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Original Article

Immune cells regulate matrix metalloproteinases to reshape the tumor microenvironment to affect the invasion, migration, and metastasis of pancreatic cancer

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Abstract: This study aimed to identify author, country, institutional, and journal collaborations and assess their impact, along with knowledge base, as well as identify existing trends, and uncover emerging topics related to matrix metalloproteinase and pancreatic-cancer research. A total of 1474 Articles and reviews were obtained from the Web of Science Core Collection and analyzed by Citespace and Vosviewer. CANCER RESEARCH, CLINICAL CANCER RESEARCH, and FRONTIERS IN IMMUNOLOGY are the most influential journals. The three main aspects of research in matrix metalloproteinases-pancreatic cancer-related fields included the pathogenesis mechanism of pancreatic cancer, how matrix metalloproteinases affect the metastasis of pancreatic cancer, and what role matrix metalloproteinases play in pancreatic cancer treatment. Tumor microenvironment, pancreatic stellate cells, drug resistance, and immune cells have recently emerged as research hot spots. In the future, exploring how immune cells affect matrix metalloproteinases and reshape the tumor microenvironment may be the key to curing pancreatic cancer. This study thus offers a comprehensive overview of the matrix metalloproteinases-pancreatic cancer-related field using bibliometrics and visual methods, providing a valuable reference for researchers interested in matrix metalloproteinases-pancreatic cancer.

Keywords: Matrix metalloproteinases, invasion and migration, metastasis, tumor microenvironment, immune cells

Introduction

Cancer has always been a significant problem plaguing humanity [1-6]. The latest cancer statistics from the US show that by 2022, there will be 1,918,030 new cancer cases and 609,360 cancer deaths in the United States. Pancreatic cancer (PC) is one of the top three causes of death among cancer patients, with 62,210 new cases and 49,830 deaths expected in 2022 [7]. The poor prognosis of pancreatic cancer is closely related to its local invasion and early metastasis [8-10]. *In vitro* studies have shown that proteolytic degradation of extracellular matrix (ECM) components is a significant step in tumor invasion, and various proteases play an integral role in this process [11-13]. Matrix metalloproteinases (MMPs) have attracted widespread attention because of their high correlation with cancer [14, 15].

MMPs are a family of ECM-modifying enzymes initially thought not to be critically involved in biological processes [14, 16]. Nevertheless, with further research, MMPs were found to be involved in various autoimmune diseases, inflammatory diseases, cancer, epithelial-mesenchymal transition, and host-microbe interac-

tions [17, 18]. Among them, MMPs are highly associated with pancreatic cancer progression and metastasis due to their ability to degrade all components of the ECM. Numerous studies have shown that pancreatic cancer tissues highly express MMP-1, MMP-2, MMP-7, MMP-9, MT1-MMP, MT2-MMP, and MT3-MMP; among which MMP-2, MMP-7, MMP-9 have been recommended as biomarkers for pancreatic cancer [19, 20]. To further explore the role of MMPs in pancreatic cancer, this study comprehensively incorporated matrix metalloproteinases-pancreatic cancer (MMPs-PC) related literature to analyze the field thoroughly.

There are many ways to systematically review a research field, among which the bibliometric method is one of the most commonly used approaches [21]. Bibliometric analysis can study the contributions and collaboration of researchers, organizations, nations, and journals qualitatively and quantitatively and assess academic research's developmental status and new tendencies. The bibliometric method can also consider conventional reviews, meta-analysis, or experimental studies, whose analysis cannot be performed using other approaches [22-24]. Based on these advantages, this method is increasingly used to assess academic tendencies and develop guidelines. Hence, we used bibliometric analysis for evaluating and summarizing MMPs-PC related studies.

This study aimed to objectively delineate the knowledge in the field and illuminate new trends in MMPs-PC research from the following four dimensions using two standard bibliometric tools, CiteSpace and VOSviewer [25, 26]. (1) We intended to quantify and identify general information in MMPs-PC studies by studying yearly articles, journals, co-cited journals, nations, organizations, researchers, and co-cited researchers. (2) We strived to identify and study the top 100 most cited articles through co-citation reference analyses to assess the knowledge base of MMPs-PC. (3) We aimed to identify the knowledge structure and hotspot evolution through keyword and co-citation reference burst analyses. (4) Meanwhile, under the analyses of the journals, countries, and keywords of the former top 100 articles and co-cited journals, combined with the analysis content of part (3), the research content and possible new directions in the field of MMPs-PC were further determined.

Materials and methods

Study design

This study used bibliometric analysis to study scientific journals investigating MMPs-PC. The study is divided into two parts: the first is the study of all the published articles in the MMPs-PC-related field using Web of Science Core Collection (WOSCC); the second is the analysis of the first 100 highly cited papers in the MMPs-PC field (**Figure 1**).

Data collection

Our team used the WoSCC database as it can offer comprehensive data required by the bibliometric software and is considered the most powerful database [27]. Data were acquired from the WoSCC database on March 16, 2022, and the relevant data can be found in Supplementary Table 10. Our main search terms were "pancreatic cancer" [28] and "matrix metalloproteinases" [29]. Part I: All articles relevant to the MMPs-PC field were downloaded from WoSCC (Time span from the establishment of WoSCC to December 30, 2021). Part II: Two independent researchers manually screened the top 100 most-cited articles relevant to the MMPs-PC field. Search conditions: The language was limited to English, and the type of article was restricted to articles and reviews. The retrieval outcomes were downloaded from the recorded content of "Full Record and Cited References".

Data analysis and visualization

The most frequently utilized bibliometric programs are VOSViewer, CiteSpace, SCI2, NetDraw, and HistCite. There is no consensus on the best bibliographic approach. After careful consideration, this study utilized VOSviewer and CiteSpace.

Our team used VOSviewer1.6.15 to determine influential journals, co-cited journals, researchers, co-cited researchers, and associated knowledge graphs based on bibliographic information [30]. Moreover, our team created keyword co-occurrence and clustering diagrams based on text data. First, the data were cleaned. For example, "matrix metalloproteinase" and "matrix metalloproteinases" were unified to "MMPs" in the keyword analysis. The project's

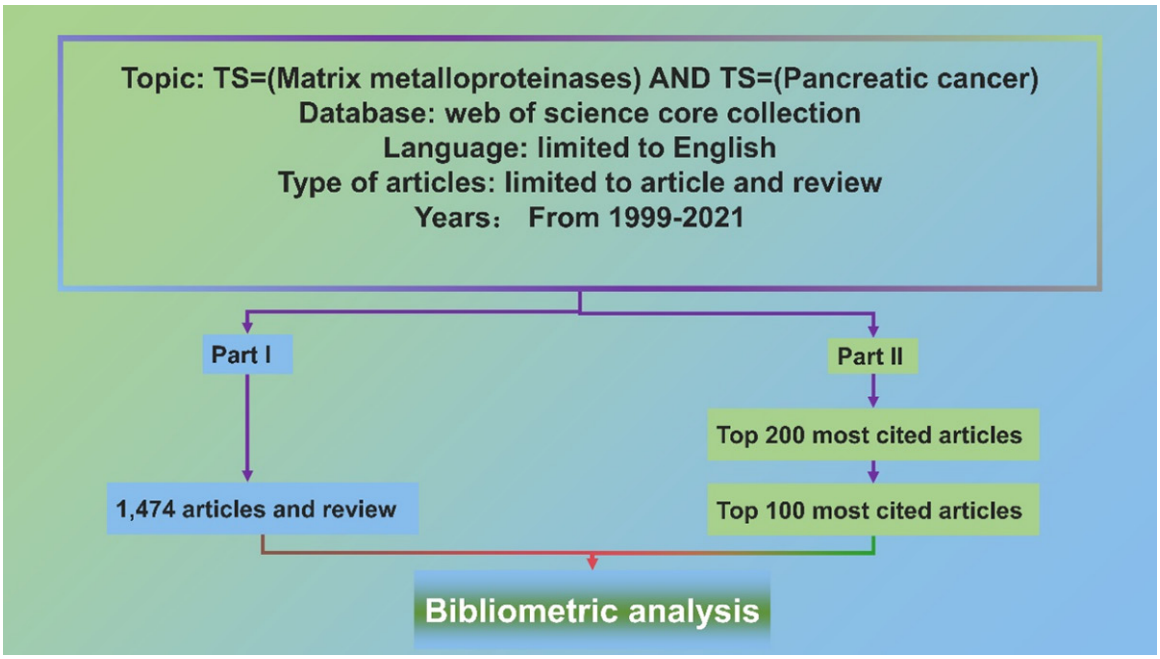

Figure 1. Research Design Roadmap.

other thresholds (T) were set according to different circumstances and marked in the relevant tables and illustrations.

CiteSpace, proposed by Professor Chen Chaomei, is a bibliometric and visualization analysis tool suitable for investigating collaboration, key points, inner architectures, and latent tendencies in a specific field [25]. Hence, our team used CiteSpace6.1.R2 to study and visualize the co-occurrence of nations and organizations, dual maps, high-frequency keyword trends, co-citation references, and citation bursts. The data were cleaned before the investigation; for example, articles from Taiwan were classified as China in the country analyses, whereas publications from England, Scotland, Northern Ireland, and Wales were assigned to the United Kingdom (UK). The CiteSpace settings are stated below: time span, 1999-2022; years per slice, 1, pruning, minimum spanning tree and pruning sliced networks; selection standards, Top N = 50; and others followed the default.

Microsoft Office Excel 2019 was used to process the annual database of articles. Furthermore, the 2021 periodical IF and JCR Division were obtained from the Web of Science in Cites Journal Citation Reports on July 22, 2022.

Results

The annual growth trend and the number of annual cited departments

As per the data acquisition method, our team obtained 1474 articles upon limiting the types of documents to articles and reviews and the language to English. A total of 1474 eligible articles (Supplementary Table 10) published between 1999 and 2021 were selected. From **Figure 2A**, we can observe that references related to MMPs-PC generally showed an increasing trend. It is worth noting that the citations of published articles in 2018-2021 have increased significantly. In addition, we also analyzed the top 10 countries with published articles (**Figure 2B**): America was leading in publishing articles until 2011 (1999-2011). Since 2012, China has shown great interest in the field of MMPs-PC, surpassing the United States to become the country with the greatest number of articles published.

Journals and co-cited journals

Our team utilized VOSviewer to analyze journals and co-cited journals to find the most influential and vital journals concerning the MMPs-PC field. The results revealed that 1474 articles related to this field were published in 477 jour-

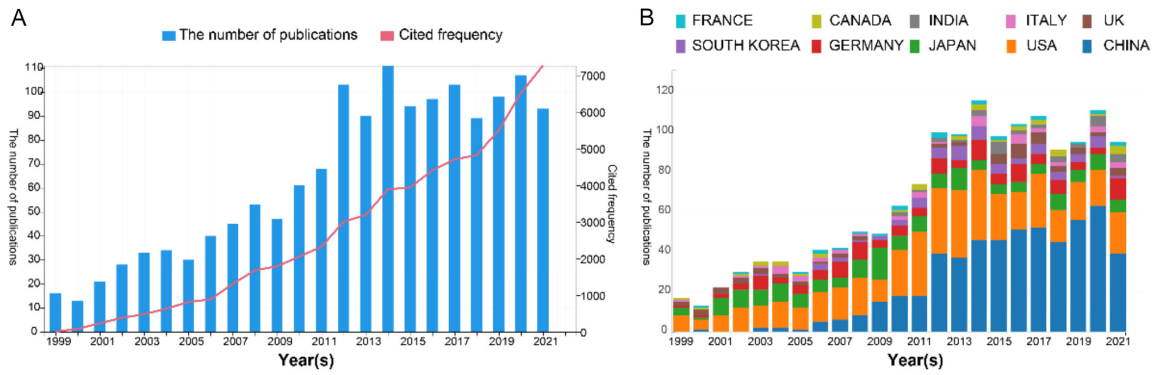

Figure 2. A. Annual publication number and citation frequency of MMPs-PC-related studies. B. Composition ratio of the top 10 countries by the publication number.

nals. The CANCER RESEARCH published the most articles (43, 2.917%) (Supplementary Table 1).The US and UK accounted for half of the publications. Among the top 10 journals, six were from the Q1 JCR division, and 7 had an impact factor (IF) above five (Supplementary Table 1). Among the 4418 most commonly cited journals, 11 were cited > 1000 times. As presented in Supplementary Table 2, CANCER RESEARCH had the greatest number of citations (N = 4661), followed by JOURNAL OF BIOLOGICAL CHEMISTRY (N = 2273) and CLINICAL CANCER RESEARCH (N = 2058). Among the top 10 co-cited journals, except for JOURNAL OF BIOLOGICAL CHEMISTRY, all other co-cited journals were from the Q1 JCR division. Meanwhile, the IF of all co-cited journals was more than 5. It is worth noting that the US and UK accounted for most of the top 10 cited journals.

The journal dual-map overlay represents the topic distribution status of journals (**Figure 3**) [31]. Citation journals are on the left, cited journals are on the right, and the color path indicates the citation relationship. Two primary citation paths were determined, which meant that research published in Molecular/Biology/Immunology and Medicine/Medical/Clinical journals was predominantly cited by a study published in Molecular/Biology/Genetics journals.

Country/region and institution

A total of 1595 institutions from 62 countries published the 1474 articles. The most significant number of publications came from China (545, 30.67%), followed by the United States (427, 24.03%) and Japan (162, 9.17%) (Supplementary Table 3). As we have presented in Supplementary Table 3, the United States, China, and Germany have made indelible contributions in the MMPs-PC field (**Figure 4A**). In addition, according to link color, the United States (1999), Germany (1999), UK (1999) and China (2000) were the first countries to conduct studies on MMPs-PC field. We used minimal spanning tree pruning to clarify the net (**Figure 4A**). The standard map of unpruned countries contained 58 nodes and 132 links with a density of 0.0859, revealing active collaboration between diverse nations. For example, the United States cooperated with 49 nations, followed by China (n = 45) and Germany (n = 42).

More than half of the top 10 institutions were from China (6/11), followed by the USA (4/11) (**Figure 4B**) (Supplementary Table 3). Shanghai Jiao Tong Univ (35, 1.09%) published the most papers, followed by China Med Univ, Nanjing Med Univ, Univ Texas MD Anderson Canc Ctr, and Xi An Jiao Tong Univ (29, 0.90%) (Supplementary Table 3).

Author and co-cited author

Eight thousand seven hundred forty-six researchers participated in MMPs-PC research. Furthermore, 11 published more than ten papers. Ma, Qingyong wrote the most articles (n = 16), followed by Guha, Sushovan (n = 14), Tanaka, Masao (n = 9) (Supplementary Table 4). To construct authors it includes authors who have authored more than five articles (T ≥ 5) (n = 91) (**Figure 5**). Such knowledge graphs

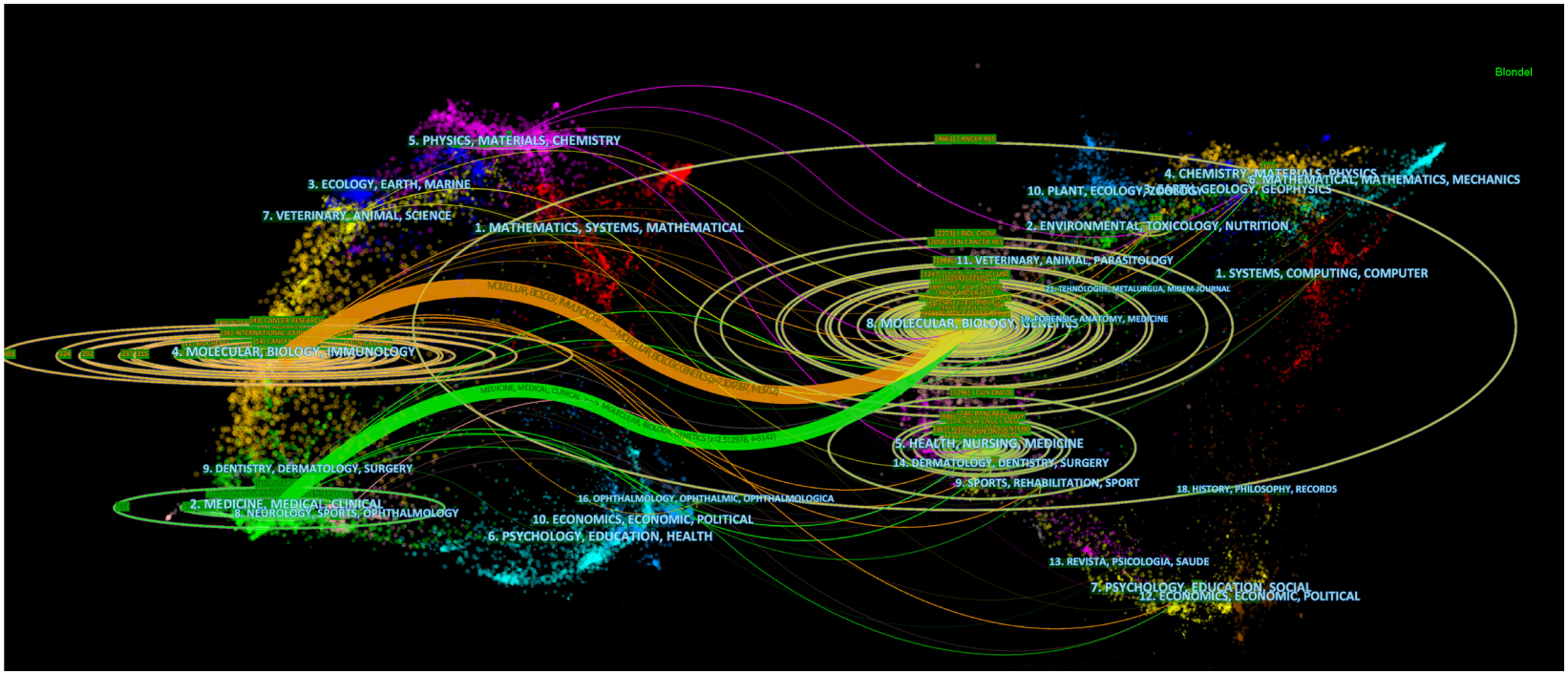

Figure 3. The dual-map overlay of journals related to MMPs-PC research. Notes: The citing journals were on the left, the cited journals were on the right, and the colored path represents the citation relationship. MMPs-PC, matrix metalloproteinases-pancreatic cancer.

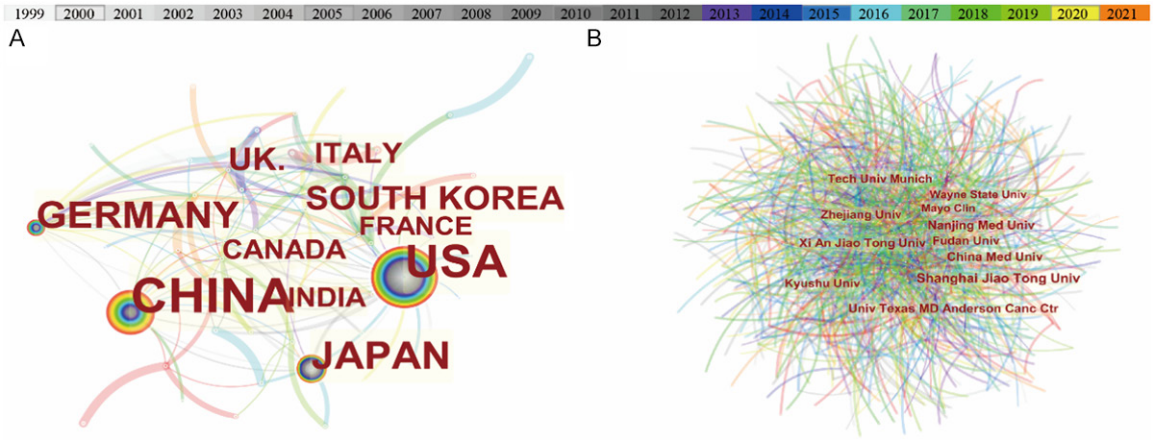

Figure 4. The co-occurrence map of (A) countries/regions and (B) institutions in MMPs-PC research (T ≥ 19). Notes: The node's size reflects the co-occurrence frequencies, and the links indicate the co-occurrence relationships. The color of the node and line represent different years. Colors vary from grey to orange as time goes from 1999 to 2022; a node with a purple round means high betweenness centrality (> 0.1). MMPs-PC, matrix metalloproteinases-pancreatic cancer.

can present high-frequency researchers. As represented in **Figure 5**, Ma, Qingyong, Wang, Zheng, and Li, were closely linked and formed a group of authors with the reddest color, indicating that the group has made outstanding contributions in the field of MMPs-PC. Batra, Surinder k, Guha, Sushovan, Aggarwal, Bharat B, and Diagaradjane, Parameswaran, constituted the second largest group of authors. Tanaka, Masao, and Imaizumi, Akira constituted the third largest group of authors.

Co-cited researchers are those who have been co-cited in a range of publications. Amongst the 37,647 co-cited researchers, 10 had more than 90 citations [32, 33]. Bramhall, Simon R. (n = 261) was ranked first, followed by Jemal, Ahmedin (n = 202) and Siegel, Rebecca L. (n = 179). The number of co-citations of the top 3 authors ranged from 179 to 261 (Supplementary Table 4). These co-cited authors (n = 100) and at least 35 co-citations (T ≥ 35) were selected to draw a network diagram of the co-cited researchers (**Figure 6**), with identical colors representing identical clusters. Co-cited authors were divided into four main clusters. Close cooperation was observed among authors in the same cluster, such as Bramhall, Simon R, Liotta, La, Bloomston, Mark P, egeblad, m, Ellenrieder, Volker, Coussens, Lisa M and Yamamoto, Hirokiin the field of MMPs-PC. Simultaneously, we also observed close cooperation between clusters such as Siegel, Rebecca L., and Jemal, Ahmedin.

Keyword co-occurrence, clustering, and development

VOSviewer was utilized to present keyword co-occurrence (Supplementary Table 5; **Figures 7** and **8**) and cluster analyses (**Figure 7**). An Overall 2747 keywords were abstracted, of which 95 occurred over six times and 76 occurred over seven times. The keyword density map (**Figure 7**) can find high-frequency co-occurrence entries and unveil hotspots in specific academic fields. As presented in Supplementary Table 5 and **Figure 7**, "invasion and migration" is a critical term, appearing 204 times in total (11.09%), followed by apoptosis, mmp-9, epithelial-mesenchymal transition (emt), mmp-2, angiogenesis, proliferation, and prognosis.

Cluster analysis can reveal the knowledge architecture of a research field [34]. The net was separated into three clusters according to the link strength of keyword co-occurrence (**Figure 8**). The keywords in each cluster were highly homogeneous. Cluster 1 (red) was the most significant cluster with 39 co-occurrence keywords, including pancreatic cancer, gemcitabine, tumor microenvironment, nf-kappa b, pancreatic stellate cells, and extracellular matrix, e-cadherin, Akt, and inflammation. The keywords of Cluster 1 were mainly related to the pathogenesis mechanism of pancreatic cancer. Cluster 2 (green) was primarily associated with how MMP affects pancreatic cancer

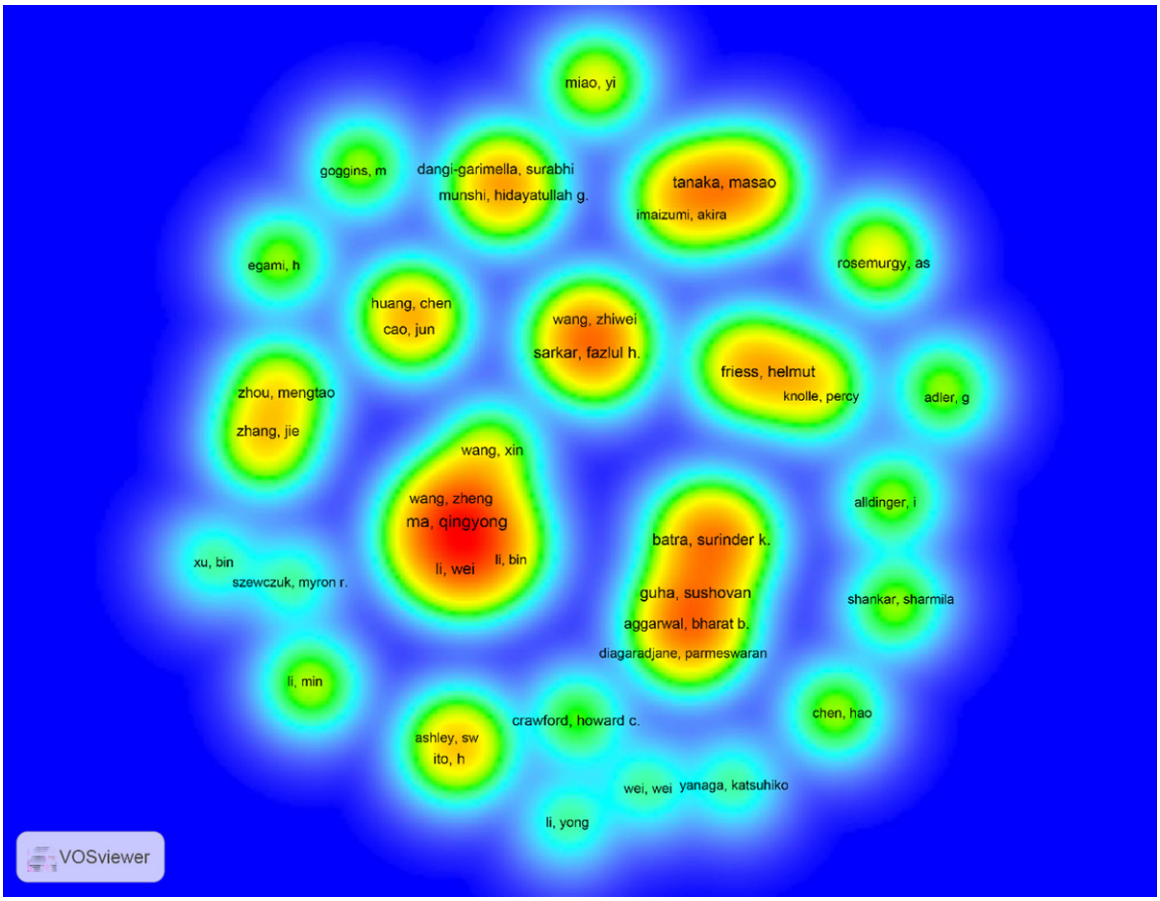

Figure 5. The density map of authors in MMPs-PC research (T ≥ 5). Notes: The size of the word, round, and the opacity of yellow are positively related to the publication frequency. MMPs-PC, matrix metalloproteinases-pancreatic cancer.

metastasis and included 35 keywords, such as invasion and migration, metastasis, mmp, apoptosis, metastasis, emt, mmp-9, mmp-2, angiogenesis, and proliferation. Cluster 3 (blue) focused on what role MMP plays in pancreatic cancer treatment and contained 22 keywords, including A Disintegrin And Metalloprotease (adam) family (adam10, adam8, adam9), biomarkers, ca19-9, pericytes, cancer therapy, diagnosis, and drug delivery.

The keyword with the most substantial citation burst was developed by CiteSpace and could present the citation status of high-frequency keywords. Keywords are sorted by citation strength, with dark blue representing how long the keyword has existed and red representing the time it has been cited in a burst. High-frequency keywords (Top 50) are presented in **Figure 9**. As per the results, the EMT, with high citation strength (10.54) has been in a state of citation burst in recent years and may continue to become a research hotspot in the future.

Co-cited reference and reference burst

Our team used CiteSpace to identify the co-cited references. (Supplementary Table 6) results show that the top 10 co-cited references were co-cited ≥ 40 times, four of which were co-cited more than 60 times. The most frequently co-cited reference is a paper written by Egeblad, Mikala, et al. published in NATURE REVIEWS CANCER in 2002 [35], entitled “New functions for the matrix metalloproteinases in cancer progression”, followed by an article entitled “Matrix Metalloproteinases: Regulators of the Tumor Microenvironment” [36].

Reference citation burst is when references are often cited over some time [37]. In CiteSpace, our team set the burst duration to ≥ 2 years. We identified 148 references with the total cita-

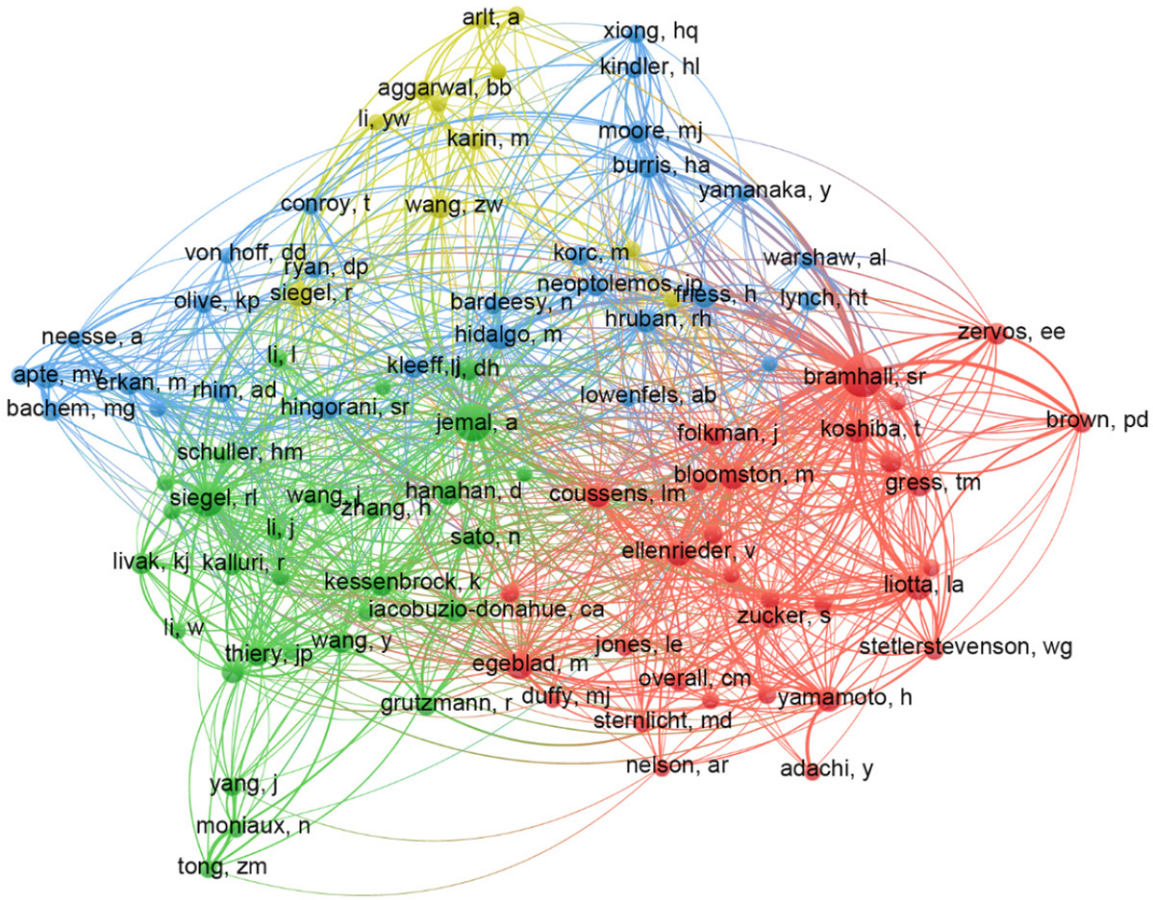

Figure 6. The co-occurrence map of co-cited authors in MMPs-PC research (T ≥ 35). Notes: The link indicates the co-occurrence relationship between authors, and the same node color represents the same cluster. MMPs-PC, matrix metalloproteinases-pancreatic cancer.

tions and selected the top 20 references as the object of analysis. **Figure 10** shows that the top 20 burst references were published after 1999 and had high citation outbreaks in 2002, 2011, and 209 (3/20, 15%). It is worth noting that by 2022, 6 references (30%) were in a state of citation burst. The most substantial citation burst reference was "Cancer statistics, 2015". Rebecca L Siegel and others have maintained a high citation rate since their publication in CA-A CANCER JOURNAL FOR CLINICIANS [38].

Analysis of journal, countries, and keywords of the top 100 most-cited articles

The top 100 most-cited articles were defined as cited articles with a high correlation with MMPs-PC. We analyzed the journals and co-cited journals of the top 100 most-cited articles (Supplementary Tables 7, 8 and **Figure 11**). Sixteen journals have published more than two articles, of which CANCER RESEARCH (n = 14) and CLINICAL CANCER RESEARCH (n = 8) ranked in the top two. The publication number of other journals in this field is maintained at 2-3, and the representative journal is ACS NANO (n = 3) and FRONTIERS IN IMMUNOLOGY (n = 2).

In the co-cited journals, CANCER RESEARCH (n = 566) was the most common, followed by CLINICAL CANCER RESEARCH (n = 229), JOURNAL OF BIOLOGICAL CHEMISTRY (n = 185), and INTERNATIONAL JOURNAL OF CANCER (n = 163). Interestingly, in the top 100 most-cited articles field, FRONTIERS IN IMMUNOLOGY is not only a high publication volume journal but also a high co-citation journal. Roughly consistent with the overall field analysis, journal analysis of the top 100 most-cited articles also identified only one primary orange citation path, which suggests that research published

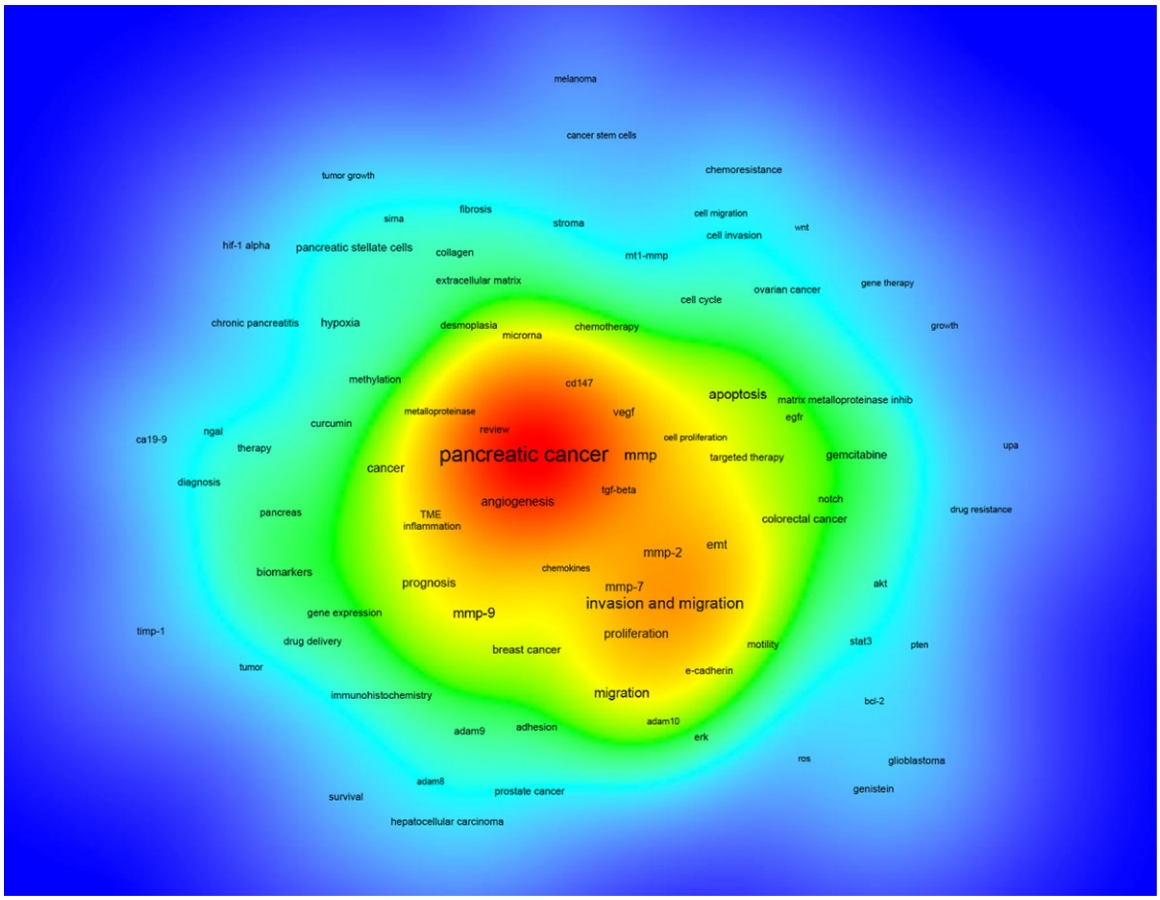

Figure 7. The density map of terms in MMPs-PC research (T ≥ 6). Notes: The word's size, round, and red opacity positively relate to the co-occurrence frequency. MMPs-PC, matrix metalloproteinases-pancreatic cancer.

in the Molecular/Biology/Immunology journal is predominantly cited by a study published in the Molecular/Biology/Genetics journal.

We also analyzed the countries with the top 100 most-cited articles (**Figure 12**). United States (n = 53) was the nation with the most papers, followed by China (n = 17). China has frequent academic exchanges with the United States, while the United States has ties with nine countries, including CHINA, JAPAN, the UK, and GERMANY. To further analyze the development content and trend of the MMPs-PC field, we analyzed the keywords of the top 100 articles. The keyword of the top 20 (Supplementary Table 9) coincided with the top 20 (Supplementary Table 5) in the MMPs-PC field, such as prognosis, pancreatic stellate cells, nf-kappa b, metastasis, invasion and migration, gemcitabine, EMT, apoptosis, and angiogenesis. This shows that the primary research content of MMPs-PC is related to the above keywords. The net was separated into three clusters according to the link strength of keyword co-occurrence (**Figure 13**). Cluster 1 (red) was the most significant cluster with 93 co-occurrence keywords, including pancreatic cancer, invasion and migration, NF-kappa beta, EMT, angiogenesis, extracellular matrix, micro-environment, and metastasis. The theme of Cluster 1 is highly correlated with the possible biological mechanism of distant metastasis of pancreatic cancer. Cluster 2 (green) was primarily associated with survival, prognosis, and pancreatic cancer biomarkers and included 17 terms, such as survival, prognosis, biomarkers, 24p3, cd147, and lipocalin. Cluster 3 (blue) focuses on MMP and contains 16 terms, such as cancer therapy, collagenase, MMP inhibitors, and TIMP (Tissue inhibitor of metalloproteinase). Cluster 4 (yellow) focuses on clinical medicine for pancreatic cancer and contains six terms: gemcitabine, marimastat, pancreatic cancer therapy, and tumor microenvironment.

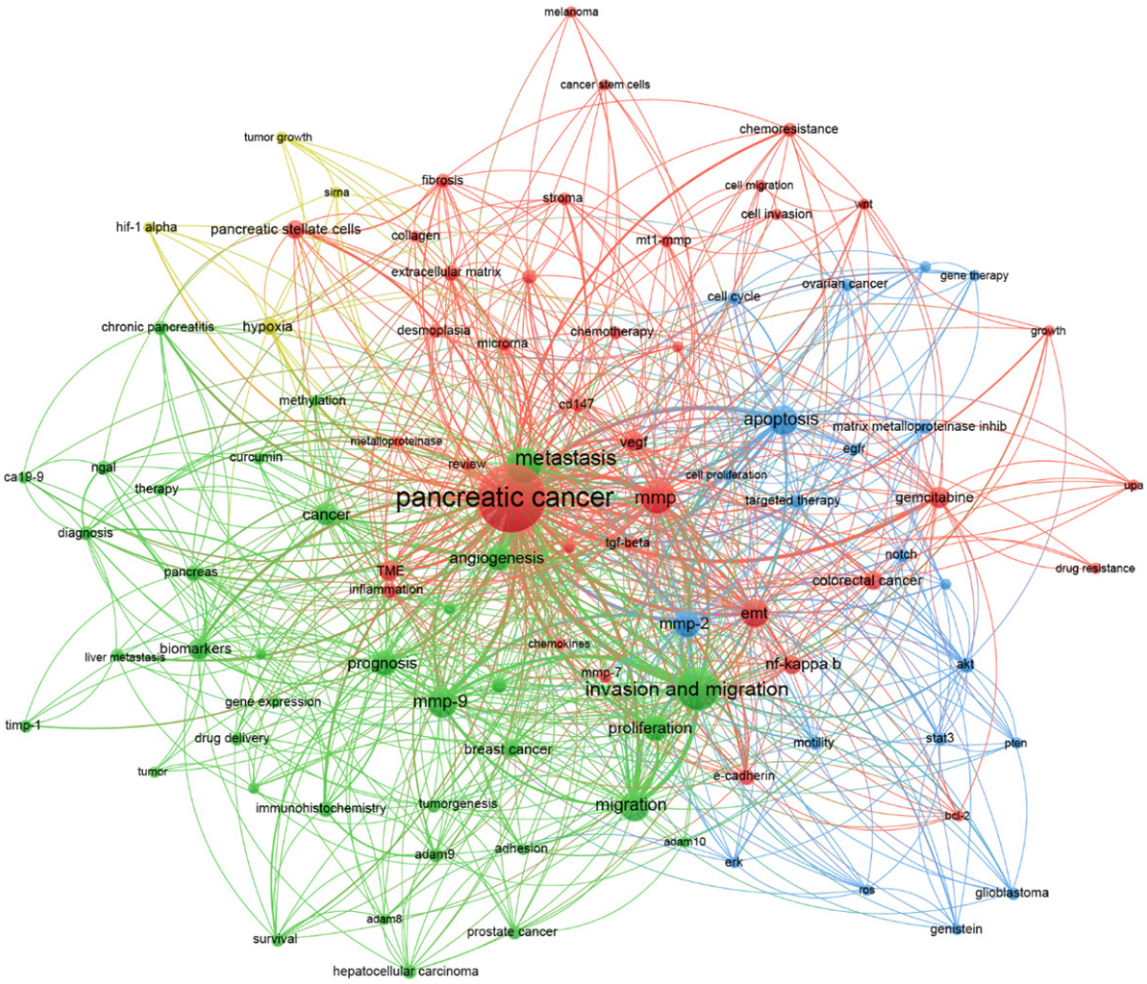

Figure 8. Keyword co-occurrence network and clusters in MMPs-PC research. Notes: The size of the node and word reflects the co-occurrence frequencies, the link indicates the co-occurrence relationship, and the same color of the node represents the same cluster. MMPs-PC, matrix metalloproteinases-pancreatic cancer.

Discussion

General information

According to data from the WoSCC database, as of June 24, 2022, 7950 authors from 1580 institutions in 62 countries have published 1474 studies on MMPs-PC in 476 academic journals.

The annual output change and cited frequency are essential indicators of the development trends in this field. In the included literature, L. Jones et al. reviewed the mechanism of matrix metalloproteinases promoting pancreatic cancer metastasis and matrix metalloproteinase inhibitors' progress in treating pancreatic cancer [39]. Since then, related articles in the field of MMPs-PC have shown an upward trend (**Figure 2**). MMPs-PC-related articles can be separated into 3 phases, namely "budding", "steady growth", and "fast developmental process". "Budding" (1999-2011): The concept of the effect of MMPs on pancreatic cancer was formally presented. There were no more than 70 articles in each of the 122 years. "Steady growth" (2012-2017): MMPs-PC received more attention from scientists, and the output every year increased stably. "Fast developmental process" (2018 to present): Although the number of articles in this phase is about the same as the number in the previous step, the citation frequency of articles in this phase has dramatically increased, indicating that MMPs-PC research has been given more attention increasingly by researchers and developed rap-

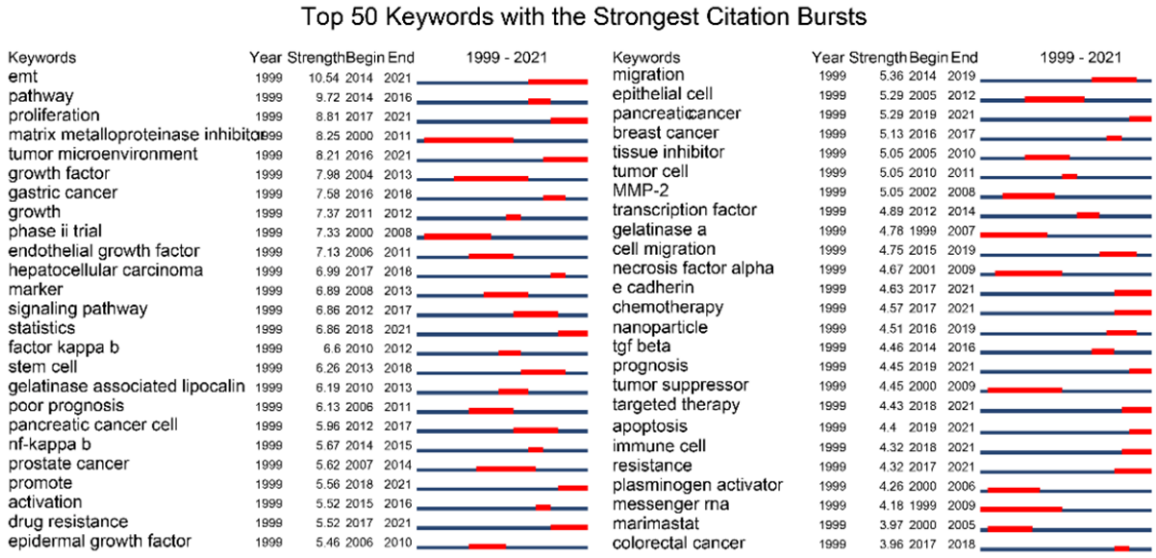

Figure 9. Top 50 keywords with the strongest citation bursts (sorted by the strength). Notes: The Blue bars mean the published reference; the red bars mean citation burstiness.

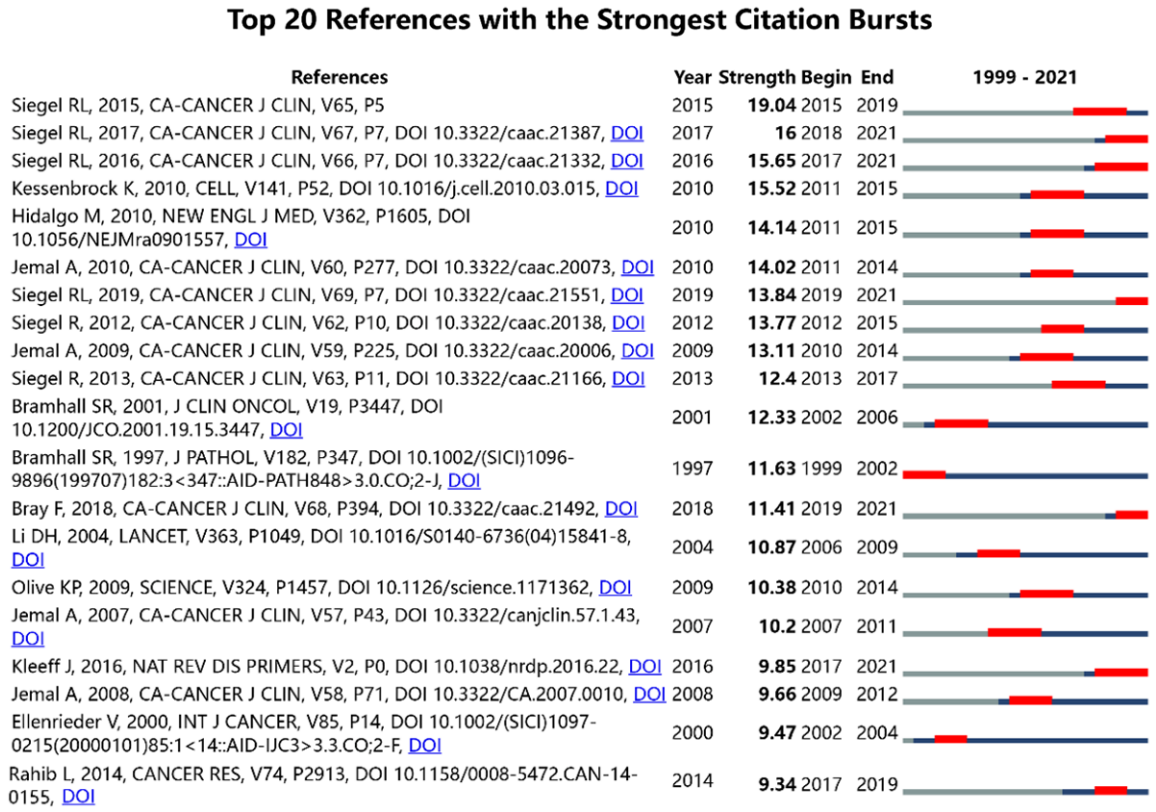

Figure 10. Top 20 references with the most powerful citation bursts (sorted by the strength). Notes: The Blue bars mean the published reference; the red bars mean citation burstiness.

idly. Furthermore, the growth trends in this field are promising.

The analysis of journals and co-cited journals (Supplementary Tables 1 and 2) revealed that

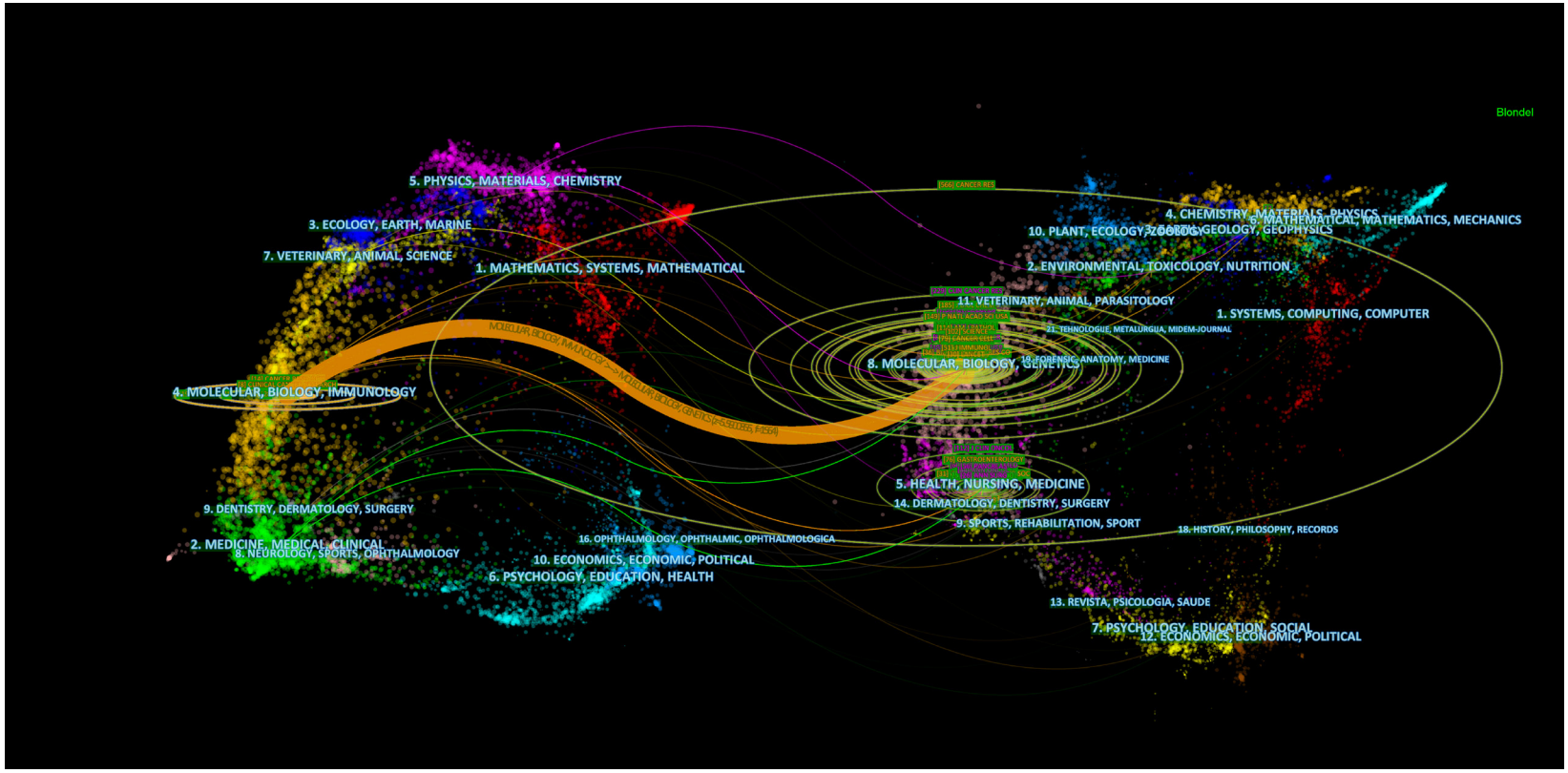

Figure 11. The dual-map overlay of journals related to the top 100 most cited references in MMPs-PC research. Notes: The citing journals were on the left, the cited journals were on the right, and the colored path represents the citation relationship. MMPs-PC, matrix metalloproteinases-pancreatic cancer.

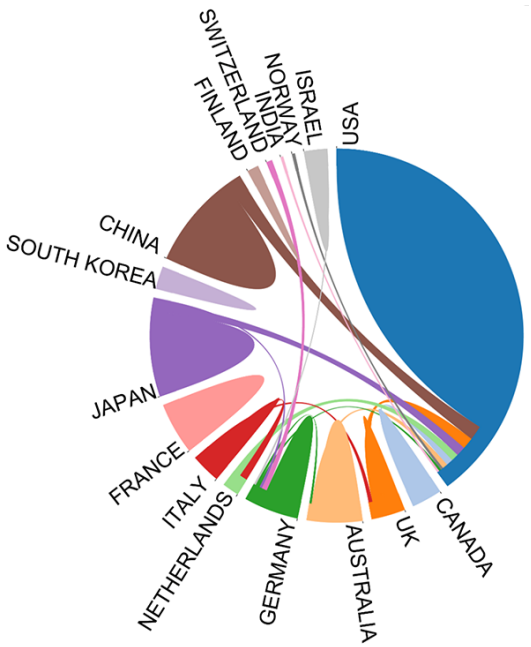

Figure 12. Country-to-country relations of Top 100 Most-cited Articles.

CANCER RESEARCH published the most significant number of studies and obtained the largest number of co-cited references in the MMPs-PC field. The main scope of the CANCER RESEARCH is captured in its primary subsections, which focus on molecular and cellular pathobiology, tumor and stem cell biology, therapeutics and targets, microenvironment and immunology, prevention and epidemiology, and integrated systems and technology, where the dual-map overlay of journals represents their theme distributional status (**Figure 3**). This overlay exhibited two central citation paths from molecular/biology/immunology and medicine/medical/clinical co-cited journals to molecular/biology/genetics journals. Concurrently, journals at the Q1 JCR division with high IF took up half of the top 10 journals (50%) and co-cited journals (90%), indicating that these journals publish studies on and are vital for MMPs-PC associated research. The analysis of countries/institutions related to MMPs-PC studies shows (Supplementary Table 3; **Figure 4**) that China, the United States, and Japan are the top three producers.

However, the United States, China, France, and Germany could potentially induce revolutionary breakthroughs. Additionally, the USA, Germany, UK, Netherlands, Japan, Canada, Italy, and Switzerland were the first nations to carry out MMPs-PC-related studies, followed by China, and Japan, among the top ten producers. This shows that America has always been fruitful and influential in studying MMPs-PC. Notably, China started relatively late but has become one of the most productive contributors in recent years. This may be related to the increased attention due to the high incidence and mortality of pancreatic cancer in China.

Furthermore, cooperation between diverse nations, particularly America, is very active, revealing that research on MMPs-PC has aroused widespread concern worldwide, and America is the primary cooperation center. The top 11 organizations come from three nations: 6 out of 11 are from China, 4 out of 11 are from the USA, and one is from Japan. Moreover, our team discovered fruitful collaborations among Shanghai Jiao Tong Univ, China Med Univ, Nanjing Med Univ, Univ Texas MD Anderson Canc Ctr, and other organizations, which has contributed remarkably to the field of MMPs-PC.

Highlighting the contributions of active scholars, such as those who co-appear or co-cite articles in a particular field, can assist researchers in moving forward along this path and offer more directions and guidance [40]. Here (Supplementary Table 4; **Figures 4** and **5**), Ma, Qingyong published the most papers, while Bramhall, Simon R has the most co-citations. Additionally, maps of researchers and co-cited researchers provide data regarding the underlying cooperators and powerful academic teams. In MMPs-PC, scholars have actively collaborated within and between organizations, particularly among researchers. Overall, 19 scholars from 12 organizations published a blockbuster review titled “Preinvasive and invasive ductal pancreatic cancer and its early detection in the mouse”. This suggests that these powerful groups might be the underlying cooperators of scholars.

Knowledge base

The co-cited references have been cited together in other articles. Nevertheless, the knowledge base is a pool of co-cited references cited by relevant academic teams, which is not entirely equal to frequently cited references. In the bibliometric analyses, in the MMPs-PC field,

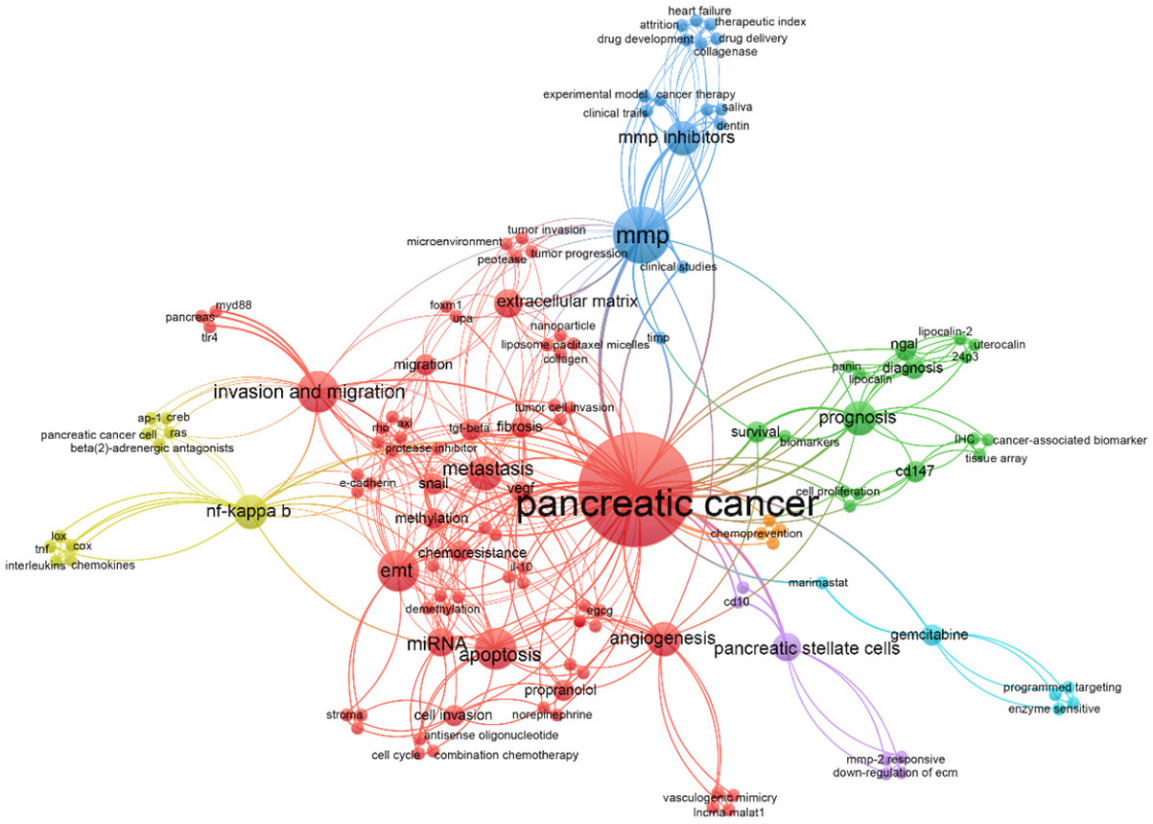

Figure 13. Keyword co-occurrence network and clusters in MMPs-PC research. Notes: The size of the node and word reflects the co-occurrence frequencies, the link indicates the co-occurrence relationship, and the same color of the node represents the same cluster. MMPs-PC, matrix metalloproteinases-pancreatic cancer.

there are many overlapping parts in the top 10 high co-cited articles and the top 20 citation burst articles (Supplementary Table 6; **Figure 10**). This shows that the knowledge base constructed in this study has a substantial reference value.

In 2002, NATURE REVIEWS CANCER published the most co-cited MMPs-PC studies by Egeblad, Mikala, et al. (n = 97) [35]. This paper describes that MMPs are not only highly related to the metastasis of pancreatic cancer but also participate in the progression of pancreatic cancer. Kessenbrock, Kai et al. wrote the second co-citation research on CELL [36]. This study overviewed that Tumor cells can change the tumor microenvironment of pancreatic cancer by regulating the number and function of MMPs, thereby further promoting the metastasis of pancreatic cancer. Bramhall, Simon R et al. (2001) published the third co-cited article in the JOURNAL of CLINICAL ONCOLOGY [41]. This randomized controlled trial comparing marimastat and gemcitabine concluded that 1-year survival in patients receiving marimastat was similar to that in patients receiving gemcitabine. MMP inhibitors are expected to provide a new therapeutic strategy for pancreatic cancer. The fourth co-cited paper was published in the ANNALS OF SURGICAL ONCOLOGY by bloomston, Mark et al. in 2001 [42]. This review mainly summarizes preclinical studies and clinical trials on MMPs in pancreatic cancer. In 2002, Hidalgo, Manuel et al. reported the fifth co-cited study in the NEW ENGLAND JOURNAL OF MEDICINE [43], which showed recent advances in the understanding and management of pancreatic cancer and proposed that pancreatic stellate cells can contribute to the development of pancreatic fibrosis by producing MMPs. The sixth article, published by Ellenrieder, Volker et al. in 2010 [44], shows that MT1-MMP and MMP-2 expression and activity strongly correlate with the degree of desmoplastic response in pancreatic cancer tissues. In 2000, LANCET published the sev-

enth co-citation study by Li, DH et al. [45]. This review discusses new therapeutic strategies based on the molecular biology of pancreatic cancer. It proposes that matrix metalloproteinase inhibitors can inhibit pancreatic cancer cell invasion and possible tumor angiogenesis. The eighth co-cited article was written by Yamamoto H et al. in JOURNAL OF CLINICAL ONCOLOGY, 2004. MMP-7 may play a vital role in the poor prognosis of pancreatic cancer and can be tried as a biomarker for pancreatic cancer [20]. In 2004, the CLINICAL CANCER RESEARCH published the ninth co-citation research completed by Jones, L.E. This paper has similar conclusions to the previous one that MMP-7 expression is a powerful independent prognostic indicator, and MMPs inhibitors improve the prognosis of pancreatic cancer mainly by inhibiting MMP-7 [46]. In 2001, the tenth co-cited paper was published in the NATURE CELL BIOLOGY by Bergers, Gabriele, and others [47]. This paper primarily states that MMP-9 is not only up-regulated in pancreatic cancer but also turns on the angiogenesis switch and induces angiogenesis in pancreatic cancer.

Overall, the top 10 co-cited papers highlighted reviews (seven reviews completed in 2001, 2002, 2004, and 2010), specific biological processes (invasion and migration, metastasis, apoptosis, EMT, angiogenesis, proliferation), MMP-related genes and drugs (mmp, mmp-9, mmp-2, gemcitabine, marimastat), possible mechanisms by which MMPs are involved in the occurrence, development, and metastasis of pancreatic cancer (prognosis, cancer, biomarkers, tumor microenvironment, Vascular endothelial growth factor (VEGF), hypoxia, pancreatic stellate cells, NF-kappa beta, and extracellular matrix).

Hot topic development, knowledge structure, and emerging topics

In bibliometric analysis, keyword/term co-occurrence (Supplementary Table 5; **Figures 7** and **8**) can indicate a hot spot in an academic field [48], and the keyword citation burst (**Figure 9**) can display the evolutionary process of novel hot spots [49]. High-frequency keywords (Supplementary Table 5 and **Figure 7**) include metastasis, MMP, apoptosis, mmp-9, EMT, mmp-2, angiogenesis, prognosis, biomarkers, gemcitabine, tumor microenvironment, VEGF, hypoxia, pancreatic stellate cells, NF-kappa beta, extracellular matrix, which are considered the focus of MMPs-PC research. With time, new topics continue to emerge (**Figure 9**). During the nascent stage (1999-2011), emerging keywords include matrix metalloproteinase inhibitor, gelatinase, poor prognosis, MMP-2, clinical trial, and so on. This is also in line with the actual situation. At this stage, researchers used marimastat as an MMP inhibitor in the first-line use of pancreatic cancer but got dismal results [41]. The above may be the failure of MMPs inhibitors to sustain the citation burst reason. In the steady growth phase (2012-2017), these keywords are mainly related to the occurrence, development, and metastasis of pancreatic cancer, such as EMT, stem cell, NF-kappa beta, migration, biomarkers, and tumor microenvironment. In the rapid developmental phase (2018-present), new topics include features of the steady growth phase and further study of the relationship between MMPs-PC and immunity in terms of the tumor microenvironment, pancreatic stellate cells, and immune cells. These emerging topics imply that MMPs may influence pancreatic cancer prognosis through the tumor microenvironment [28, 36].

Unfortunately, although most studies have focused on the relationship between MMPs inhibitors and pancreatic cancer in MMPs-PC and have explored how MMPs affect the occurrence, development, and metastasis of pancreatic cancer (epithelial-mesenchymal transition, angiogenesis, extracellular matrix, pancreatic stellate cells), there are few studies have investigated the appropriate timing of MMPs inhibitors in pancreatic cancer [20].

In addition, keyword clusters can indicate knowledge of the inner architecture and unveil academic frontiers of these disciplines. Cluster analyses show three primary clusters in the field of MMPs-PC (**Figure 7**), similar to the pathogenesis mechanism of pancreatic cancer, how MMP affects the metastasis of pancreatic cancer, and what role MMP plays in pancreatic cancer treatment, partially representing the three primary dimensions of MMPs-PC research. It is well known that MMPs play an integral role in pancreatic cancer's occurrence, development, and metastasis. For example, MT1-MMP, MMP-2, MMP-7, and MMP-9 have been proposed as predictive biomarkers for pancreatic cancer [20]. However, the poor efficacy of MMP inhibitors in pancreatic cancer

remains unresolved. With the progress of research, the tumor microenvironment may be an essential target for MMPs inhibitors to affect pancreatic cancer [12, 17].

Studies presenting strongly-cited breakthroughs (**Figure 10**) can also characterize new topics in a field. Surprisingly, the top 3 citation burst articles were all published by the same author (Siegel RL) and in the same journal (Cancer statistics): Cancer statistics, 2015, Cancer statistics, 2017, and cancer statistics, 2016 [50-52]. Moreover, among the top 20 references with the most substantial citations (**Figure 10**), five remained in the tumultuous period. These five references reflect the most recent MMPs-PC themes and are, therefore, worthy of further discussion. According to the burst intensity, the second, third and seventh article (strength = 15.97, 15.64, and 13.84) was published by Siegel RL. in CA-A CANCER JOURNAL FOR CLINICIANS in 2017, 2016, and 2019 respectively [51-53]. Three articles summarize the general distribution of cancer in the United States from a macro point of view and elaborate on the prevalence, mortality, and future trends of pancreatic cancer. The 13th strongest citation burst (strength = 11.39) represented an article published in CA-A CANCER JOURNAL FOR CLINICIANS by Bray F et al., They provide cancer burden from a global perspective and focus on geographical differences between cancers. It also describes the differences in the incidence and mortality of pancreatic cancer in different countries, hoping to obtain possible prevention and treatment methods [54]. Kleeff J et al. published the 17th study in "Nature Reviews Disease Primers" in 2017 (strength = 9.98). This review summarizes the current significant pathophysiological, molecular, translational, and clinical understanding of pancreatic cancer [55]. In addition, the possible application value of MMPs in pancreatic cancer was also proposed.

To precisely analyze MMPs-PC research-related content, we analyzed journals, co-cited journals, and national and keyword analyses of the top most cited 100 articles. The study of journals and co-cited journals (Supplementary Tables 7 and 8) demonstrated that CANCER RESEARCH, CLINICAL CANCER RESEARCH, AND INTERNATIONAL JOURNAL OF CANCER published the highest number of articles on MMPs-PC but also acquired the most co-cited references. The contribution of FRONTIERS IN IMMUNOLOGY in MMPs-PC research is also noteworthy. In the field of top 100, the journal is not only a high-output journal and a highly co-cited journal but is also published as a highly cited journal in this field. Gregg B. Fields reviewed the possible role of matrix proteases in promoting angiogenesis and also expounded that MMP-9 plays a dual role in pancreatic cancer [56]. MMP-9 plays an essential role in the angiogenesis of pancreatic islet cancer in the early stage. At the same time, decreasing MMP can promote the invasion and metastasis of pancreatic cancer in the later stage of pancreatic cancer metastasis.

The dual-map overlay analyses of the top 100 most-cited articles as well as all articles in the field (**Figure 11**) show only one of the primary citation paths from Molecular Biology/Immunology co-cited journals to Molecular Biology/Genetics journals, which indicates that MMPs-PC studies highlight fundamental research, whereas the research on conventional methods remains insufficient. The nation-wise analysis findings of the top 100 most-cited papers are consistent with those of all articles in the field, showing that China, the USA, and Japan are the largest producers. Additionally, cooperation between the United States and other countries is active, indicating that MMPs-PC-related research has attracted worldwide attention. The keyword analysis of the top 100 most-cited articles showed that they were divided into three clusters: Possible mechanism of invasion, migration, and metastasis of pancreatic cancer, development of MMPs inhibitors, and possible ways of MMPs affecting the prognosis of Pancreatic Cancer. Although this is slightly different from fundamental domain cluster analysis, there are common themes (angiogenesis, pancreatic stellate cells, EMT, miRNA, metastasis, Tumor microenvironment (TME), biomarker).

The possible focus of future research

Researchers have been exploring the role of MMPs in pancreatic cancer, and immune cells and tumor microenvironment are the focus of research in recent years. Many studies have suggested that MMPs play an essential role in remodeling the extracellular matrix in the tumor

microenvironment [17, 57-64]. Still, people now pay more attention to how immune cells affect MMPs. For example, M1 macrophages can express ADAM10 and ADAM17, which is related to a better prognosis [65]. In contrast, Tumor associated macrophage (TAM) can promote the secretion of MMP-9 and MMP-14, resulting in a shorter survival time [66, 67]. Therefore, studying how immune cells regulate MMPs and reshape the tumor microenvironment may provide a new strategy for treating pancreatic cancer.

Limitations

The present study had some inherent flaws in bibliometrics. First, data were acquired from the WoSCC database, excluding some research not in WoSCC. Nevertheless, WoSCC is the most frequently used scientific econometric research database; data from WoSCC can cover the majority of information to a certain extent. Second, all data were acquired via bibliometric tools based on machine learning and natural language processing, which may cause biases in other bibliometric studies. Third, in the included article, part of the review also describes other diseases in expounding pancreatic cancer, which may lead to analysis deviation. Nevertheless, compared to the most recent conventional reviews, the results herein are consistent and provide scholars with more objective data and insights.

Conclusion

In summary, research on MMPs-PC is fast-developing, and global collaboration is active, wherein America and China is the primary collaboration center. Currently, the research predominantly highlights the fields of molecule-level analysis and biology. The three primary aspects of MMPs-PC-related studies include the pathogenesis mechanism of pancreatic cancer, how MMP affects the metastasis of pancreatic cancer, and what role MMP plays in pancreatic cancer treatment. The latest hotspots are the TME, pancreatic stellate cells, drug resistance, and immune cells. Future research may focus on immune cells affecting invasion, migration, and metastasis by regulating MMP to reshape the tumor microenvironment of pancreatic cancer. It is possible that targeted drugs on MMP will be back on the agenda in the future. Our study is the first to research MMPs-PC-associated articles using bibliometrics and knowledge graph systems. In contrast to conventional reviews, the present study offers preliminary and objective insights into MMPs-PC studies. We believe that the results of the current report will provide valuable references for future research.

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Disclosure of conflict of interest

None.

Abbreviations

MMPs, Matrix metalloproteinases; PC, Pancreatic cancer; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; WOSCC, Web of Science Core Collection; TME, Tumor microenvironment; MMPs-PC, Matrix metalloproteinases-Pancreatic cancer; Timp, Tissue inhibitor of metalloproteinase; VEGF, Vascular endothelial growth factor; TAM, Tumor associated macrophage; ADAM, A Disintegrin And Metalloprotease; UK, United Kingdom.

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Supplementary Table 1. The top 10 journals of MMPs-PC-related research

RANK	Journal	N	(%)	IF (2021)	JCR division	Country
1	CANCER RESEARCH	43	2.917	13.312	Q1	USA
2	INTERNATIONAL JOURNAL OF ONCOLOGY	40	2.714	5.884	Q2	GREECE
3	PLOS ONE	37	2.51	3.752	Q2	USA
4	ONCOLOGY REPORTS	30	2.035	4.136	Q3	GREECE
5	CLINICAL CANCER RESEARCH	29	1.967	13.801	Q1	USA
6	PANCREAS	29	1.967	3.243	Q3	USA
7	INTERNATIONAL JOURNAL OF CANCER	26	1.764	7.316	Q1	SWITZERLAND
8	CANCER LETTERS	24	1.628	9.756	Q1	NETHERLANDS
9	CANCERS	21	1.425	6.575	Q1	SWITZERLAND
	CARCINOGENESIS	21	1.425	4.741	Q2	UK
	MOLECULAR MEDICINE REPORTS	21	1.425	3.423	Q3	GREECE
10	ONCOGENE	19	1.289	8.756	Q1	UK

MMPs-PC, matrix metalloproteinases-pancreatic cancer.

Supplementary Table 2. The top 10 co-cited journals of MMPs-PC-related research

RANK	co-cited journal	N	IF (2021)	JCR division	Country
1	CANCER RESEARCH	4661	13.312	Q1	USA
2	JOURNAL OF BIOLOGICAL CHEMISTRY	2273	5.486	Q2	USA
3	CLINICAL CANCER RESEARCH	2058	13.801	Q1	USA
4	INTERNATIONAL JOURNAL OF CANCER	1589	7.316	Q1	SWITZERLAND
5	ONCOGENE	1543	8.756	Q1	UK
6	JOURNAL OF CLINICAL ONCOLOGY	1296	50.717	Q1	USA
7	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	1247	12.779	Q1	USA
8	NATURE	1172	69.504	Q1	UK
9	CELL	1143	66.85	Q1	USA
10	BRITISH JOURNAL OF CANCER	1132	9.075	Q1	UK

MMPs-PC, matrix metalloproteinases-pancreatic cancer.

Supplementary Table 3. The top 10 countries/regions and institutions involved in MMPs-PC-related research

RANK	Country/ region	N	Percent (%)	Centrality	Institution	N	Percent (%)	Country/ region	Centrality
1	CHINA	545	30.66966798	0.2	Shanghai Jiao Tong Univ	35	1.086956522	CHINA	0.04
2	USA	427	24.0292628	0.59	China Med Univ	29	0.900621118	CHINA	0.11
3	JAPAN	162	9.116488464	0.02	Nanjing Med Univ	29	0.900621118	CHINA	0.08
4	GERMANY	122	6.865503658	0.27	Univ Texas MD Anderson Canc Ctr	29	0.900621118	USA	0.03
5	SOUTH KOREA	64	3.601575689	0.06	Xi An Jiao Tong Univ	29	0.900621118	CHINA	0.02
6	UK.	59	3.320202589	0.12	Kyushu Univ	25	0.776397516	JAPAN	0.01
7	ITALY	40	2.250984806	0.05	Fudan Univ	24	0.745341615	CHINA	0.14
8	INDIA	33	1.857062465	0.02	Zhejiang Univ	24	0.745341615	CHINA	0.05
9	CANADA	32	1.800787845	0.07	Tech Univ Munich	23	0.714285714	USA	0.07
10	FRANCE	26	1.463140124	0.18	Mayo Clin	20	0.621118012	USA	0.11
					Wayne State Univ	20	0.621118012	USA	0.04

MMPs-PC, matrix metalloproteinases-pancreatic cancer.

Supplementary Table 4. The top 10 authors and co-cited authors of MMPs-PC-related research

RANK	Author	Count	Citation	H-index	Co-cited author	H-index	co-citation	cluster
1	ma, qingyong	16	685	40	Bramhall, Simon R.	39	261	1
2	guha, sushovan	14	1648	43	Jemal, Ahmedin	126	202	2
3	tanaka, masao	13	887	11	Siegel, Rebecca L.	64	179	2
4	batra, surinder k.	12	782	78	liotta, la	81	109	1
5	friess, helmut	12	1066	112	Bloomston, Mark P	31	107	1
6	li, wei	12	452	32	egeblad, m	36	106	1
7	sarkar, fazlul h.	12	903	100	hidalgo, m	7	103	3
8	aggarwal, bharat b.	10	2233	30	Ellenrieder, Volker	40	97	1
9	banerjee, sanjeev	10	804	62	Coussens, Lisa M	7	92	1
10	wang, zheng	10	349	29	Yamamoto, Hiroki	12	90	1
	xu, qinhong	10	466	29				

MMPs-PC, matrix metalloproteinases-pancreatic cancer

Supplementary Table 5. The top 20 keywords of MMPs-PC-related research

RANK	Keyword	Occurrences	N (%)
1	pancreatic cancer	556	30.23382273
2	invasion and migration	204	11.09298532
3	metastasis	120	6.525285481
4	mmp	107	5.818379554
5	apoptosis	71	3.86079391
6	mmp-9	71	3.86079391
7	emt	64	3.480152257
8	mmp-2	58	3.153887983
9	angiogenesis	52	2.827623709
10	proliferation	52	2.827623709
11	prognosis	51	2.77324633
12	cancer	41	2.229472539
13	biomarkers	35	1.903208265
14	gemcitabine	34	1.848830886
15	tumor microenvironment	26	1.413811854
16	vegf	26	1.413811854
17	immune cell	25	1.359434475
18	pancreatic stellate cells	22	1.196302338
19	nf-kappa b	21	1.141924959
20	extracellular matrix	21	1.141924959

Supplementary Table 6. Top 10 co-cited references for MMPs-PC-related research

RANK	ID	Title	Journal	Co-citation	Year	type of article
1	Egeblad, Mikala	New functions for the matrix metalloproteinases in cancer progression	NATURE REVIEWS CANCER	97	2002	review
2	Kessenbrock, Kai	Matrix Metalloproteinases: Regulators of the Tumor Microenvironment	CELL	80	2010	review
3	Bramhall, Simon R	Marimastat as first-line therapy for patients with unresectable pancreatic cancer: A randomized trial	JOURNAL OF CLINICAL ONCOLOGY	68	2001	Article
4	Bloomston, Mark	Matrix metalloproteinases and their role in pancreatic cancer: A review of preclinical studies and clinical trials	ANNALS OF SURGICAL ONCOLOGY	61	2001	review
5	Hidalgo, Manuel	Pancreatic Cancer	NEW ENGLAND JOURNAL OF MEDICINE	57	2002	review
6	Ellenrieder, Volker	Role of MT-MMPs and MMP-2 in pancreatic cancer progression	INTERNATIONAL JOURNAL OF CANCER	56	2010	review
7	Li, DH	Pancreatic cancer	LANCET	55	2004	review
8	Yamamoto, H	Expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases in human pancreatic adenocarcinomas: Clinicopathologic and prognostic significance of matrilysin expression	JOURNAL OF CLINICAL ONCOLOGY	44	2004	Article
9	Jones, L. E	Comprehensive analysis of matrix metalloproteinase and tissue inhibitor expression in pancreatic cancer: Increased expression of matrix metalloproteinase-7 predicts poor survival	CLINICAL CANCER RESEARCH	43	2004	review
10	Bergers, Gabriele	Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis	NATURE CELL BIOLOGY	42	2001	Article

MMPs-PC, matrix metalloproteinases-pancreatic cancer.

Supplementary Table 7. The top 10 journals of top 100 cited articles research

RANK	Journal	N	IF (2020)	JCR division	Country
1	CANCER RESEARCH	14	13.312	Q1	USA
2	CLINICAL CANCER RESEARCH	8	13.801	Q1	USA
3	ACS NANO	3	18.027	Q1	USA
4	INTERNATIONAL JOURNAL OF CANCER	3	7.316	Q1	SWITZERLAND
5	JOURNAL OF CLINICAL ONCOLOGY	3	50.717	Q1	USA
6	MOLECULAR CANCER THERAPEUTICS	3	6.009	Q2	USA
7	ONCOGENE	3	8.756	Q1	UK
8	FRONTIERS IN IMMUNOLOGY	2	8.786	Q1	SWITZERLAND
9	AMERICAN JOURNAL OF PATHOLOGY	2	5.77	Q1	USA
10	BMC CANCER	2	4.638	Q2	UK
	BRITISH JOURNAL OF CANCER	2	9.075	Q1	UK
	CANCER BIOLOGY & THERAPY	2	4.875	Q2	USA
	GASTROENTEROLOGY	2	33.883	Q1	USA
	MOLECULAR CANCER RESEARCH	2	6.333	Q2	USA
	NATURE REVIEWS CANCER	2	69.8	Q1	UK
	PANCREAS	2	3.243	Q3	USA

Supplementary Table 8. The top co-cited 20 journals of top 100 cited articles research

RANK	co-cited journal	Citations	IF (2021)	JCR division	Country
1	CANCER RESEARCH	566	13.312	Q1	USA
2	CLINICAL CANCER RESEARCH	229	13.801	Q1	USA
3	JOURNAL OF BIOLOGICAL CHEMISTRY	185	5.486	Q2	USA
4	INTERNATIONAL JOURNAL OF CANCER	163	7.316	Q1	SWITZERLAND
5	ONCOGENE	158	8.756	Q1	UK
6	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	149	12.779	Q1	USA
7	NATURE	145	69.504	Q1	UK
8	BRITISH JOURNAL OF CANCER	123	9.075	Q1	UK
9	CELL	117	66.85	Q1	USA
10	AMERICAN JOURNAL OF PATHOLOGY	114	5.770	Q1	USA
11	JOURNAL OF CLINICAL ONCOLOGY	112	50.717	Q1	USA
12	SCIENCE	102	63.714	Q1	USA
13	NATURE REVIEWS CANCER	82	69.8	Q1	UK
14	CANCER CELL	79	38.585	Q1	USA
15	GASTROENTEROLOGY	76	33.883	Q1	USA
16	JOURNAL OF CLINICAL INVESTIGATION	76	19.456	Q1	USA
17	NEW ENGLAND JOURNAL OF MEDICINE	60	76.079	Q1	USA
18	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	56	12.779	Q1	USA
19	PANCREAS	56	3.243	Q3	USA
20	FRONTIERS IN IMMUNOLOGY	51	8.786	Q1	SWITZERLAND

Supplementary Table 9. The top 20 keywords of top 100 cited articles research

RANK	Keyword	Citations
1	pancreatic cancer	176.8095
2	mmp	172.125
3	apoptosis	211.2
4	emt	156.4
5	invasion and migration	119.4
6	angiogenesis	225.25
7	metastasis	159.5
8	nf-kappa b	353.5
9	prognosis	226.75
10	extracellular matrix	133.6667
11	microrna	163
12	pancreatic stellate cells	227.6667
13	cd147	133
14	cell invasion	105.5
15	chemoresistance	144
16	diagnosis	234
17	fibrosis	117
18	gemcitabine	280.5
19	matrix metalloproteinase inhibitors	137.5
20	methylation	131.5