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Systematic Review

Research Trends in the Early Diagnosis of Ovarian Cancer during 2001–2020: A Bibliometric Analysis

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Abstract

Background: Ovarian cancer (OC) is the most fatal gynecologic malignancy tumor, and early diagnosis is difficult. There are few bibliometric studies on the early diagnosis of OC. This study aims to visualize the research trends on early diagnosis of OC through a bibliometric analysis. **Methods**: Publications on early diagnosis of OC from the Web of Science Core Collection (WoSCC) were downloaded. We used the CiteSpace software for bibliometrics and visualization analysis of publications, authors, cited authors, countries, institutions, references, cited journals, and keywords, *etc*. **Results**: 464 institutions in 70 countries published a total of 1015 articles during 2001–2020. The number of articles increased annually. With the United States of America (USA) and China as leading contributors. University College London (UCL) and the University of Texas MD Anderson Cancer Center were the major research institutions, with a majority of top 10 institutions located in the USA. Gynecologic Oncology was the most published journal as well as the most co-cite. Usha Menon was the most frequently published author and Ian J. Jacobs was the most frequently cited author. Co-citation cluster labels revealed characteristics of 17 main clusters: CA125, proteomics, diagnostic/prognostic biomarkers, gene expression profiling, BRAF, randomized controlled trial (RCT), exosome, prognosis, epidemiology, salpingectomy, HE4, symptoms, human, ovary, the prognosis of OC, mucinous carcinoma, and tumor-associated antigens. Keywords burst detection showed that HE4, algorithm, pathway, expression, collaborative trial, RCT, serous carcinoma, and prognosis were recent research trends. **Conclusions**: This study used bibliometrics and visualization methods to illustrate research trends in the early diagnosis of OC during 2001–2020. In-depth study of traditional tumor markers, the discovery of DNA and non-coding RNA and exosomes, as well as gene chip, proteomics, mass spectrometry, immunohistochemistry, liquid biopsy, prophylactic Salpingectomy, and epidemiology in the diagnosis of early stage OC have important research value and application prospects. Finding more accurate biomarkers on the basis of basic and clinical studies, and carrying out larger and multi-center clinical trials, will be the focal points in the future.

Keywords: ovarian cancer; early diagnosis; early detection; bibliometrics; trends; CiteSpace

1. Introduction

The early symptoms of ovarian cancer are insidious and difficult to detect, with more than 75% diagnosed in advanced stages [1]. Approximately 313,959 new cases of Ovarian cancer (OC) and 207,252 deaths were reported globally in 2020 [2]. According to The World Ovarian Cancer Coalition, the global incidence of OC will rise by 55%, and the death rate will increase by 67% by 2035, with 15% of OC patients dying within two months of diagnosis and the five-year overall survival rate below 50% [3]. The high heterogeneity, rapid progression, and lack of appropriate early detection methods are tremendous challenges in the early detection of OC. Though pathological examination is the gold standard for diagnosis, it is not typically used for the early detection of ovarian cancer, making the research for reliable biomarkers all the more criticial.

In recent years, researchers have discovered different methods (traditional serum tumor markers, gene chips, Proteomics, mass spectrometry, *etc.*) for the early diagnosis of OC. While the diagnostic value of these methods vary, the combined detection of multiple indicators can improve diagnostic accuracy. However, the combination of tumor markers, suitable for the early diagnose of OC, has yet to be established clinically, and still requires much additional research and verification. Although numerous experimental and clinically relevant data have been published over the past 20 years, a systematic review of such data is lacking. Accordingly, collecting data from relevant publications can help researchers assimilate the collected literature and understand the prevailing research trends in this field.

Bibliometrics, formerly known as Statistical Bibliography, first appeared in 1969. It is a method of applied mathematics and statistics, that expresses the characteristics and processes of the development of the subject through narration and analysis. Experts have confirmed that CiteSpace can adequately reflect the objective situation of scientific development [4]. Bibliometrics, combined with CiteSpace's visual processing, present the research frontiers and trends in knowledge and information intuitively with striking visual images.

This study aims to comprehensively understand the research progress of early diagnosis of OC by analyzing the

related studies published in Web of Science (WOS) over the past 20 years. Interpreting and summarizing these articles can help predict possible research trends and provide some points of references for future researchers.

2. Materials and Methods

2.1 Literature Search and Data Collection

A search of publications on the early diagnosis of OC was conducted with the Web of Science Core Collection (WoSCC) database on 25 September 2021. WoSCC was selected for it's comprehensive collection of medical journals. The search strategy was as follows: advanced search on Web of Science Core Collection, TI = (ovarian OR ovary OR adnexal OR pelvic) AND TI = (cancer* OR carcinoma* OR neoplasm* OR tumor* OR mass* OR cyst*) AND TS = ("earl* diagnos*" OR "earl* detect*"), with a timespan from 2001 to 2020, and "Document Type" set to include "Articles OR Review", Language = English (Fig. 1). The total number of publications reached was 1015 (800 articles and 215 reviews) according to our search strategy. The retrieved publications were exported as "full records and cited references" files, saved as plain text files, and stored in "download_txt" format.

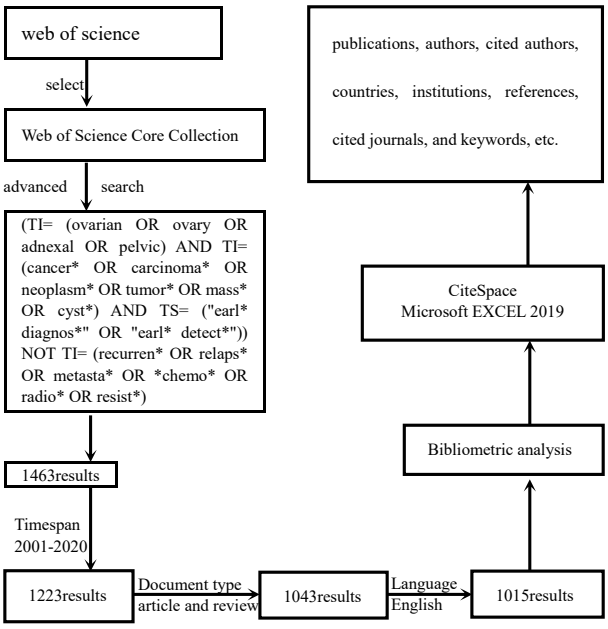

Fig. 1. Flowchart of publication selection and research.

2.2 Analysis Tools

CiteSpace software (5.8 R2, 64 bits, Drexel University, Philadelphia, PA, USA, https://sourceforge.net/projects/citespace/), invented by Professor Chen Chaomei of Drexel University, is a citation visualization analysis software based on Java language. Publications, stored in "download_txt" format, were imported into the CiteSpace software (5.8 R2, 64 bits) according to the following settings: Time slicing = January 2001 to December 2020, years per slice = 1, selection criteria = top 50. The selection used a modified g-index in each slice with a scale factor of k = 25. Select Cosine for the connection strength between the data of the analysis object, and Scope: Within Slices. To simplify the network and highlight its important structural features, the Pruning parameters area "Pathfinder" and "Pruning the merged network" or "Pruning sliced networks" were chosen to work when in need. "Author, Institution, Country, Keyword, Reference, Cited author, Cited Journal" was selected in the Node Types area separately, depending on research purpose. For the dual-map overlay of journals, "Journal Citation Reports (JCR) journal maps" were selected in the Overlap Maps. Finally, additional settings were left as defaults.

In the visualization network, the node represents various elements, such as authors, countries, and keywords. The more frequent the occurrence (or citations), the larger the node. The color and thickness in the node circle indicate the frequency of occurrence (or citations) in the corresponding time zone. The color gradient from dark to light indicates the increase in years [5]. The node with the purple circle is important in the network, demonstrating high betweenness centrality [6]. The line between nodes represents co-occurrence or co-cited [7]: the thicker the line, the stronger the intensity of co-occurrence or co-cited. Line color represents the year when co-occurrence or co-cited first appeared.

3. Results

3.1 Quantity and Trend Analysis of Publications

We entered the number of annual publications into Microsoft Excel 2019 (Microsoft Corporation, Redmond, Washington, USA, https://www.microsoft.com/zh-cn/download/office.aspx?q=office) to determine the trend of publications. The total volume of publications showed a steady growth trend. Moreover, it can be predicted that at least 1564 publications on the early diagnosis of OC will be published from 2021 to 2030 (see forecast figure). As this field garners greater attention (Fig. 2A). The citation frequency is 39,074, the h-index count is 80, and the average number of citations per paper is 38.5 (Fig. 2B).

3.2 Countries and Institutions Analysis

The collaboration network of countries is drawn according to the status of national collaboration in citing literature. If two authors' countries appear in the same article, it is regarded as collaboration, and the same principle is applied to the institutional collaboration network too. The distribution and intensity of collaboration between countries can be obtained by analyzing the collaboration network between countries. The distribution of research power in each field can be obtained through the analysis of institutional collaboration networks. 464 institutions in 70 countries

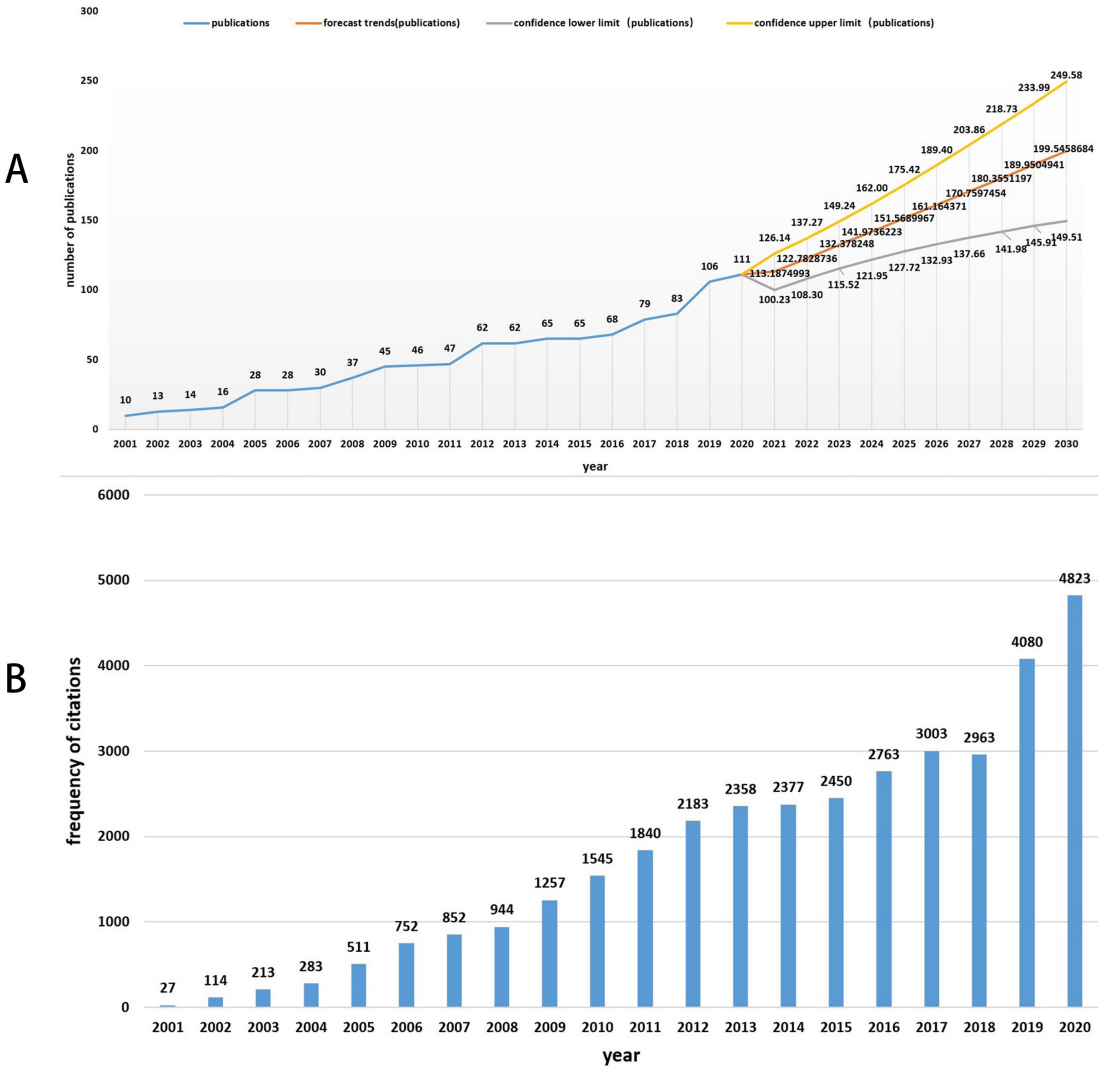

Fig. 2. Annual changes in the number of publications and in the citation frequency. (A) Annual changes and forecast trends in the number of publications on the early diagnosis of ovarian cancer. (B) Annual changes in the citation frequency.

published a total of 1015 articles. The collaboration network map of countries and institutions involving this topic is exhibited in figures individually (Fig. 3). Furthermore, the names of the top 10 most productive countries and institutions are listed in Table 1.

The USA (430, 42.36%) ranked first in the number of publications, followed by China (200, 19.70%), England (99, 9.75%), Italy (60, 5.91%), Canada (49, 4.83%), Australia (41, 4.04%), Germany (41, 4.04%), Japan (40, 3.94%), India (40, 3.94%), and South Korea (28, 2.76%), suggesting that these countries are in a leading position on this topic, especially the USA. The centrality of the USA is highest, suggesting that it plays a critical intermediary role in the national collaborative network.

The top two prolific institutions are University College London (UCL) (33, 71.12%) in the United Kingdom (UK) and the University of Texas MD Anderson Cancer Center (27, 58.19%) in the USA, followed by eight institutions within the USA, indicating that contributions from the USA and UCL are central to this field; in particular, American research institutions have carried out deeper and lasting research on the project with significant results. Interestingly, the connection is closer between countries or institutions with fewer publications, their contributions demand recognition as well.

3.3 Journals and Cited Journals Analysis

There are 467 journals that have published 1015 articles related to the early diagnosis of OC. The journal with the largest number of outputs is Gynecologic Oncology (57, 5.616%), followed by the International Journal of Gynecologic Cancer (30, 2.956%), PLOS One (29, 2.857%), Jour-

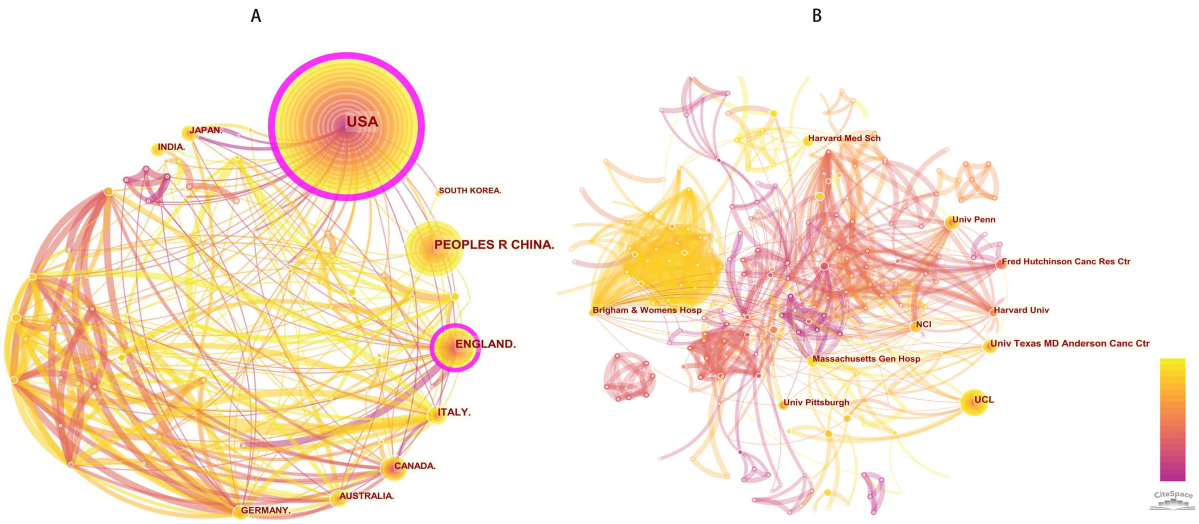

Fig. 3. Collaboration network of countries and institutions. (A) Collaboration network of countries. (B) Collaboration network of institutions. The larger the node, the more publications the country or institution has. The node with the purple circle has high betweenness centrality. The thickness of lines between nodes represents the collaboration strength, and its color represents the year in which the collaboration first appeared.

Table 1. TOP 10 publications from different countries and institutions.

Rank	Country	Publications (%)	Centrality	Rank	Institution	Publications (%)	Centrality
1	USA	430 (42.36%)	0.5	1	UCL	33 (71.12%)	0.02
2	China	200 (19.70%)	0.03	2	Univ Texas MD Anderson Canc Ctr	27 (58.19%)	0.02
3	England	99 (9.75%)	0.2	3	Fred Hutchinson Canc Res Ctr	22 (47.41%)	0.04
4	Italy	60 (5.91%)	0.05	4	Univ Penn	22 (47.41%)	0.05
5	Canada	49 (4.83%)	0.06	5	NCI	21 (45.26%)	0.05
6	Australia	41 (4.04%)	0.04	6	Brigham & Womens Hosp	20 (43.10%)	0.07
7	Germany	41 (4.04%)	0.08	7	Harvard Univ	20 (43.10%)	0.03
8	India	40 (3.94%)	0	8	Harvard Med Sch	19 (40.94%)	0.05
9	Japan	40 (3.94%)	0.03	9	Massachusetts Gen Hosp	17 (36.64%)	0.04
10	South Korea	28 (2.76%)	0	10	Univ Pittsburgh	17 (36.64%)	0.02

UCL, University College London; NCI, National College of Ireland.

nal of Ovarian Research (19, 1.872%), European Journal of Gynaecological Oncology (18, 1.773%), Cancer Epidemiology Biomarkers Prevention (15, 1.478%), and Clinical Cancer Research (15, 1.478%), *etc*. Among the top 10 journals, nine are of oncology professionals, and the current highest Impact Factor (IF, as of 2020) is with Clinical Cancer Research (IF:12.531, Q1), followed by the International Journal of Cancer with an IF of 7.396, Q1. It is helpful to identify core journals by analyzing the distribution of the source of published articles.

Ten journals were cited over 350 times among 630 co-cited journals. Gynecologic Oncology (720) was the most frequently cited journal, followed by Cancer Research (536) and Clinical Cancer Research (472). Among the top 10 journals, CA: A Cancer Journal for Clinicians had the highest IF (508.702), followed by New England Journal Medicine with an IF of 91.253. Table 2 shows that nine out of the top 10 co-cited journals were distributed in the Q1 region of the Journal Citation Reports. The cited journal analysis should help researchers understand different scopes of each journal, and to find proper theories and methods when constructing their research. The co-citation frequency represents the impact of a journal in this research field (Fig. 4).

The double map overlay of journals shows the topic distribution of academic journals. As shown in Fig. 5, there are four main citation paths, including two orange and two green paths. The orange or green path indicates that studies published in Molecular/Biology/Genetics journals and Health/Nursing/Medicine journals are cited for studies in Molecular/Biology/Immunology journals and Medicine/Medical/Clinical journals, respectively.

Table 2. Top 10 journals and co-cited journals.

Rank	Journal	Publications (%)	IF (2020)	JCR	Rank	Co-cited journal	Counts	IF (2020)	JCR
1	Gynecologic Oncology	57 (5.616%)	5.482	Q1	1	Gynecologic Oncology	720	5.482	Q1
2	International Journal of Gynecologic Cancer	30 (2.956%)	3.437	Q2	2	Cancer Research	536	12.701	Q1
3	PLOS One	29 (2.857%)	3.24	Q2	3	Clinical Cancer Research	472	12.531	Q1
4	Journal of Ovarian Research	19 (1.872%)	4.234	Q1	4	Journal of Clinical Oncology	455	44.544	Q1
5	European Journal of Gynaecological Oncology	18 (1.773%)	0.196	Q4	5	International Journal of Gynecologic Cancer	413	3.437	Q2
6	Cancer Epidemiology, Biomarkers & Prevention	15 (1.478%)	4.254	Q1	6	CA: A Cancer Journal for Clinicians	409	508.702	Q1
7	Clinical Cancer Research	15 (1.478%)	12.531	Q1	7	British Journal of Cancer	405	7.64	Q1
8	Oncology Letters	15 (1.478%)	2.967	Q4	8	Proceedings of the National Academy of Sciences of the United States of America	386	11.205	Q1
9	International Journal of Cancer	13 (1.281%)	7.396	Q1	9	International Journal of Cancer	386	7.396	Q1
10	Cancer Prevention Research	12 (1.182%)	3.491	Q2	10	New England Journal of Medicine	356	91.253	Q1

IF, Impact Factor; JCR, Journal Citation Reports; Q, quartile.

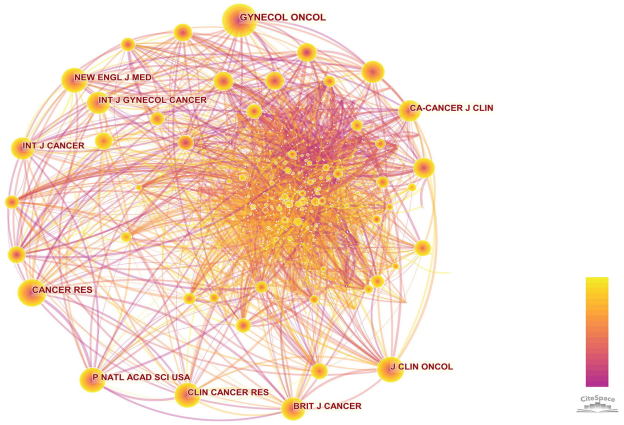

Fig. 4. Collaboration network of cited Journals. The larger the node, the more citations of the cited journal. The thickness of lines between nodes represents the co-cited strength, and its color represents the year when the co-cited first appeared.

3.4 Authors and Co-cited Authors Analysis

In our research, there are 605 authors and 789 co-cited authors. The top 10 authors of by published contributions in this field are Usha Menon (34, 3.350%), Robert C. Bast (33, 3.251%), Ian J. Jacobs (22, 2.167%), Aleksandra Gentry-Maharaj (21, 2.096%), Nicole Urban (20,1.970%), Karen H Lu (19, 1.872%), Steven J. Skates (14, 1.379%), Li Li (13, 1.281%), Andy Ryan (13, 1.281%) and Daniel W. Cramer (11, 1.084%) (Table 3). Usha Menon from UCL had the highest number of published papers, followed by Robert C.Bast from the University of Texas MD Anderson Cancer Center. We found that the centrality of authors is relatively low ($\leq$0.03), indicating that although some authors have published more literature, there is less collaboration with other authors. The collaboration network of authors is shown in Fig. 6A. The co-cited author refers to the phenomenon in which two authors are simultaneously cited in other literature (Fig. 6B). Of the 789 co-cited authors, only two authors were co-cited more than 200 times (Table 3).

3.5 Co-cited References Analysis

Co-cited references refer to the phenomenon whereby two references are cited in other literature simultaneously (Fig. 7A). Among the 941 cited references, 11 were co-cited more than 25 times. Table 4 and Fig. 7A lists the 11 most co-cited references in this field. Among these papers, Ian J. Jacobs (St Bartholomew's Hospital, London) ranked first in terms of the number of citations. Three out of the top 11 co-cited references belonged to Rebecca L. Siegel (American Cancer Society) (Table 4), underscoring that two authors have made outstanding contributions in this field. The most frequently cited reference was "Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial" [8]. Most of the top 11 co-cited references are published in the top journals: Lancet (IF = 79.321), Lancet Oncol (IF = 31.777), Lancet (IF = 60.30), CA Cancer J Clin (IF = 508.702), JAMA (IF = 56.672). These results encourage the development of research related to the early diagnosis of ovarian cancer. All 11 of the most co-cited articles are worth reading if researchers want to construct rigorous research.

Cluster view can show the distribution of research fields from different angles. The top 17 major clusters of citing articles are shown in Fig. 7B. Salient noun phrases were extracted as cluster labels from the title of citing ar-

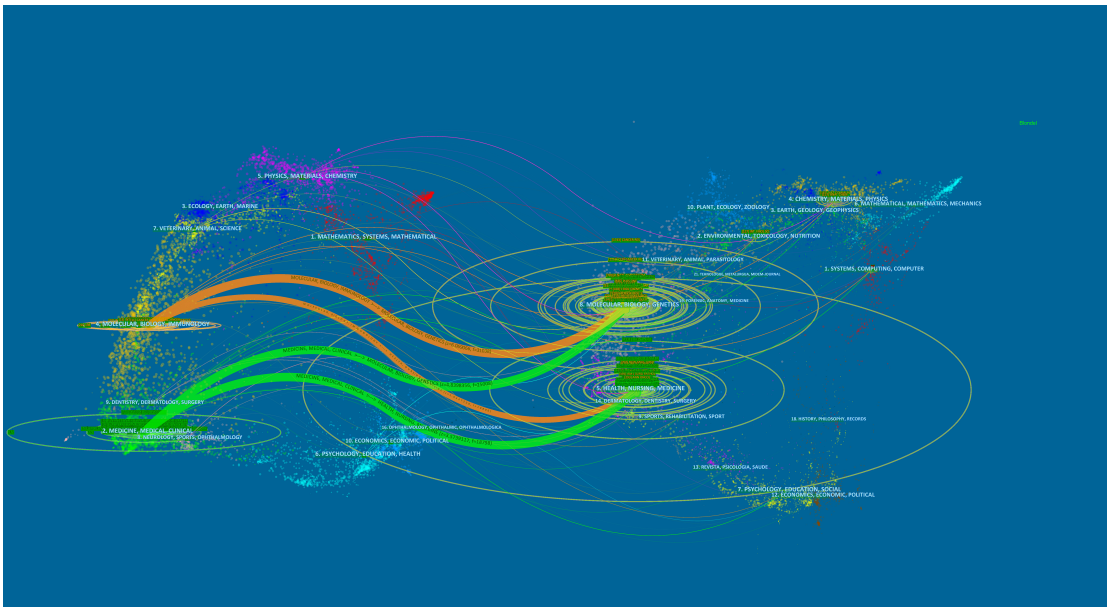

Fig. 5. The dual-map overlay of journals. On the left are citing journals, on the right are cited journals. The colored paths between them represent the cited relationships. At left, the more papers a journal contains, the longer the vertical axis of the ellipse, and the more authors there are, the longer the horizontal axis of the ellipse.

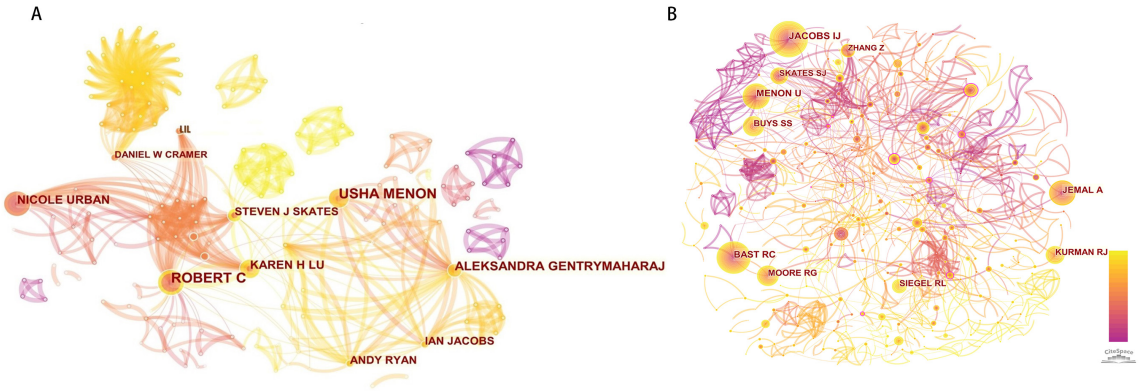

Fig. 6. Collaboration network of Authors and cited Authors. (A) Collaboration network of Authors. (B) Collaboration network of cited Authors. The larger the node, the more publications of authors, or the more citations of cited authors. The node with the purple circle has high betweenness centrality. The thickness of lines between nodes represents the collaboration strength, and its color represents the year in which the collaboration first appeared.

Table 3. Top 10 authors and co-cited authors.

Rank	Author	Record count (%)	Centrality	Co-cited authors	Citations	Centrality
1	Usha Menon	34 (3.350%)	0	Ian J. Jacobs	303	0.02
2	Robert C. Bast	33 (3.251%)	0.03	Robert C. Bast	225	0.02
3	Ian J. Jacobs	22 (2.167%)	0.01	Usha Menon	170	0.09
4	Aleksandra Gentry-Maharaj	21 (2.096%)	0.02	Ahmedin Jemal	157	0.01
5	Nicole Urban	20 (1.970%)	0	Richard G. Moore	130	0.01
6	Karen H Lu	19 (1.872%)	0.01	Robert J. Kurman	129	0.02
7	Steven J. Skates	14 (1.379%)	0.02	Saundra S. Buys	129	0.02
8	Li Li	13 (1.281%)	0	Rebecca L. Siegel	113	0.01
9	Andy Ryan	13 (1.281%)	0.01	Steven J. Skates	104	0.09
10	Daniel W. Cramer	11 (1.084%)	0.03	Zhang Zhen	88	0.03

Table 4. Top 11 co-cited references.

NO	Author	Co-cited references	Count	Centrality	Year
1	Ian J. Jacobs	Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial	64	0.02	2016
2	Usha Menon	Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)	49	0.04	2009
3	Saundra S. Buys	Effect of Screening on Ovarian Cancer Mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial	41	0.05	2011
4	Emanuel F. Petricoin	Use of proteomic patterns in serum to identify ovarian cancer	38	0.08	2002
5	Rebecca L. Siegel	Cancer death rates in US congressional districts	36	0.01	2015
6	Irene Visintin	Diagnostic Markers for Early Detection of Ovarian Cancer	34	0.11	2008
7	Rebecca L. Siegel	Cancer Statistics, 2016	34	0	2016
8	Rebecca L. Siegel	Cancer Statistics, 2012	29	0	2012
9	Daniel L. Clarke-Pearson	Screening for Ovarian Cancer	26	0.06	2009
10	Richard G. Moore	The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass	25	0.18	2008
11	Robert J. Kurman	The Dualistic Model of Ovarian Carcinogenesis Revisited, Revised, and Expanded	25	0.02	2016

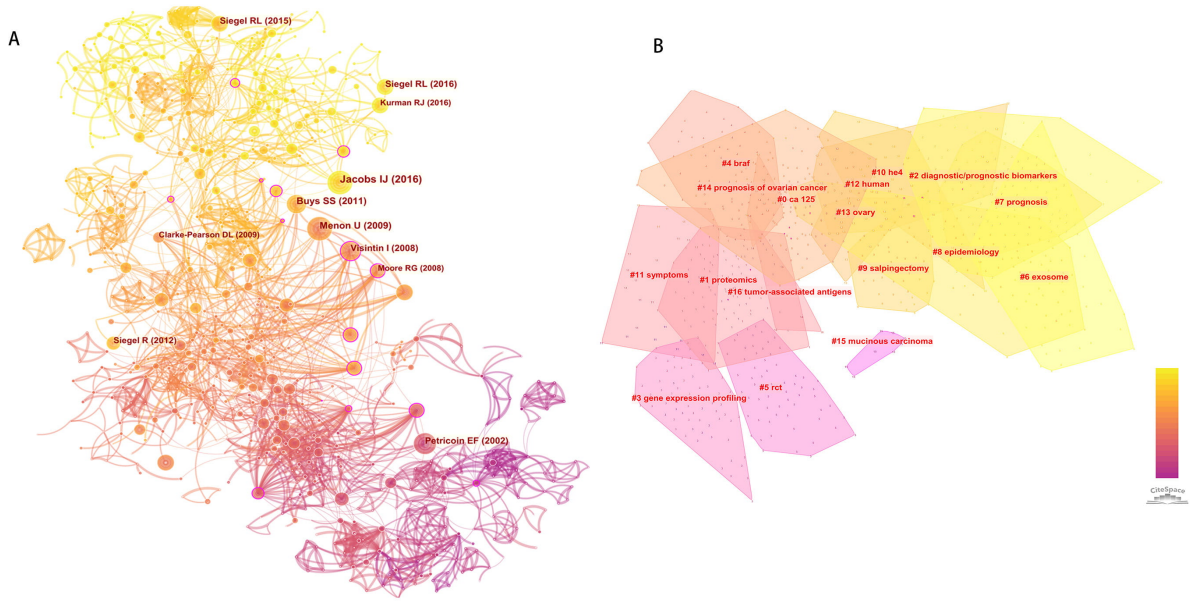

Fig. 7. Document co-citation network and the top 17 largest clusters of citing articles. (A) Document co-citation network. (B) The top 17 largest clusters of citing articles. The bigger the node, the more citations of cited references. The node with the purple circle has high betweenness centrality. The thickness of lines between nodes represents the collaboration strength, and its color represents the year in which the collaboration first appeared.

ticles using the LLR algorithm, including #0 CA125, #1 proteomics, #2 diagnostic/prognostic biomarkers, #3 gene expression profiling, #4 BRAF, #5 randomized controlled trial (RCT), #6 exosome, #7 prognosis, #8 epidemiology, #9 salpingectomy, #10 HE4, #11 symptoms, #12 human, #13 ovary, #14 prognosis of ovarian cancer, #15 mucinous carcinoma, and #16 tumor-associated antigens (Fig. 7B). The smaller the cluster tag number, the more articles the cluster contains. It can be seen that the research field of the early diagnosis of OC mainly focuses on tumor markers and related gene detection.

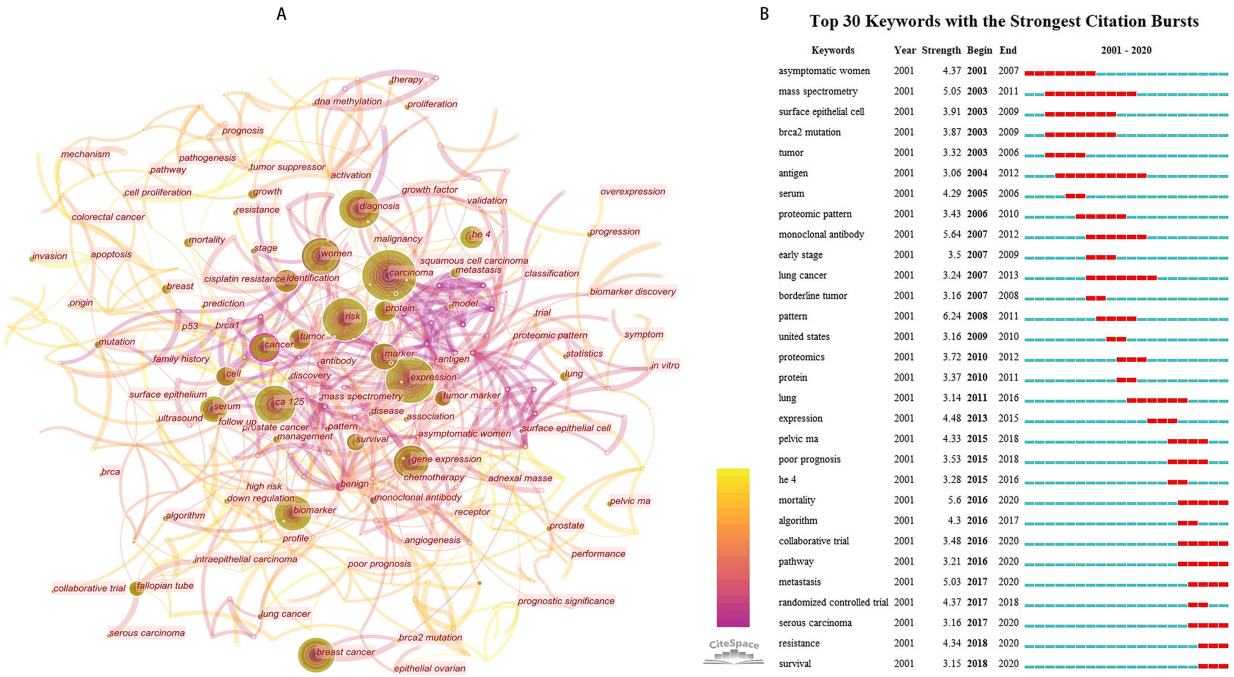

Fig. 8. Keywords co-occurrence network and Keywords with the Strongest Citation Bursts. (A) Keywords co-occurrence network. The bigger the node, the more frequency of keywords. The nodes with the purple circle have high betweenness centrality. The thickness of connections between nodes represents the co-occurrence strength, and its color represents the year in which the co-occurrence first appeared. (B) Keywords with the Strongest Citation Bursts. The red line represents periods of a sudden increase in keywords, and the blue line is the opposite.

3.6 Keywords Analysis

Keywords co-occurrence network can reflect the current and past research trends (Fig. 8A). Biomarkers are warranted for the early diagnosis of OC, and can also predict the prognosis of patients with OC. Therefore, they have always been research focus points, especially CA125 and HE4. At present, gene expression profiling, proteomics, immunohistochemistry, predication model, and other methods have gradually become the trends in the early diagnosis of OC (Fig. 8A). Keywords burst detection reflects the research trends in a certain period, while the duration of such research focus can predict the research trend (Fig. 8B). Antigen and mass spectrometry jointly ranked first, and they were the main research trends from 2003 to 2012. Pattern, with a strength of 6.24, was ranked first, followed by monoclonal antibody (5.64), which was considered a research trend from 2007 to 2012. Clinical trials (collaborative trial, RCT) and prognosis (mortality, metastasis, resistance, survival) have drawn increasing interest since 2013. This is a typical transition from early diagnosis to prognosis prediction.

4. Discussion

Early diagnosis of OC is a critical but challenging goal of clinical work. In this study, 1015 articles related to early diagnosis of OC that met inclusion criteria were searched from WOS, and bibliometric analysis was conducted using CiteSpace. This analysis can help scholars visualize and understand the research trends in the early diagnosis of OC, while answering key questions through case studies.

4.1 Publications, Countries, Institutions, Authors, Cited Authors, Journals, Cited Journals

Based on analysis of the number of previous publications and predicted publications, it can be concluded that this research field will always show a trend of steady growth. The countries studied are mainly the USA, China, and the UK. The intermediary center degree of the USA and the UK is the highest, indicating that they pay more attention to the cooperation between teams. Most of the top 10 institutions are located in the United States, which has taken the lead in this research area. The top two are UCL in the UK and the University of Texas MD Anderson Cancer Center in the USA. Evidently, European and American scientific research institutions pay more attention to cooperation between teams than China. They also have more advantages in scientific research development. However, most cooperative institutions are still limited to internal contacts, while cross-border cooperation and exchange of research results are also reduced greatly, especially outside Europe or the USA. This has hindered the development of this research area. There appears to be a relative lack of

studies examining ethnic/racial differences in early detection. Therefore, it is strongly recommended that research institutions remove academic barriers, cooperate and communicate actively, carry out more large-scale studies, and promote the further development of the early diagnosis of OC.

The most frequently published authors were Menon (University College London) and Bast (University of Texas MD Anderson Cancer Center) with 34 and 33 articles, respectively. It is worth noting that although Usha Menon published the most, she ranked third among co-cited authors, while Robert C. Bast ranked second among co-cited authors. The main research content of their teams is the application value of biomarkers and related genetic tests in the early diagnosis of OC, and the status quo and future development of early screening of ovarian cancer, *etc.* We found that the centrality of authors is relatively low. Notably, while the screening trials led by Menon and Jacobs are central to the citation networks, the backbone of early diagnosis accounting for all of the publications listed, there have not been well-cited follow-up efforts to these trials, nor large-scale studies outside Europe or the USA focused on early detection. Interestingly, some authors with low co-cited numbers demonstrated higher centrality (Fig. 6B).

Most studies for early OC diagnosis are published in influential oncology journals such as Clinical Cancer Research and International Journal of Cancer, but some reproductive medicine journals also publish articles on the subject. As for co-cited academic journals, we can see that most of the research comes from high impact journals with significant impact on the international community that influences the direction of research in their respective academic fields. In Fig. 5, scholars combine basic research with clinical research to explore more accurate methods for the early diagnosis of OC.

4.2 Research Trends

From the perspective of references and keywords, the research trends in the early diagnosis of OC mainly focused on the following aspects:

4.2.1 Early Diagnosis of OC Based on Gynecological Tumor Marker Test and Related Gene Test

Tumor markers are protein antigens or bioactive substances generated by abnormal expression of tumor cells that can be detected in tumor patients' tissue, blood, body fluids, and excreta [9], contributing to tumor diagnosis, differential diagnosis, efficacy, and prognosis monitoring [10]. With the development of molecular biology, gynecological tumor marker examination and related gene detection have gradually become the research focus in the early diagnosis of OC. As can be seen from Fig. 7B, the main areas of study have eight clusters, namely, #0 CA125, #1 Proteomics, #2 Diagnostic/Prognostic biomarkers, #3 Gene expression profiling, #4 BRAF, and #6 Exosome, #10 HE4, #16 Tumor-associated antigens.

There are various types of antibodies against tumor cell antigens in the serum of tumor patients; antigens related to tumorigenesis are called tumor-associated antigen (TAA). Research has demonstrated that anti-TAA autoantibodies can be regarded as potential diagnostic markers for the detection of OC, a model of three anti-TAA autoantibodies (GNAS, p53, and NPM1) that may improve immunodiagnosis of OC [11]. In 1983, Bast was first to measure the serum CA125 threshold of 35 U/mL by radioimmunoassay and used it as a biomarker for epithelial ovarian cancer (EOC) [12]. In Fig. 7B, CA125 is the largest cluster and the most widely used biomarker for OC diagnosis. However, CA125 is also elevated in some gynecological benign tumors, endometriosis, inflammation, and other diseases. Serum CA125 lacks sensitivity and specificity and cannot be used as a single marker for the early detection of OC.

In 2011, HE4 was approved by the USA Food and Drug Administration as a novel, specific serum tumor marker for the early diagnosis of OC. HE4 is not expressed in the normal ovarian surface epithelium but is significantly overexpressed in ovarian serous and endometrioid carcinoma. Both CA125 and HE4 are protein-based biomarkers. The study showed that CA125 combined with HE4 demonstrated superior clinical value in the early diagnosis, disease monitoring, postoperative recurrence monitoring of EOC, and the differential diagnosis of benign tumor. In addition, CA125 and HE4 have been widely used in the development of various OC risk models, such as the Risk of Ovarian Malignancy Algorithm (ROMA), Risk of Malignancy Index (RMI), Risk of Ovarian Cancer Algorithm (ROCA), *etc.* by way of triaging patients. Patients with low risk were followed up or treated in general gynecology, while patients with high risk were transferred to the gynecological oncology department for treatment. CA199, CA153, CA724, CEA, Osteopontin, Mesothelin, VCAM-1, PRSS8, ApoA1, Kallikrein, B7–H4, leicht2 M, CTAPIII, and TT can also be used for early diagnosis. However, their potential to be used as a biomarker is still controversial. Various tumor markers are often detected in combination in clinical practice. As a non-invasive method, blood-based tumor markers are simple and fast, but their sensitivity and specificity must be further improved.

Mass spectrometry is the most important analytical technique in the field of protein research and biological macromolecule research. Based on the rapid development of mass spectrometry and proteomics, new tumor markers and diagnostic models for OC are gradually discovered and further explored, providing great hope for the early diagnosis of OC. Weiland identified junction plakoglobin (JUP) as a promising new biomarker for EOC by ovarian blood sampling–proteomics method, which in combination with CA125 may help the screening of OC [13]. Enroth S *et al.* [14] constructed a plasma protein biomarker signature model consisting of 11 biomarkers (FCGR3B, TRAF2,

GKN1, CST6, SEMA4C, NID2, CEACAM1, CLEC6A, MILR1, CA3, and CDH3) in addition to age, that could improve the early diagnosis accuracy of OC. Harry J constructed a performing model, consisting of CA125, HE4, CHI3L1, PEBP4, and/or AGR2. The sensitivity and specificity of this model are 85.7% and 95.4%, respectively, one year prior to diagnosis. This model achieved 95.5% sensitivity at 95.4% specificity in Type II cases, especially in most high-grade serous carcinoma (HGSC) [15]. There are many comparable models in clinical practice, each with its own diagnostic value that may be related to the study population and different biological macromolecules. More large-scale and multi-center studies are needed to verify the accuracy of these models. As can be seen from keyword burst detection, the research involving this topic has been a significant trend from 2003 to 2012.

With the rapid development of science and technology, gene detection has attracted the attention of scholars. ctDNA, miRNA, circRNA, lncRNA, and other genes have become research trends in the early diagnosis of OC.

The average length of circulating cell-free DNA (cf DNA) is 140 to 170 base pairs. Ct DNA is part of cf DNA. ctDNA mainly contains *TP53*, *BRCA1*, *BRCA2*, BRAF, KRAS, PTEN, RB1, ARID1A, ERBB2, RAD51C, RAD51D, PIK3CA, PALB2, BRIP1, ATM. Autoantibodies against *TP53* were able to detect 20% of early-stage OC in eight months before CA125 levels were elevated and 22 months before clinical diagnosis. The EOC was related to mutations of BRCA1 and BRCA2. The cumulative lifetime risk ranging of BRCA1 and BRCA2 is 40%–50% and 20%–30%, respectively. *BRCA1* mutations are four times more common than *BRCA2* mutations. *BRCA* gene detection is crucial in providing accurate guidance and suggestions for the prevention, treatment, and prognosis of OC. Therefore, patients with OC, those with a high risk of OC, and those with the intention of early screening for OC should pay attention to *BRCA* testing [16].

CancerSEEK [17], a blood test, is designed to detect 16 ctDNA (including *TP53*) and eight protein biomarkers (including CA125). This DNA-on-protein model could enable early screening for many types of cancer, as it is still in the experimental stage, further research is needed. ctDNA, in combination with other non-DNA-based biomarkers, has great potential for clinical application and may be a key component in early cancer detection. However, further experiments are needed to remove the interference of confounding factors. In addition, studies have shown that DNA methylation is the earliest event of tumor occurrence and is more suitable as a diagnostic marker, but mechanisms of its initiation remain poorly understood [18]. Recently, a repetitive element aneuploidy sequencing system (RealSeq) detected less than 3 pg aneuploidy ctDNA in relatively little plasma, suggesting a promising advance in enhancing the sensitivity of early-stage high grade ovarian cancers with copy number abnormalities [19]. Comparative genomic hybridization (CGH), loss of hybridization (LOH), spectrokaryotyping (SKYP), and serial analysis of gene expression (SAGE) were included in Whole-genome sequencing, or the sequencing of individual genomes of species whose genome sequence is unknown, marking another recent research trend [20].

18–24 base long nucleotide sequences comprise MicroRNAs (miRNAs) that are evolutionary conserved noncoding RNA molecules involved in several regulatory biological processes (differentiation, development, apoptosis, and proliferation of cells). A large number of clinical studies have shown that for the early diagnosis of OC [21,22], the miRNA expression profiles in serum/plasma are more relevant than in histological specimens. The latter is only used for intraoperative diagnosis confirmation. Thus far, various types of research have focused on single microRNA, whereas few studies have used molecular clustering analysis to verify miRNA expression profiles. A panel of miRNAs usually may be more useful than a single. A recent study demonstrated that serum miR-26b had a lower expression and that miR-21 was higher in OC than in healthy people. miR-26b combined with miR-21 is crucial for the diagnosis of expression, which has reached 0.916 AUC, 87.5% sensitivity, and 90.4% specificity. Moreover, clinical stage, lymph node metastasis, and 3-year survival rate of OC patients are also related to the expression of miR-26b and miR-21 [23]. A study shows that miR-26b+miR-21, miR-200a, miR-125b, miR-30a-5p, and miR-200c are the most significant diagnostic miRNA biomarkers of EOC. But other studies suggest that the panelof five miRNAs (miR-205-5p, miR-145-5p, miR-10a-5p, miR-346, miR-328-3p), miRNAs in plasma exosomes, and miRNAs in urine, can all distinguish OC patients and healthy volunteers [24–26]. In addition, the level of miRNA in individuals is unrelated to the level of CA125; miRNA is an independent detection indicator. A rapid, efficient, and cost-effective detection of expression in early stages requires the best microRNAs-based assays. However, because miRNA binds to target genes in different depending on the organism, and can interact with a variety of proteins, it is difficult to establish an effective and universally applicable identification and detection method.

CircRNA is a member of short non-coding RNAs, primarily including circ ABCB10, circ MAN1A, circ BNC2, circ EXOC6B, circ FAM13B, circ N4BP2L2, circ RHOBTB3, and circ CELSR1. The techniques used to detect circRNAs expression include real-time fluorescence quantitative PCR (QRT-PCR), gene chip analysis, Northern Blot, Fluorescence In Situ Hybridization (FISH), and biotin-coupled circRNA capture. In addition, these techniques simultaneously detect the expression levels of circRNAs and related miRNAs to further study the role of miRNA molecules as “sponges” of circRNAs; this is another notable trend. Due to its high stability and abundance in OC tissues and body fluids, circ RNA is an ideal

source for the development of emerging tumor markers in the early diagnosis of OC. The Research has found that Circular RNAs (circRNAs) within exosomes are remarkably higher in OC patients than healthy volunteers [27]. However, circRNA has not been widely used in the clinical setting, and thus confirmation by large sample RCT is still needed.

The length of long non-coding RNAs (lncRNAs) is over 200 nucleotides. Through various mechanisms such as DNA methylation and imprinted genes, some lncRNAs can enter peripheral blood and body fluids, indicating their application prospects in non-invasive detection [28]. The diverse functions of long non-coding RNAs (lncRNAs) in OC are attracting more attention. Severial studies have shown that interference of abnormal expression of lncRNAs in tumor tissues and cells at the molecular level by siRNA technology can effectively reverse tumor progression. This suggests that lncRNAs, as a new class of biomarkers, have extraordinary potential in early diagnosis [29,30], prognosis evaluation, or efficacy in the monitoring of tumors. With the development and application of RNA sequencing technology, gene chip technology, and biochemical and molecular biological mechanisms, the rate of discovering new lncRNAs is increasing rapidly. An increasing number of studies focus on the role of lncRNAs in ovarian cancer, but only a few lncRNAs have clear characteristics of expression in OC. Even fewer of them have clinical applications. In addition, few studies reveal the functional sites related to the binding of lncRNAs to miRNAs or proteins. Accordingly, more studies are warranted to elucidate the mechanism and signaling pathway of lncRNAs in OC at the molecular level and to apply them to clinical practice.

The title of Cluster 6 is exosome. Exosomes are a class of extracellular vesicles with a diameter of 40–160 nm that are polycystic formed by continuous invagination of the cell membrane. Exosomes, containing cell-specific DNA, RNA, protein, and other bioactive substances, are widely distributed in various body fluids, such as blood, saliva, follicular fluid, and uterine cavity fluid. Numerous studies have proved that exosomes promote the occurrence and progression of OC by participating in tumor cell proliferation, epithelial-mesenchymal transition (EMT), regulation of the immune state, peritumor angiogenesis, and formation of tumor microenvironment before metastasis. To date, there are still relatively few studies on exosome non-coding RNAs in OC, but the advantages of high stability, abundance, and tissue specificity make exosome non-coding RNAs very suitable as biomarkers for early diagnosis and prognosis assessment of OC. Furthermore, proteomic and lipidomic analysis on exosomes of OC cells (SKOV-3) and ovarian surface epithelial cells (HOSEPIC) [31] has shown that exosomes in protein and liquid are of significance for the early diagnosis of OC. Despite significant advances in the use of circulating tumor cells and cell-free DNA in the diagnosis of OC, their potential for early detection or monitoring of progression remains unclear. The value of exosomes in the early diagnosis of OC has recently received greater attention.

4.2.2 Imaging Examination

Transvaginal ultrasound (TVS), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) offer some assistance in the early diagnosis of OC. The Prostate, Lung, Colorectal, and Ovarian (PLCO) is a RCT [32] in the USA; screening for OC with both Transvaginal ultrasound (TVUS) and CA125 does not reduce the mortality of OC. UKCTOCS used TVUS and CA125 to screen 200,000 asymptomatic postmenopausal women. It was found that the specificity of CA125 combined with ultrasound was improved (99.8%), but the sensitivity was not significantly improved [33]. Combined TVUS and CA125 are promising but limited as screening methods in identifying early-stage EOC [34]. Furthermore, the value of imaging examination in the differential diagnosis of benign and malignant ovarian tumor is poor, and cannot accurately distinguish OC from common ovarian diseases (benign ovarian masses, endometriosis). Combined with the keywords co-occurrence diagram and the reference cluster diagram, it can be seen that there are few studies on imaging examination in the early diagnosis of OC, and no cluster has been formed, indicating that imaging examination is not the preferred method for the early diagnosis of OC.

4.2.3 Prophylactic Salpingectomy

As seen in Fig. 7B, cluster 9 is Salpingectomy. Clicking on Cluster Explorer, it can be seen that published literature related to the early diagnosis of OC dates primarily from 2010 to 2016. Eleven articles were published in 2012 and 201, indicating that prophylactic Salpingectomy was one of the research trends in that period. It is believed that EOC, especially HGSC, is directly related to the mucosal cells at the parasitoid end of the oviduct. The “dualism” theory of the origin of OC suggests that OC can originate either from the ovary itself or from the epithelium of the fallopian tube [35]. According to the theory, part of HGSC is formed by the exfoliation and spread of tumor cells from the Serous Tubal Intraepithelial Carcinoma (STIC) of the fallopian tube and microscopic invasive cancer and precancerous lesions. As a highly heterogeneous disease, EOC is clinically characterized by asymptomatic onset and is generally not diagnosed until advanced stages. The new molecular genetic data, especially those derived from next-generation sequencing, further underline the heterogeneity of ovarian cancer [36]. There appears to be a lack of studies examining the heterogeneity of ovarian cancer in early detection.

Prophylactic bilateral salpingectomy (PBS) reduces the incidence of OC and minimizes its impact on the body. PBS is also called opportunistic salpingectomy (OS) for the general population. PBS before menopause is associated

with iatrogenic estrogen deficiency, and although the risk of ovarian and fallopian tube cancer is reduced, the risk of coronary heart disease, stroke, hip fracture, depression, and anxiety is significantly increased [37]. Risk-reducing salpingo-oo-phorectomy (RRSO) referring to the prophylactic bilateral adnexectomy, is usually recommended for those at high risk of hereditary OC (age greater than 40 years, perimenopausal status, and family history of multiple germline or system mutations, such as *BRCA1/2* mutations). Prophylactic salpingectomy with delayed oophorectomy (PSDO) refers to bilateral salpingectomy for patients at high risk of hereditary OC, followed by then bilateral oophorectomy several years later depending upon age and other subjective and objective factors. This not only reduce the risk of ovarian cancer but also avoids, to the greatest extent possible, damage of premature oophorectomy to the patient's body.

Prophylactic salpingectomy can reduce the risk of OC and fallopian tube cancer, without increasing surgical complications, and can preserve ovarian function to the maximum extent in high risk OC patients, according to the "dualism" theory of ovarian cancer and existing clinical studies. Bilateral salpingectomy is superior to tubal ligation when performing hysterosparing surgery [38], but more large-scale, multi-center, clinical trials are needed to verify this. This approach is expected to be a trend in future studies.

4.2.4 The Epidemiological Study of Ovarian Cancer

Cluster 8 shows epidemiology, the science of studying the distribution rules and influencing factors of diseases so as to explore etiology, clarify the epidemic rules, and formulate countermeasures and measures to prevent, control and eliminate diseases. Epidemiological studies have found that risk factors for ovarian cancer include childlessness and infertility, while multiple pregnancies and lactation and oral contraceptives have protective effects. Dietary habits and family history of cancer may also be related to the incidence of ovarian cancer. Eliminating these risk factors in advance may reduce the incidence of ovarian cancer. Presently, however, less research has focused on cancer epidemiology compared to gene expression profiling or proteomics. This may present a fruitful focal point for future research.

4.2.5 Study on the Correlation between Early Diagnosis and Prognosis

The ultimate goal of early diagnosis is to improve survival time and prognosis. Most patients seek medical treatment because of symptoms, such as abdominal pain and abdominal distension in the late stage. It takes an average of six months for women to be diagnosed with OC from the first appearance of symptoms [1]. Numerous studies have shown that early diagnosis of OC can guide the formulation of treatment; avoid misdiagnosis, missing diagnosis, and unnecessary referrals or inappropriate initial surgery; and reduce the complications such as physiological and psychological trauma. This, together with reducing economic burden, further improves the prognosis of patients, but the early diagnosis of OC remains clinically challenging.

Clusters 2, 7, and 14 in Fig. 7B are all associated with prognosis. As shown in the keywords burst detection results of this study, more clinical trials in this field (collaborative trial, RCT.) and prognosis research (mortality, metastasis, resistance, survival) has been conducted, to find clinical evidence. One RCT frequently cited by other studies shows that OC mortality significantly decreases with annual multimodal screening (MMS) when prevalent cases are excluded [8]. However, the definitive mortality benefit was not suggested in any RCTs. As shown in this study's keywords burst detection results, screening asymptomatic women was a trend in the early diagnosis of OC from 2001 to 2007. The availability of routine screening in the general population has been controversial. New screening models, longitudinal biomarker algorithms, and the development of better risk stratification tools can offer potential improvements to future screening strategies.

Liquid biopsy is one of the important approaches for precision medicine by detecting and analyzing free tumor DNA fragments from non-solid biological tissues such as blood to conduct early screening, establish gene expression profiles and provide more comprehensive tumor DNA information [39]. It can monitor tumor progress in real-time and further evaluate and predict prognosis. Circulating tumor cells (CTCs), cfDNA and extracellular vesicles are the main biomarkers for liquid biopsy. Early detection and effective clinical management of OC patients can be achieved through genetic testing and appropriate risk management, i.e., a population-based risk assessment [40]. The keywords burst detection in this research also indicated that early diagnosis of OC is closely related to the patient's prognosis, but more large-scale clinical trials (collaborative trial and RCT) are warranted to verify these associations.

4.3 Limitations

There are still some limitations in this study: (1) the possibility of manual error was not ruled out when the irrelevant literature was cleared; (2) some databases have not been analyzed, such as PubMed, Scopus, Wan Fang, among others; (3) bibliometric analysis uses network indicators for analysis, and the results may be slightly different from the actual research situation; (4) there are different abbreviations of the same author, institution, and keywords in different articles. Although CiteSpace can be used to merge the above content, there may still be a scenario whereby content with low frequency cannot be merged; (5) only part of the research content on early diagnosis of ovarian cancer was interpreted herein, and may thus not be sufficiently in-depth. For the research trends that may be missed, a more accurate analysis should be made based on the knowledge graph constructed by CiteSpace and combined with specific literature.

5. Conclusions

The Visualization analysis of the research status in early diagnosis of OC using CiteSpace software shows that in 2001, screening asymptomatic women with traditional tumor markers (CA125, *etc*.) or vaginal ultrasound was the research focus of scholars; however, the results of relevant large-scale screening tests were not ideal. In 2003, mass spectrometry technology emerged in the field of early diagnosis of ovarian cancer, which promoted in-depth study of traditional tumor markers, the development of exosomes, and DNA and non-coding RNA, bringing about a major breakthrough in the early diagnosis of OC. Gene chip, proteomics, and mass spectrometry, immunohistochemical, liquid biopsy and epidemiology in the diagnosis of early stage OC have important research value and application prospects. For women at high risk of OC, Prophylactic Salpingectomy reduces OC incidence. Early diagnosis can effectively improve patient prognosis. Since 2010, scholars have searched for more accurate biomarkers on the basis of basic and clinical studies, and carried out larger and multi-center clinical trials, hat promise to be the prevailing research trends in the future.

Author Contributions

CX and XL designed the research study. CX performed the research, analyzed the data and wrote the manuscript. XL provided help and advice on the editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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