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# Global research trends in liquid biopsy for ovarian cancer from 1999 to 2023: A 25-year bibliometric analysis

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ABSTRACT

*Background:* Ovarian cancer (OC) is a major cause of gynecological cancer-related death in the world. Liquid biopsy has shown great potential in improving the ovarian cancer detection and treatment. The aim of this study is to explore the previous studies, current hotspots, and future trends of liquid biopsy for OC from a bibliometric perspective.

*Methods:* Articles on liquid biopsy in the field of OC were collected from Web of Science (Clarivate Analytics). Subsequently, bibliometric and visual analyses was conducted using *bibliometrix*, *VOSviewer*, *CiteSpace*, and *Microsoft Excel*.

*Results:* A total of 504 scientific papers were retrieved over a 25-year period, of which 285 papers were in the language of English. China has the highest number and other papers came from 41 countries or regions. The journal with the highest publication count was Cancers. There were 2013 authors in total, and Kasimir-Bauer S emerged as the most productive author. The key words that are still exploding are recurrence, predictive value and survival.

*Conclusion:* Research on liquid biopsy is booming in the field of OC. This article comprehensively elucidates the subject matter over recent years, and points out emerging trends for in-depth exploration.

## 1. Introduction

Ovarian cancer (OC) poses a significant threat to women's health and life, with its burden exhibiting a clear upward trend over the past three decades. In Europe, there has been a notable increase in the incidence rate from 4.9 to 6.1 cases per 100,000 women between 1982 and 2008 [1]. According to the American Cancer Society, in 2020, there were an estimated of 21,750 new cases of OC in the USA , with 13,940 deaths attributed to this disease, making OC the fifth leading cause of cancer-related deaths among women in the country [2]. Relevant research surveys have reported that, in 2019 alone, China recorded nearly 45,000 new cases of OC, along with more than 29,000 deaths [3].

Prognostic indicators and survival rates in OC intricately depend on the disease's stage at detection. Regrettably, the mild symptoms exhibited by OC in its early stages, coupled with the high heterogeneity and the limitations of traditional diagnostic methods, contribute to significant challenges in early diagnosis. Consequently, approximately 70 % of OC cases are diagnosed at an advanced stage [4]. Furthermore, the substantial recurrence rate and pronounced chemotherapy resistance are factors that contributed to the poor prognosis of OC, resulting in a 5-year survival rate as low as 47.4 % [5]. Thus, identifying new diagnostic and therapeutic methods for clinical application has become the primary research direction in OC. Recent years have seen significant progress in OC treatment research. The development of targeted therapies, such as PARP inhibitors, has transformed the treatment of advanced epithelial ovarian cancer (EOC), particularly for patients with *BRCA* gene mutations [6,7]. Additionally, research has revealed that the most common type of OC, high-grade serous carcinoma, often originates in the fallopian tubes rather than the ovaries [8]. This has led to the consideration of preventive strategies involving the removal of fallopian tubes instead of the entire ovaries in high-risk individuals. Novel immunotherapy strategies, such as Genelux's Olvi-Vec, are being investigated for OC treatment [9]. Olvi-Vec is a modified vaccinia virus that aims to convert the tumor microenvironment from immunosuppressive to immunostimulatory, leading to promising response rates in clinical trials [10].

Liquid biopsy, a non-invasive diagnostic approach, has garnered

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increasing attention in OC research. It encompasses the examination of tumor-released nucleic acids such as cell-free DNA, microRNA, and non-coding RNA, circulating tumor cells (CTCs), and extracellular vesicles (EVs). This approach offers a precise detection of genomic and transcriptomic alterations, providing deeper insights into tumor heterogeneity compared to traditional tissue biopsy. Liquid biopsy is revolutionizing cancer management across various fronts, including early diagnosis, targeted therapy selection, and surveillance for recurrence.

Amid the rapid expansion of liquid biopsy research in OC, there has been a pressing need for innovative methodologies to organize and understand the wealth of knowledge generated. Bibliometrics method stands out as a suitable solution to this challenge with its capacity to analyze a vast number of publications in both general and focused fashions, alongside its independence from specific subject domains. It investigates literature distribution through mathematical, statistical, and other measurement techniques, evaluating shifts in structure, volume, and trends. Bibliometrics is becoming increasingly popular, especially in the field of medical research [11]. A previous study showed that among the approximately 17,500 bibliometric publications indexed in *Scopus*, more than one third were from the medical field [12]. However, comprehensive bibliometric research in the liquid biopsy field for OC is still lacking, indicating a need for detailed literature research to summarize and analyze global trends in this area.

This present bibliometric analysis aimed to uncover the evolving trends in the application of liquid biopsy for OC diagnosis and management from 1999 to 2023. Employing scientometric methods and visualization tools, our study examines the research on liquid biopsy in the field of OC. Our objective is to elucidate the current status and anticipate future advancements pertaining to the integration of liquid biopsy into OC management protocols (Supplementary Fig. S1).

## 2. Method

### 2.1. Data sources and search strategies

A single database was chosen for this study to streamline the process, reduce unnecessary operations, and decrease the possibility of human error. Therefore, it was chosen to search for bibliometric information on the *Web of Science (Clarivate Analytics)* website. As this was a comprehensive bibliometric analysis, ethical approval was not required. The collection of bibliometric information was completed on July 20, 2023 to avoid bias caused by daily updates of open databases. To ensure the completeness of the information search, we determined the final search formula based on Medical Subject Headings (MeSH) keywords:

((TS=(liquid-biopsy) OR TS=(fluid-biopsy) OR TS=(circulating-tumor-cell) OR TS=(CTC) OR TS=(cell-free-tumor- DNA) OR TS=(cfDNA) OR TS=(ctDNA) OR TS=(circulating-tumor-DNA) OR TS=(exosome)) AND (TS=(sensitivity) OR TS=(specificity) OR TS=(diagnosis) OR TS= (screening) OR TS=(accuracy)) AND (TS=(Ovar*- Cancer*) OR TS=(Ovar*- Neoplasm*))). Among the various types of publications, only original articles and reviews written in English were included.

### 2.2. Data collection and cleaning

Initially, raw data were extracted from the *Web of Science (Clarivate Analytics)* database. The recorded information consisted of the "full record with cited references". Subsequently, the exported information was subjected to a cleaning process that involved removing duplicates and eliminating data unrelated to the study's content. The detailed process of data cleaning is illustrated in Fig. 1. The final data were processed using bibliometric analysis softwires *Bibliometrix*, *CiteSpace*, and *VOSviewer*, and figures and tables were generated using *Origin 2021*, *Scimago*, *Figdraw* and *Microsoft Excel*.

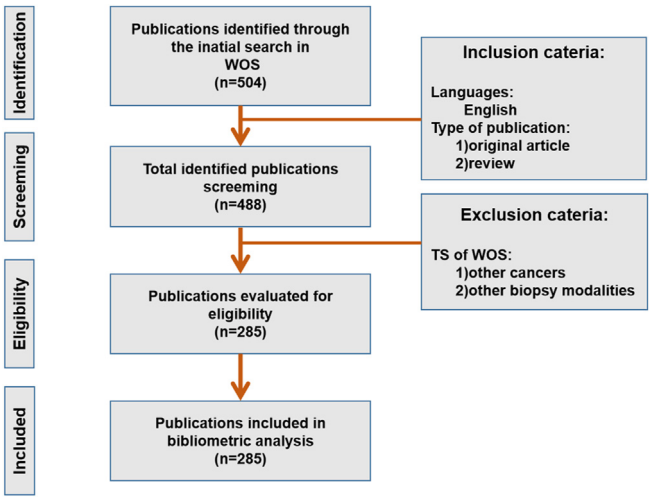


**Fig. 1.** Flowchart of the screening process.

## 3. Result

### 3.1. Overview

There were 504 publications initially retrieved from *Web of Science*. After data cleaning, a total of 285 publications were included for analysis (Fig. 2). Among these publications, 198 were original articles, and 87 were reviews. To assess the publication trend in the field, the number of publications from 1999 to 2023 was analyzed. The findings reveal a remarkable surge in publications beginning in 2013, with an average of 2 annual publications before this time. Since 2013, the average number of publications per year has soared to 25.27. Particularly noteworthy were 2021 (56) and 2022 (51), which stand out as the peak years with over 50 publications annually. Regression analysis of the annual publication numbers ($R^2 = 0.95$) indicated a clear upward trajectory, with expectations of surpassing 80 publications by 2025 (Fig. 2).

### 3.2. Country

There were 285 publications from 41 countries, of which China took the lead with 97 publications. Following China were the USA (73), Germany (26), Italy (18), and the United Kingdom (15) (Table 1).

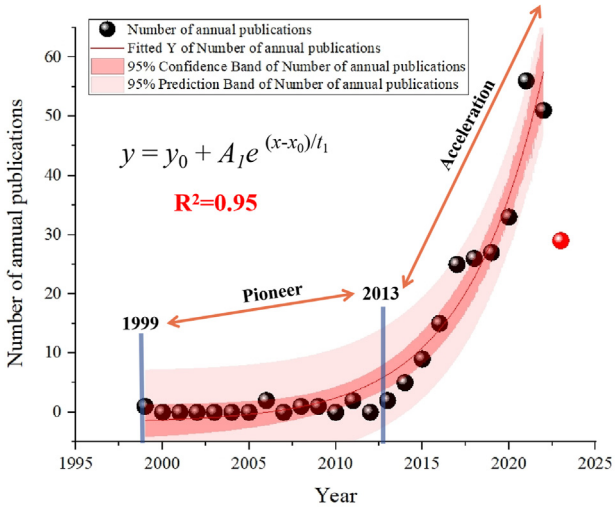


**Fig. 2.** The annual variation in the number of articles published on the application of liquid biopsy in OC from 1999 to 2023.

**Table 1**
The top 10 countries by number of publications.

| Rank | Country | Publications | Citations | Average Citation/ Publication |
|---|---|---|---|---|
| 1 | China | 97 | 2164 | 22.3 |
| 2 | USA | 73 | 6029 | 82.6 |
| 3 | Germany | 26 | 765 | 29.4 |
| 4 | Italy | 18 | 1712 | 95.1 |
| 5 | United Kingdom | 15 | 678 | 45.2 |
| 6 | South Korea | 14 | 285 | 20.4 |
| 7 | Canada | 12 | 297 | 24.8 |
| 8 | Australia | 10 | 1921 | 192.1 |
| 9 | Austria | 9 | 107 | 11.9 |
| 10 | France | 8 | 129 | 16.1 |

Notably, publications from China alone contributed to 34 % in total, underscoring its strong productivity. Regarding average citations, Australia (192.1), Italy (95.1), and the USA (82.6) ranked as the top three countries, while China ranked sixth with 22.3 citations per publication.

Collaboration analysis showed 39 countries were involved in international collaborative research on liquid biopsy (Fig. 3). The USA led in international collaborative publications with 51 papers, working with 21 other countries, followed by Germany (28), China (24), the United Kingdom (22), and Austria (15). Notably, the USA and China demonstrated the strongest collaboration, jointly producing 13 publications [13].

### 3.3. Journal

*Cancers* had published a total of 25 publications, making it the most prominent journal in this field. *Gynecologic Oncology* (13) ranked second, followed by *International Journal of Molecular Sciences* (12), *Journal of Ovarian Research* (12), and *Oncotarget* (9) (Supplementary Table S1).

The fluctuation in the number of publications of the top five journals over time is shown in Supplementary Fig. S2. The graph reveals minimal fluctuations in the number of annual publications for *Gynecologic Oncology*. However, *Cancers* experienced a significant surge in annual publications from 2020 to 2022. *Oncotarget* had a smaller number of articles but ranked first in terms of average citations. This highlights the high quality of its published literature.

Bradford's Law can be applied to identify journals with high local impact. The core journals filtered according to Bradford's Law are shown in Supplementary Fig. S3, which is also the top 9 journals with the highest publication volume, ranging from *Cancers* to *International Journal of Cancers* (Supplementary Table S1).

The overlay map shows that journals in the fields of *4.Molecular, Biology, Immunology,* and *2.Medicine, Medical, Clinical* exhibited strong citation relationships with journals in the field of *8.Molecular, Biology, Genetics*. Moreover, journals related to *Molecular, Biology, Genetics* had a higher number of publications, authors and citations, indicating that most of the relevant research is focused here (Fig. 4(B)).

### 3.4. Author

Kasimir-Bauer S had the most publications, with 9 papers, followed by Wimberger P and Buderath P, each with 6 papers. To assess the scholarly impact of authors, we calculated the H-index based on physicist Jorge Hirsch's method. Sehouli J had the highest H-index (54), highlighting the significance of his research in the field [14]. Kasimir-Bauer S stand out with the largest number of collaborators on the collaborative network map (Fig. 4(A)). Additionally, she was the most productive researcher, having published nine publications with an average of 72.9 citations per publication. Moreover, Buderath P and Zeillinger R, two researchers affiliated with the same cluster and closely connected to her, demonstrated significant productivity in their research endeavors. (Table 2).

### 3.5. Publication

Among the 285 publications analyzed, the study titled “Detection and

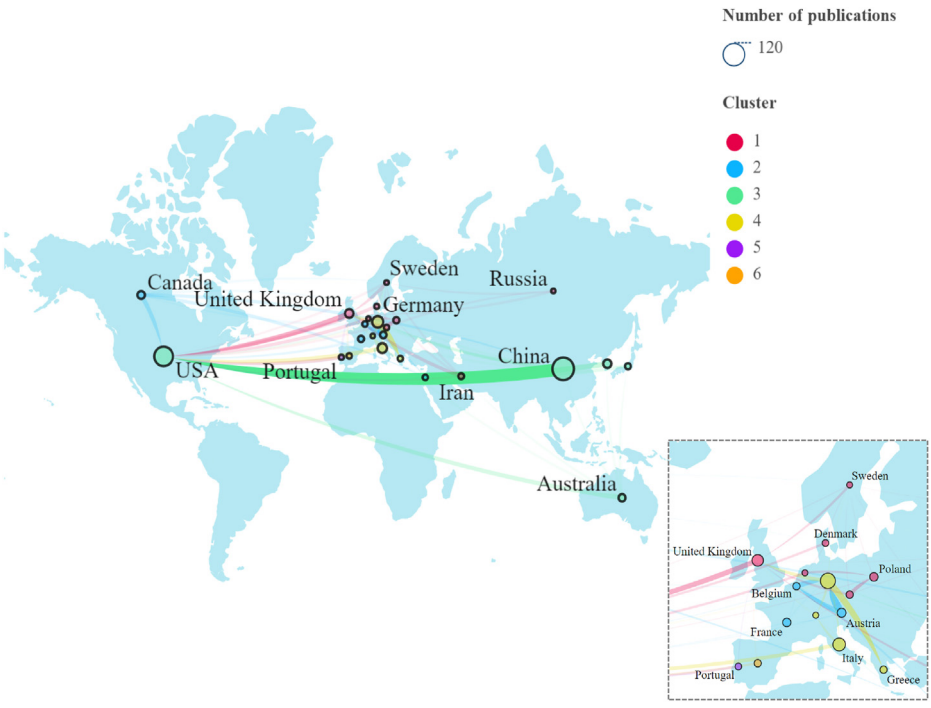


**Fig. 3.** Diagram of collaborative relations between countries. The color of the circles represents different research clusters. The size of the circles represents the number of publications, and the thickness of the line connecting two countries indicates the strength of their collaborative relations. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

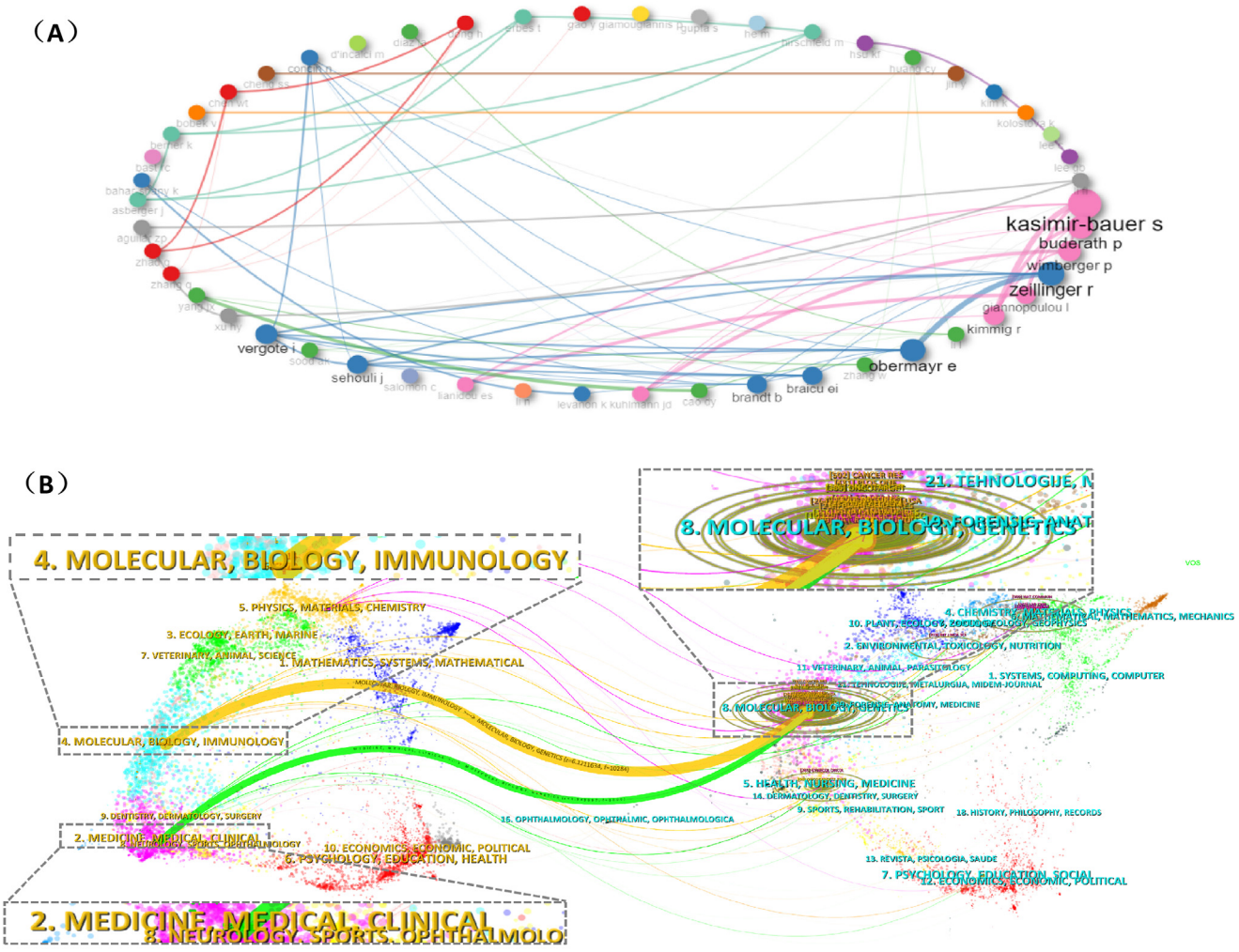


**Fig. 4.** **(A)** Author collaboration network map. Each circle represents a different author, with various colored circles representing distinct clusters. The number of links indicates the number of collaborations. **(B)** The overlay map of journals, with the citing graph on the left and the cited graph on the right. Use *CiteSpace* to perform a dual graph overlay of journals and fields to study the deeper connections behind the journals. The length of the ellipse corresponds to the number of authors, while the width represents the number of publications. The trajectory depicts the correlation among cross-disciplinary classifications.

**Table 2**
The top 10 authors with the most publications.

| Rank | Author | Publications | Citations | Average Citation/Publication | H-index | Local Citation |
|---|---|---|---|---|---|---|
| 1 | Kasimir-Bauer, Sabine | 9 | 386 | 42.9 | 32 | 96 |
| 2 | Wimberger, Pauline | 6 | 293 | 48.8 | 47 | 80 |
| 3 | Buderath, Paul | 6 | 175 | 29.2 | 17 | 38 |
| 4 | Braicu, Elena Ioana | 4 | 43 | 10.8 | 35 | 17 |
| 5 | Giannopoulou, Lydia | 5 | 139 | 27.8 | 6 | 29 |
| 6 | Kimmig, Rainer | 5 | 253 | 50.6 | 20 | 70 |
| 7 | Kuhlmann, Jan Dominik | 4 | 207 | 51.8 | 17 | 47 |
| 8 | Obermayr, Eva | 5 | 84 | 16.8 | 11 | 29 |
| 9 | Sehouli, Jalid | 5 | 51 | 10.2 | 54 | 19 |
| 10 | Zeillinger, Robert | 5 | 84 | 16.8 | 49 | 29 |

localization of surgically resectable cancers with a multi-analyte blood test," attracted the highest number of total citations and annual average standardized citations [15]. This article had been cited 1575 times, an average of 262.5 citations per year. The top two highly cited articles primarily focused on the diagnostic aspect of cancer. Notably, articles ranked third through sixth primarily focused on optimizing the processing of liquid biopsy-associated molecules (Table 3).

### 3.6. Keyword

We used *CiteSpace* to extract and sort out all the keywords from 285 publications. The analysis categorized the keywords into nine clusters based on topics (Fig. 5(B)). These clusters encompassed "ovarian cancer" along with commonly detected molecules in liquid biopsy, such as exosomes, CTCs, ctDNA, and tumor-educated platelets (TEPs). Furthermore, "fundamental medicine", "DNA methylation", "cell invasion", and

**Table 3**
Highly cited publications.

| Rank | Publications | Total Citations (TC) | TC per Year |
|---|---|---|---|
| 1 | Detection and localization of surgically resectable cancers with a multi-analyte blood test. | 1575 | 262.5 |
| 2 | Direct detection of early-stage cancers using circulating tumor DNA. | 636 | 90.86 |
| 3 | A microfluidic ExoSearch chip for multiplexed exosome detection towards blood-based ovarian cancer diagnosis. | 441 | 55.13 |
| 4 | Integrated Magneto-Electrochemical Sensor for Exosome Analysis. | 316 | 39.5 |
| 5 | Ultrasensitive detection of circulating exosomes with a 3D-nanopatterned microfluidic chip. | 286 | 57.2 |
| 6 | Ultrasensitive microfluidic analysis of circulating exosomes using a nanostructured graphene oxide/polydopamine coating. | 260 | 32.5 |
| 7 | Characterization and proteomic analysis of ovarian cancer-derived exosomes. | 212 | 19.27 |
| 8 | Proteomic profiling of NCI-60 extracellular vesicles uncovers common protein cargo and cancer type-specific biomarkers. | 162 | 20.25 |
| 9 | Exploratory Analysis of TP53 Mutations in Circulating Tumour DNA as Biomarkers of Treatment Response for Patients with Relapsed High-Grade Serous Ovarian Carcinoma: A Retrospective Study. | 158 | 19.75 |
| 10 | Exosomes: an overview of biogenesis, composition and role in ovarian cancer. | 149 | 13.55 |

"treatment" emerged as significant clusters for keyword analysis. In addition, the 285 publications also frequently mentioned other keywords such as "diagnosis", "markers", "progression", "proliferation", "chemotherapy", "resistance", and "metastasis" (Fig. 5(A)).

Burst words indicated research hotspots over a specific time frame. Among all the keywords, there were 21 keywords with burst strength greater than 1.5. Out of these, "metastasis" exhibited the strongest burst intensity at 3.42, followed by "circulating tumor cell" (3.39) and "recurrence" (3.23). Notably, "survival" (2.3) and "predictive value" (1.92) were keywords currently in the eruption process (Fig. 5(C)).

## 4. Discussion

### 4.1. Research status and global cooperation trends

In recent years, there has been growing recognition of the critical role that molecular data plays in the clinical management of OC patients. Advancements in genomic profiling and molecular characterization have provided significant insights into the underlying biology and heterogeneity of OC. One of the key developments has been the identification of distinct molecular subtypes of OC, such as the TCGA-defined Differentiated, Immunoreactive, Mesenchymal, and Proliferative subtypes [16]. These subtypes have been shown to have prognostic significance and may inform treatment selection. Furthermore, the integration of liquid biopsy-associated molecular data has significantly enhanced our understanding of OC heterogeneity, disease progression, and treatment responsiveness. CTCs, ctDNA, and exosomes have been investigated as sources of biomarkers for early detection, monitoring disease progression, and predicting treatment response. The continued efforts to translate these molecular insights into improved diagnostic, prognostic, and

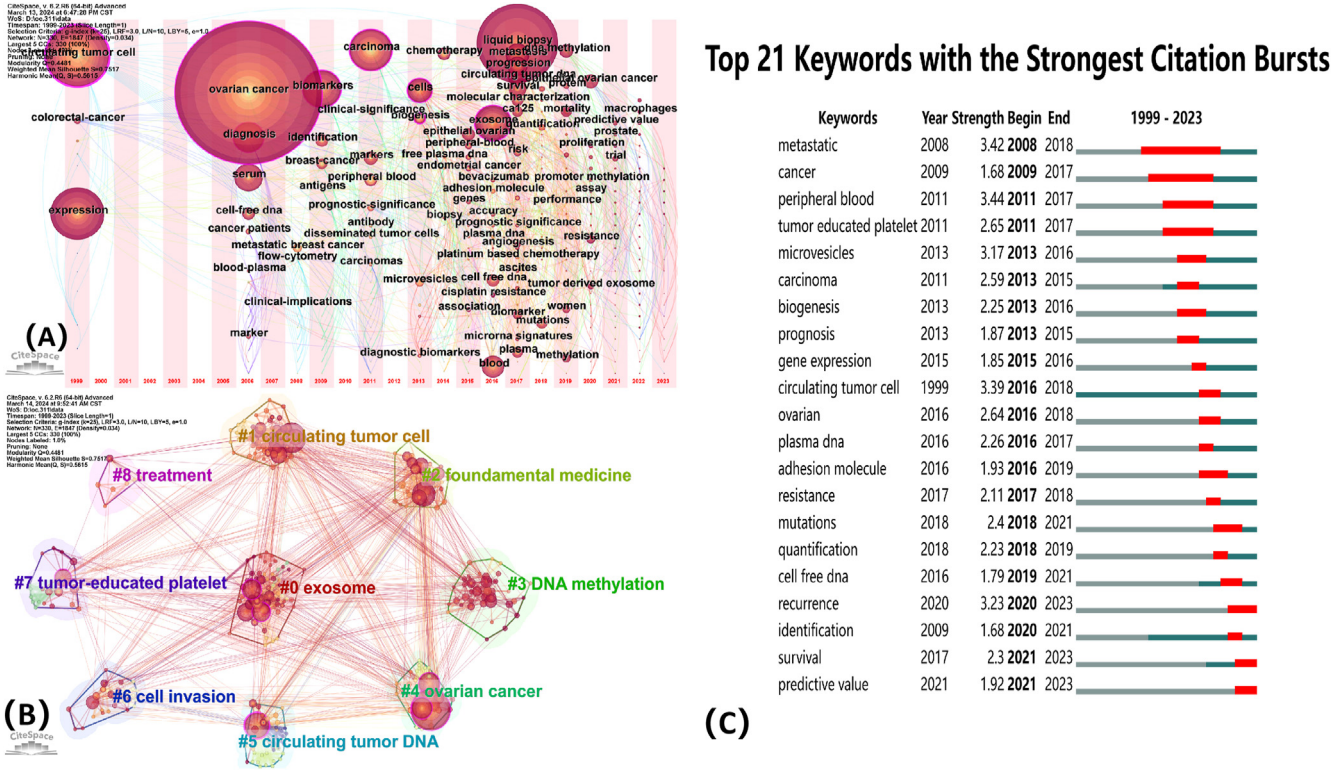


**Fig. 5.** **(A)** Temporal overlay of keywords. Each sphere symbolizes a unique keyword, with the combined size of overlapping spheres indicating the total occurrences of that keyword. Yellow denotes earlier publications, while fuchsia signifies more recent ones. The intertwining colors on the spheres create a ring pattern. Connections between nodes within the temporal dimension signify the co-occurrence of keywords. **(B)** Keyword Cluster Analysis. All keywords were classified into nine clusters based on the number of co-occurrences of the keywords and the strength of the connections. The central cluster serving as the core, exhibits robust connections to all other clusters. Each circle symbolizes a keyword, while each line signifies a co-occurrence relationship. **(C)** Top 21 keywords with the strongest citation bursts for research on liquid biopsy in ovarian cancer. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

therapeutic strategies are crucial for enhancing patient care and outcomes in OC [17].

Through bibliometric analysis, our research offered a comprehensive review of past findings, current trends, and future directions concerning the three main molecules in OC liquid biopsy: exosomes, CTCs, and ctDNA. In recent years, there had been a notable upswing in academic publications on liquid biopsy in OC. Additionally, the field had experienced a substantial surge in global publications since 2013.

#### 4.1.1. Emergence of U.S.-centered international cooperation

Between 1999 and 2023, China and the United States demonstrated the highest productivity in this field, attributable to their large population bases and extensive international cooperation. Furthermore, Australia, Italy, and the United States led in the number of citations per publication, indicating the consistently high quality of publications from these nations. Among all countries, the United States and China had the most robust collaborations, facilitated by the United States' abundance of research teams and China's largest number of active researchers. Unfortunately, despite being the country with the highest number of publications, China's performance in terms of citations per article has been subpar. This underscores the need for China to prioritize not only the quantity but also the quality of its publications. Further analysis of international collaborations showed the establishment of a collaborative network centered on the United States. The United States, with its globally renowned academic status, strong financial resources, and favorable academic environment, attracted foreign researchers for collaborations.

#### 4.1.2. International cooperation's role in enhancing authors' productivity

Recently, the number of highly productive researchers has significantly increased, totaling ten individuals who have published five or more publications. These researchers have actively collaborated with counterparts from different countries, contributing to the global exchange of scientific knowledge and expertise. The analysis of authors revealed that Kasimir-Bauer S stands out not only as the most productive author but also as one with strong collaborations. These collaborations extend beyond her home country, involving researchers from various nations. This observation underscored the correlation between collaborations and high productivity, emphasizing the importance for researchers to engage their research beyond national boundaries.

### 4.2. Research attention of hot publications

After conducting a thorough review of the literature, we identified the ten most influential publications, each accumulating over 100 citations. This result underscore the significant impact of these papers on the field. The top two highly cited publications primarily focused on the diagnostic aspect of OC. Notably, the third through sixth ranked articles all focused on optimizing the processing of liquid biopsy target molecules, specifically in the context of extracting, examining, and analyzing molecules needed for liquid biopsy. Additionally, other highly cited publications focus on basic medical research, studying the underlying mechanisms applicable to clinical practice. The above results highlight the trending research interest in the application of liquid biopsy in clinical settings. However, there remains a critical need to optimize the detection process and enhance the efficiency of liquid biopsy technology.

### 4.3. Research on keyword analysis

Keyword analysis is crucial for understanding the internal structure of a field, identifying research hotspots, and offering guidance for future studies. The investigation of keywords in the included publications revealed nine distinct clusters. Two of the nine clusters did not primarily address the molecular aspects of liquid biopsy or the biological behavior of ovarian cancer cells, but rather focused on specific research domains: “fundamental medicine” and “treatment".

Further investigation into the mechanisms and biological significance of liquid biopsy components is crucial before their clinical adoption.

Liquid biopsy has emerged as a promising approach for the early detection and monitoring of OC. While its primary utility lies in early diagnosis, liquid biopsy's scope has expanded to include the monitoring of treatment response, assessment of disease recurrence, and identification of potential therapeutic targets. As researchers delve deeper into the molecular landscape of OC, liquid biopsy continues to show promise in revolutionizing cancer diagnostics and personalized treatment strategies.

Liquid biopsy-associated molecules have been extensively studied for their role in early OC diagnosis.

Among exosomes, CTCs, and ctDNA, CTCs stand out as the most comprehensive and direct source of tumor information [18]. However, CTC-based diagnostics encounter challenges due to the limited tumor load. Research indicates that advanced tumors tend to shed more CTCs, often indicating metastasis, which aids in their identification. Consequently, CTC detection strongly correlates with advanced OC stages (III and IV) [19]. However, there are conflicting findings from some studies. The experimental outcomes of these studies indicate that alterations in CTCs are more pronounced in patients with early-stage OC (I and II) [20]. Therefore, further studies are needed to develop enhanced methods for increasing the sensitivity of CTCs detection and to establish consensus on testing standards, preparing it for more regular use in the early diagnosis of OC. Circulating tumor DNA, originating from primary tumor sites, also serves as a valuable source of tumor information such as methylation patterns, gene copy number variations, and mutation profiles of ctDNA. This information serves as a source of valuable biomarkers and offer insights into early-stage tumor characteristics. Several prior studies have consistently supported the diagnostic value of methylation alterations in genes like *BRCA1*, *HOXA9*, *ESR1*, *RASSF1*, and *RASSF2*, detected in plasma samples, for OC diagnosis [21–24]. Despite promising experimental findings, extensive large-scale studies are lacking to validate these marker's effectiveness as early diagnostic indicators for OC.

The diagnostic potential of exosomes hinges on their contents, particularly miRNA, due to their enhanced stability and ease of isolation. Several miRNAs, such as miR-1260a, miR-4732-5p, miR-192-5p, miR-320d, miR-4479, and miR-6763-5p, were notably down-regulated in plasma exosomes of OC patients [25–27]. Moreover, alterations in exosomal proteins may mirror changes in the primary OC site and the tumor microenvironment, offering promising data for early OC detection [28]. Prior large-scale studies have underscored the value of tumor cell exosomal proteins in diagnosing various cancers in lung, liver, and pancreas [29]. Nonetheless, there remains a scarcity of large-scale proteomic analyses in OC research.

Liquid biopsy, such as ctDNA analysis, has a potential to detect chemotherapy resistance [30]. Numerous studies have highlighted that alteration in exosome composition and gene variations in CTCs and ctDNA, involving methylation and copy number changes, are indicative of chemotherapy resistance in OC [31,32]. Methylation of *SLFN11*, *BRCA1* promoter, and *HOXA9* has emerged as indicators of drug resistance in OC, with ctDNA levels serving as markers for tumor chemotherapy resistance. During early treatment (within 14 days), ctDNA levels may initially rise slightly, possibly due to tumor cell death, but usually decrease rapidly over time if treatment is effective [33]. Similarly, CTCs features gene changes associated with drug resistance, which is a viable method for monitoring chemotherapy resistance in OC. However, there remains a lack of significant enough correlation to precisely infer chemotherapy resistance from CTCs counts. Additionally, exosome-derived miRNAs, including miR-6836, miR-223, miR-21-3p, miR-21-5p, and miR-891-5p, are implicated in reflecting chemoresistance in OC [34–37].

### 4.4. Current research hotspot: predictive value of liquid biopsy in OC

Overlay maps of journals can illustrate the macro-level evolution of research directions, while temporal overlays can depict changes in

research hotspots at a micro level [38].

In the overlay map of journals, the “citing journals” are typically seen as the forefront of research, whereas cited journals form the foundation. As dual graph overlay of journals shown that research on liquid biopsy in OC has primarily focused on basic medicine historically, particularly molecular biology. However, recent research advancements have sparked a significant directional shift. There is a greater focus on clinical medicine aspects related to molecular biology, which is an natural direction of a fast developing field.

The temporal overlay offers insights into historical trends, facilitating a detailed understanding of past advancements in the field. Burst words assist in identifying current research hotspots through keywords. Initially, the temporal keyword overlay indicated the prevalence of “maker"-related keywords, but by 2017, the emergent term “survival” gained prominence. Furthermore, the analysis of burst keywords revealed that “predictive value,” “recurrence,” and “survival” are currently more prevalent. Synthesizing the findings from the overlay map and keyword analysis reveals a shift in current research focus from mechanistic elucidation to the clinical application of liquid biopsy. Particularly, there is increased emphasis on the predictive value of liquid biopsy for OC, encompassing both recurrence and survival prediction.

Liquid biopsy holds the potential to timely prediction and monitoring of treatment effectiveness. Although most OC patients achieve complete remission after primary tumor-reducing surgery and adjuvant chemotherapy, 70 % of them experience recurrence during subsequent treatments [39]. Intra-tumor heterogeneity, representing genomic variation within a lesion due to tumor cell evolution during multistep tumorigenesis, is identified as the primary cause of treatment failure [30,40]. Liquid biopsy offers the potential for a more comprehensive analysis of tumor heterogeneity, enabling the longitudinal monitoring of tumor evolution throughout treatment. Thereby, liquid biopsy can aid in predicting OC progression and OC patients' survival [41].

Currently, there is a lack of prognostic assessment of a large sample size to draw consensus in the competency of liquid biopsy as a prognostic indicator in clinical practice. In addition, finding more targets related to the predictive value of OC and elucidating how the targets act with OC could be the next step in the development of the liquid biopsy field.

## 5. Limitations

To counter subjective errors resulting from merging databases, we opted for a single database, Web of Science. However, it was inevitable to introduce information bias as daily updates of the database after the data collection were not included, and thus, we can only guarantee the accuracy of the data at the time of information counting (July 20, 2023).

During the process of inclusion and exclusion of 504 publications, a meticulous strategy was established. Two researchers, unaware of each other's knowledge, were independently and simultaneously assigned to carry out the task. Nonetheless, the selection of papers may still entail an unavoidable degree of subjectivity.

In the analysis of literature keywords, the merging of certain synonyms, such as “cancer” and “cancers,” was required. Despite our best efforts to merge all synonyms, there remains the possibility that some hidden synonyms might remain unmerged.

In our data analysis, software variations in algorithms may lead to slight result variations. However, we have made efforts to use identical algorithms across various software platforms to maintain consistency in our conclusions and to guarantee the reliability of all discussed results in this paper.

## 6. Conclusion

The bibliometric analysis conducted in this study provides a comprehensive overview of the current state and emerging trends in the research of liquid biopsy for OC. The findings indicate that research in this field has been steadily growing over the past 25 years, with a significant increase in publication output in recent years.

The key areas that are currently experiencing rapid growth and exploration include the use of liquid biopsy for disease recurrence monitoring, predictive biomarker identification, and survival prognosis. These findings highlight the potential clinical utility of liquid biopsy in improving the management and treatment of OC patients. EVs, especially exosomes, have gained significant attention as a rich source of biomarkers [42]. For instance, Salem et al. employed an immunoassay to capture and detect ovarian cancer EVs, achieving excellent performance in discriminating OC from noncancer controls [43]. Cooper et al., Jo et al., and Lai et al. identified EOC-specific protein markers in EVs through proteomic profiling, effectively distinguishing EOC from noncancer controls [44–46].

The successful implementation of liquid biopsy in OC relies on the availability of robust and reliable methodological approaches to evaluate various biomarkers [47]. Key methodological considerations include standardized sample collection and processing protocols, sensitive analytical techniques for biomarker quantification and characterization, rigorous biomarker validation to establish clinical utility, sophisticated data analysis and interpretation, and effective integration of liquid biopsy biomarkers into clinical decision-making [48,49]. By addressing these methodological challenges, researchers and clinicians can enhance the reliability, reproducibility, and clinical value of liquid biopsy biomarkers in the management of OC, ultimately leading to improved patient outcomes.

As the field continues to evolve, future research should focus on further validating the clinical performance of liquid biopsy-based approaches, exploring novel biomarker candidates, and developing integrated diagnostic and prognostic models that leverage the advantages of this minimally invasive technology. Continued efforts in this direction will be crucial in translating the promising potential of liquid biopsy into tangible improvements in OC patient outcomes.

## Contributions statement

Jixian Wan performed all data analyses and wrote the original manuscript. Zechuan Rao and Huaichao Liu wrote and critically reviewed the manuscript. Jipeng Wan conceived, designed, and directed the study.

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## Data availability

This study used data from the *Web of Science* database, further inquiries can be directed to the corresponding authors.

## Human and animal rights

This article does not involve any studies with human participants or animals conducted by any of the authors.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jlb.2024.100158.

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