors, participate in inflammatory responses, and promote a variety of inflammatory diseases, but they also act on the central nervous system, causing related mood disorders[41]. Therefore, inflammatory cytokines may be intermediate mediators that have an essential role in the pathogenesis of depressive disorders in cancer patients. However, the inflammatory

Table 5 Clusters of the top 100 keywords

Cluster	Keyword	Count	Rank	Cluster	Keyword	Count	Rank
1	Chemotherapy	72	13	4	Colonoscopy	38	33
1	Survival	66	17	4	Risk-factors	27	46
1	Expression	53	22	4	Adenomas	24	50
1	Therapy	35	35	4	Flat	23	54
1	Association	33	38	4	Screening	22	60
1	Metastasis	24	48	4	Resection	20	68
1	Apoptosis	22	56	4	Surveillance	20	69
1	Invasion	18	76	4	Lesions	19	73
1	Activation	17	81	4	Efficacy	16	92
1	Cancer patient	17	82	4	Guidelines	16	93
1	Oxaliplatin	17	83	4	Endoscopic mucosal resection	15	96
1	Proliferation	17	84	5	Quality-of-life	425	1
1	Prognosis	15	95	5	Anxiety	157	2
1	Epidemiology	14	99	5	Psychological distress	98	3
1	Mechanisms	13	102	5	Survivors	95	5
2	Prevalence	88	8	5	Health	92	6
2	Women	81	9	5	Care	62	19
2	Impact	72	14	5	Social support	54	21
2	Mortality	53	23	5	Surgery	44	28
2	Follow-up	35	36	5	Stress	37	34
2	Comorbidity	31	40	5	Adjustment	35	37
2	Disorders	24	49	5	Intervention	24	51
2	Mental health	23	53	5	Self-efficacy	24	52
2	Age	21	62	5	Of-life	23	55
2	Interventions	21	63	5	Randomized controlled-trial	22	61
2	Adults	19	70	5	Stoma	18	79
2	Burden	19	71	6	Validation	71	15
2	Quality	19	72	6	Population	52	24
3	Risk	90	7	6	Predictors	45	27
3	Fatigue	65	18	6	Questionnaire	39	31
3	Symptoms	61	20	6	Validity	28	45
3	Depressive symptoms	48	26	6	Functional assessment	26	47
3	Prostate cancer	38	32	6	Reliability	21	66
3	Meta-analysis	31	41	6	Health-related quality of life	19	74
3	Inflammation	29	43	6	Long-term survivors	19	75
3	Physical activity	29	44	6	Instrument	17	88
3	Breast cancer	22	57	6	Personality	14	100
3	Exercise	22	58	7	Hospital anxiety	97	4
3	Survivorship	22	59	7	Distress	81	10
3	Physical activity	21	64	7	Depression scale	42	29
3	Prevention	21	65	7	Communication	21	67

3	Cancer survivors	18	77	7	Nonpolyposis colorectal-cancer	17	89
3	Patient-reported outcomes	18	78	7	Genetic testing	16	94
3	Adjuvant chemotherapy	17	85	7	Experience	15	97
3	Older adult	17	86	7	Ovarian-cancer	14	101
3	Sleep	17	87	8	Oncology	68	16
3	Cancer survivorship	16	91	8	Scale	33	39
4	Diagnosis	79	11	8	Pain	30	42
4	Colon	50	25	8	Life	15	98
4	Management	39	30	9	Outcomes	75	12
4	Colonoscopy	38	33	9	Morbidity	18	80

cytokines that contribute to the development of depressive symptoms may differ in patients with different cancers. Some studies have found that the plasma IL-6 level of cancer patients with depression was significantly higher than that of cancer patients without depression, suggesting that the occurrence of cancer-related depression may be related to an increase in plasma IL-6 level[42,43]. Studies have shown that recombinant IL-2 may cause psychological and psychiatric problems in patients with CRC[44], but the mechanism was not investigated. The pathogenesis of CRC may be related to chronic inflammation[45]. It is speculated that elevated levels of inflammatory mediators may be a risk factor for depressive symptoms in patients with CRC. It is therefore worth considering controlling its level as a potential therapeutic target[46].

The role of microRNA in the development of depressive disorders in CRC

There are five keywords in this research direction, microRNA (miRNA), brain, gene expression, inhibition, and cell proliferation. Unlimited replicative capacity is the key to carcinogenesis. MiRNAs regulate genes involved in checkpoints, DNA repair, and genes encoding essential proteins that regulate the cell cycle. They affect mRNA translation at multiple levels within the cell cycle, which has crucial roles in CRC development[47]. Cognitive dysfunction is considered a trait symptom of depression and one of the leading causes of poor social function recovery in patients in remission. Growing evidence suggests that plasma-circulating miRNAs may be biomarkers of cognitive impairment in cancer patients. The primary function of miRNAs is to regulate gene expression at the post-transcriptional level, thereby inhibiting the translation or degradation of mRNA[48]. Some miRNAs are essential regulators of multiple biological functions in the brain, such as synaptic plasticity and neurogenesis. They may indirectly affect neurogenesis by regulating the proliferation and repair of neural stem cells. The most critical miRNAs associated with cognitive impairment are miRNA-206, miRNA-132, and miRNA-134. These miRNAs are overexpressed in patients with cognitive impairment, and even higher levels of miRNAs are associated with the rate of cognitive decline. Several studies have shown that detection of these miRNAs can be useful for early diagnosis of mild cognitive impairment[49-51].

Pro-depressant effects of anticancer drugs 5-fluorouracil and oxaliplatin

There were five keywords in this research direction, 5-fluorouracil (5-Fu), fluorouracil, gut microbiota, oxaliplatin, and peripheral neuropathy. For many years, 5-Fu and its derivatives have been the first choice for chemotherapy in CRC[52]. However, studies have indicated that 5-Fu has the potential to harm the intestinal mucosa, resulting in gastrointestinal symptoms like vomiting and diarrhea[53], decreasing the relative abundance of Firmicutes[54], and increasing the prevalence of Bacteroidetes, Actinomycetes, and warts microflora[55]. This, in turn, leads to an ecological dysbiosis or structural imbalance of the intestinal microbiota and metabolic disturbances in the intestinal flora and prefrontal cortex. Numerous studies, including functional imaging, lesion tissue studies, and brain stimulation studies, provide extensive neuroscientific evidence supporting a strong correlation between depressive disorders and the prefrontal cortex[56,57]. Several studies have employed rat models to examine this hypothesis and investigate whether the chemotherapeutic drug 5-Fu triggers symptoms of depression. Experimental results have consistently shown that 5-Fu induced depressive-like behavior in rats, as evidenced by a lack of pleasure and behavioral despair[58-60]. Similarly, chemotherapy-induced peripheral neuropathy caused by oxaliplatin can significantly affect the quality of life of patients with CRC[61,62]. We speculate that patients with CRC may develop depressive disorders through the action of fluorouracil analogs, oxaliplatin, and other chemotherapy drugs during chemotherapy.

Antitumor properties of antidepressant SSRIs

Keywords in this research direction include antidepressants, TCAs, serotonin reuptake inhibitors, apoptosis, toxicity, aspirin, nonsteroidal anti-inflammatory drugs, and neurotoxicity. Antidepressants include TCAs, serotonin-norepinephrine reuptake inhibitors, and SSRIs. The SSRIs are a new class of antidepressants, scientifically known as pentraxin reuptake inhibitors[63] that selectively inhibit the recycling of 5-hydroxyl tryptamine by presynaptic membranes and are used as the first choice of antidepressants in countries around the world. Recent studies have shown that some SSRIs, such as paroxetine and sertraline, have potent anticancer activity[64-66] and TCAs do not have similar activity[66]. Paroxetine is the only SSRI with anticholinergic antidepressant activity. Studies have shown that paroxetine

combined with fluorouracil inhibited tumor-cell growth in mice with CRC and depression by inhibiting the expression of the cytokine IL-22[67]. Paroxetine is immunosuppressive in human lymphocytes and has significant cytotoxicity in several types of cancer cells[68]. Paroxetine and sertraline were shown to have pro-apoptotic activity in HT29 human CRC cells[69], which may have been caused by inhibition of mesenchymal epidermal transforming factor and glial growth factor receptors; in addition, *in vivo* studies have demonstrated that paroxetine reduced tumor growth in xenografted mice[70-73].

Study limitations

This study used a bibliometric approach to analyze the evolution and trends of research related to depressive disorders in patients with CRC. Bibliometric analyses are comprehensive and objective, but as with previous studies, some limitations. are unavoidable. Publications in this study on depressive disorders in patients with CRC were extracted from only the WoS Core Collections database. Although it is widely used and is a comprehensive database, some publications are not indexed by the WoS Core Database.

CONCLUSION

Publication of articles on depressive disorders in CRC patients grew steady from 2001 to 2022. In the past 5 years, relevant studies entered a period of rapid development. Co-occurrence cluster analysis of keywords revealed nine research directions, including study of the physiological mechanism of the bidirectional effect of CRC and depression; the influence of mental and psychological factors on the prognosis of CRC patients; functional research on the brain cognition of CRC patients; study of the association between depression and the progression of CRC; post-operative psychosocial factors in CRC patients; psychological intervention research in CRC patients; research on the risk and influencing factors of depression in CRC patients; and pain intervention and palliative care in CRC patients and special care for elderly patients. Keywords such as quality of life, anxiety, psychological stress, hospital anxiety, and survival were at the center of visual network diagrams, suggesting that the quality of life of CRC patients suffering from depressive disorder and special psychological care for cancer patients with anxiety and stress are research hotspots. The roles of cytokines and miRNAs in the occurrence and development of depressive disorders in CRC, antidepressant activity of anticancer drugs, and antitumor activity of antidepressants are worthy of further research. This study highlights current trends, global collaboration patterns, research hotspots, and emerging frontiers in research on depression and CRC patients.

FOOTNOTES

Author contributions: Yuan Y conceived and revised the full text; Yan ZW systematically collected literature and drafted the manuscript; Liu YN processed some of the data and proofread the manuscript; Xu Q was partially involved in the study design; All authors have read and approved the final manuscript. Yan ZW and Liu YN contributed equally to this work as co-first authors.

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Country of origin: China

ORCID number: Yuan Yuan 0000-0002-7394-9036.

S-Editor: Chen YL
L-Editor: Filipodia
P-Editor: Zhang L

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