Mapping Research on miRNAs in Cancer: A Global Data Analysis and Bibliometric Profiling Analysis

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Abstract: miRNAs biomarkers are emerging as an essential part of clinical oncology. Their oncogenic and tumour suppressor properties playing a role in malignancy has generated interest in their potential for use in disease prognosis. While several studies on miRNA have been carried out across the globe, evaluating the clinical implications of miRNAs in cancer diagnosis and prognosis research has currently not been attempted. A study delineating the area of miRNA research, including the topics presently being focused on, the seminal papers in this field, and the direction of research interest, does not exist. This study aims to conduct a large-scale, global data analysis and bibliometric profiling analysis of studies to evaluate the research output of clinical implications of miRNAs in cancer diagnosis and prognosis research. A systematic search strategy was followed to identify and extract all relevant studies, subsequently analysed to generate a bibliometric map. SPSS software (version 27) was used to calculate bibliometric indicators or parameters for analysis, such as year and country of affiliation with leading authors, journals, and institutions. It is also used to analyse annual research outputs, including total citations and the number of times it has been cited with productive nations and H-index. The number of global research articles retrieved for miRNA-Cancer research over the study period 2003 to 2019 was 18,636. Between 2012 and 2019, the growth rate of global publications is six times (n = 15,999; 90.71 percent articles) that of 2003 to 2011. (2704; 41.29 per cent articles). China published the most publications in the field of miRNA in cancer (n = 7782; 41%), while the United States had the most citations (n = 327,538; 48%) during the time span. Of these journals, Oncotarget has the highest percentage of article publications. The
1. Introduction

MicroRNAs (miRNAs) are small, non-coding RNA that measure 21–23 nucleotides in length and the expression of these miRNAs in the form of miRNA profiles in cancerous states has been found to be highly informative, containing signals for tumour developmental lineage and differentiation state [1]. In comparison to normal tissues, tumours display a general downregulation of miRNAs. Furthermore, researchers have used miRNA expression profiles to identify poorly differentiated tumours, while messenger RNA profiles were ineffective when applied to the same samples. These findings demonstrate the utility of miRNA profiling in research [1].

Since their discovery in 1993, microRNAs (miRNAs) have been proven to play critical roles in gene regulation [2,3]. MiRNAs were previously assumed to be degraded RNA fragments, but their importance in cancer research and therapy became clear with the discovery of their aberrant expression in a variety of clinical events and their role in carcinogenesis [3–10]. The most important characteristic of miRNA is its stability and longevity while being stored [3,11–17]. They are well preserved in extracted blood, formalin-fixed tissues, and paraffin-embedded tissues [3,18]. This allows scientists to run a variety of analyses on a large number of tissue samples, presenting them with massive amounts of data.

MiRNAs are hypothesised to have a dual function in carcinogenesis, acting as both oncomirs and tumour suppressors [19–21]. This theory is reinforced by the fact that miRNA expression in tumours can be up- or down regulated in contrast to normal tissue [3,22–34]. Tumour miRNA expression analysis has provided a lot of conceptual understanding of tumour differentiation and lineages [3,35–39]. MiRNA signatures can be used as a diagnostic tool, prognosis variable, predictive factor, prospective therapeutic target, and pharmacodynamics marker, in addition to providing sufficient information on tumour biology [3,40–42]. Multiple studies have assessed the prognostic utility of miRNA, with few studies highlighting specific miRNA's that have a significant prognostic effect across multiple patient populations [43–53].

Circulating miRNAs have the potential to be employed as biomarkers in diagnostic, prognostic, and therapeutic studies [46,54–62]. Although the stability of miRNAs assists in determining their presence in the blood, the majority of procedures are performed using biopsies collected from primary tumours and metastases [63,64]. Without attempting to provide a thorough overview, we have illustrated the clinical feasibility of miRNAs being utilised as biomarkers from any of the aforementioned sources [1,3,65]. Accurate miRNA studies can be used to monitor carcinogenesis and its progression [66–68]. A precise and personalised approach provides a higher success rate and clinical efficacy than traditional medicines [69,70].

2. Study Objective

The objective of this study was to examine a large-scale, global data analysis and bibliometric profiling analysis of studies to provide an in-depth evaluation of the research output of miRNAs in cancer diagnosis and prognosis listed in the Scopus database. Statistics and data extracted from Scopus ascertain the diagnostic and prognostic role of miRNA in cancer and its malignancy. In the era of precision oncology, determining the aberrant
expression of miRNA and its role in cancer development and progression can help better understand tumour biology and aim at personalised and targeted therapies. A detailed study of the field of miRNA and cancer would help researchers learn more about current scientific patterns and to gain insight into the contributions made by particular countries, institutions, partnerships, and contributing authors. The h-index could be used to rank universities, apply for grants, and create a scientific reputation in the scientific community.

3. Methods

The data for this study was extracted from the Scopus database. Scopus is an Elsevier database that includes comprehensive Medline coverage for over 20,000 publications and has a 20% coverage edge over Web of Science. The following Scopus attributes were used as data items for this study: citation analysis, contribution by nation and author, source names, and productivity per year. For the search of studies, the investigation period was set between 2003 and 2019. Search engines such as Scopus was used to select subject categories consisting of life, social, health, and physical sciences.

All documents featuring “miRNA in cancer” as the primary keyword were screened. Further refinement of the search was carried out using the categories of “country”, “author”, “affiliation”, “source” and “year”. Subsequently, using Scopus’ citation tracker, all relevant papers published in Scopus were retrieved and examined. The following inclusion/exclusion criteria were used for the secondary screening of the full-texts of studies.

3.1. Selection Criteria

- The keywords were chosen based on the number of queries and the bibliometric graph’s density variation.
- These keywords appear in the majority of miRNA in cancer research papers.

3.2. Inclusion Criteria

- miRNA expression papers focused on cancer prognosis or diagnosis or clinical cancer or clinical outcomes or treatments.
- The definition also comprises studies that are designed to evaluate the miRNAs that are downregulated or upregulated in cancer patients (specifically the magnitude of down/upregulation and their impact on patient prognosis).
- Manuscripts in all languages were included.
- All papers published in Scopus journals were included in the study to improve the precision of our search.
- All records, including errata, articles, book chapters, and conference papers, were included, making this a systematic review that included all sources related to miRNA in cancer and covered a broad range of research.
- Documents with clinical prognosis in cancer patients and patients’ survival or recurrence related to clinical diagnoses were considered.

3.3. Exclusion Criteria

Manuscripts that were labelled as abstracts, dissertation reports, case reports, case series, or un-defined types of documents were excluded.

The collected data were transferred to the MS Office Excel sheet that permitted us to collate the information contained in the records and to retrieve bibliometric indicators. After refining the findings with Scopus software online, all the documentation and results were collected. All the values retrieved from the Scopus website were collected and analysed after sorting by keywords.

3.4. Global Data and Bibliometric Profiling Analysis of Studies

The validity of our strategy was tested by observing the first 100 most often cited documents retrieved by utilising the procedure mentioned above. All the documents were published in high impact, reputed oncology journals.
The important indicators for analysis offered in this study were

- The form and language of published documents,
- Nation and institutional affiliation,
- Source/journal-title in which documents were published,
- Most active authors,
- Most cited papers,
- Collaboration trends and

Their related h Index. (Difference in the number of articles published during that period/number of articles published at the start of the period) × 100 was used to calculate the growth rate of production.

3.5. Publication Productivity

The leading authors and institutions of miRNA-Cancer research in this field.

3.6. Overview of the Research Output and Growth of miRNA-CANCER Research

A number of research indicators were included in order of importance. The total number of references was used to identify the most important papers in the subject, while the number of publications was used to estimate research production.

3.7. Core Bibliometric Indicators

The Scientific Journal Ranking (SJR) of journals were obtained using the SCImago Journal and Country Ranking website as a measure of journal quality.

The Hirsch index (h-index) was used to determine the number and quality of publications by region, institution, and author. When a country or an entity publishes x articles, each of which has at least x citations, it earns an h-index of x.

The World Bank’s online databases (Countries and Economies, http://data.worldbank.org/nation, accessed on 1 July 2020) is used to standardise the research effectiveness of different countries are ranked by population and national gross domestic output (GDP).

Other parameters for analysis were estimated using SPSS software. An excel graph analyses the year, nation, number of citations, number of publications, GDP, population, h-index, affiliation, and source. All calculations, such as average and total, were performed after creating appropriate tables from the data obtained from Scopus.

The IRB ethics approval for the investigation was exempted as the information was obtained from publicly available electronic sources and did not relate to specific patients’ information or profiles.

4. Results

4.1. General Data

Between 2003 and 2019, a total of 18,663 journal papers were retrieved. About 70.1 percent of the submissions were research articles, while the remaining 21.9 percent were review posts, book chapters, conference papers, short surveys, articles in the press, notices, erratum, letters, editorials, books, retracted articles, and conference reviews (Table 1). Figure 1 depicts the document type distribution as a pie map. English was the most frequently encountered language in the article retrieval (n = 18,067; 96.81 per cent), with Chinese, Japanese, Russian, German, Czech, French, Spanish, Polish, and Persian accounting for the remainder (n = 588, 3.19 per cent) (Table 2) (Figure 2).
Table 1. The number and frequency of different source types based on bibliometric search for the topic of miRNA research in cancer.

| Document Type          | Number | Frequency % |
|------------------------|--------|-------------|
| Article                | 14,572 | 78.08%      |
| Review                 | 2909   | 15.59%      |
| Book Chapter           | 485    | 2.60%       |
| Conference Paper       | 266    | 1.43%       |
| Short Survey           | 178    | 0.95%       |
| Article in Press       | 89     | 0.48%       |
| Note                   | 40     | 0.21%       |
| Erratum                | 31     | 0.17%       |
| Letter                 | 26     | 0.14%       |
| Editorial              | 25     | 0.13%       |
| Book                   | 17     | 0.09%       |
| Retracted              | 15     | 0.08%       |
| Conference Review      | 10     | 0.05%       |
| Total                  | 18,663 | 100.00%     |

Figure 1. Document types of retrieved articles on miRNA in cancer (2003–2019).
Table 2. Top 10 languages of retrieved articles on miRNA in cancer (2003–2019).

| Language | Total No. of Articles | % of Articles |
|----------|----------------------|---------------|
| 1st English | 18,067 | 96.81% |
| 2nd Chinese | 463 | 2.48% |
| 3rd Japanese | 24 | 0.13% |
| 4th Russian | 22 | 0.12% |
| 5th German | 20 | 0.11% |
| 6th Czech | 15 | 0.08% |
| 7th French | 15 | 0.08% |
| 8th Spanish | 13 | 0.07% |
| 9th Polish | 9 | 0.05% |
| 10th Persian | 7 | 0.04% |

Figure 2. Year-wise article analysis.

4.2. Publications with Time

When compared to the first half of the time period between 2003 and 2011 (2704; 9.29 per cent articles), the number of retrieved published papers increased by about six times ($n = 15,959$; 90.71 percent articles) in the second half of the time period from 2012 to 2019. Between the first half of the study period (2003–2011) and the second half (2012–2019), the number of citations increased sevenfold. In 2017, the overall number of citations per paper published was the highest, but in 2018, the number of publications and citations published was the highest. For the entire time span, the average citation per document was 36.19. Figure 2 shows the frequency of publication and citation over the period of pre-2004 to 2019.

Table 3 displays the total number of articles retrieved, together with their access type and the number of citations per year, as well as the average number of citations per document.
Table 3. Number of published articles and citations per year (2003–2019).

| Year | Open Access | Closed Access | Total Articles | Citations | Average Citation per Document |
|------|-------------|---------------|----------------|-----------|-----------------------------|
| 2019 | 296         | 520           | 816            | 30,808    | 37.75490196                |
| 2018 | 1324        | 1486          | 2810           | 104,985   | 37.36120996                |
| 2017 | 1344        | 1132          | 2476           | 99,818    | 40.31421648                |
| 2016 | 1199        | 1175          | 2374           | 91,943    | 38.72914912                |
| 2015 | 1204        | 1091          | 2295           | 86,001    | 37.47320261                |
| 2014 | 1037        | 1026          | 2063           | 75,003    | 36.35627727                |
| 2013 | 882         | 920           | 1802           | 60,639    | 33.6509434                 |
| 2012 | 672         | 651           | 1323           | 43,723    | 33.04837491                |
| 2011 | 438         | 533           | 971            | 32,016    | 32.97219361                |
| 2010 | 314         | 380           | 694            | 23,399    | 33.71613833                |
| 2009 | 216         | 238           | 454            | 13,884    | 30.5814978                 |
| 2008 | 146         | 147           | 293            | 8028      | 27.39931741                |
| 2007 | 90          | 87            | 177            | 3607      | 20.37853107                |
| 2006 | 41          | 41            | 82             | 1249      | 15.23170732                |
| 2005 | 11          | 15            | 26             | 326       | 12.53846154                |
| 2004 | 2           | 2             | 4              | 51        | 12.75                       |
| <2004| 1           | 2             | 3              | 11        | 3.666666667                 |
| Total (<2004–2019) | 9217 | 9446 | 18,663 | 675,491 | 48.9227894 |
| Average (<2004–2019) | 542.1764706 | 555.6470588 | 1097.823529 | 39,734.76 | 53.76919883 |

4.3. Countries

There were 106 countries represented in the publications on miRNA in cancer, as well as 150 papers from unidentified places (Figure 3). Table 4 lists the top ten countries by a number of papers published and citations, as well as their h-indices. China published the most publications in the field of miRNA in cancer (n = 7782; 41%), while the United States had the most citations (n = 327,538; 48%) during the time span. China and the United States contributed approximately 68 per cent of article publishing, while Italy, Japan, Germany, the United Kingdom, India, Canada, South Korea, and Spain contributed approximately 29 per cent. Figure 4 shows the country-wise frequency of publication and citation, on the topic of miRNA mapping and cancer.
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**Table 4. Top 10 productive countries in miRNA in cancer article publication.**

| Country Name | Total Citation | h Index | Total Article | % Article | % Citation |
|--------------|----------------|---------|---------------|-----------|------------|
| China        | 168,314        | 145     | 7782          | 0.416974763 | 0.249172824 |
| United States| 327,538        | 244     | 4832          | 0.258908   | 0.48488877  |
| Italy        | 61,473         | 108     | 1137          | 0.060922681 | 0.091004913 |
| Japan        | 47,847         | 106     | 958           | 0.051331512 | 0.07083292  |
| Germany      | 42,641         | 102     | 946           | 0.050688528 | 0.063125934 |
| United Kingdom| 30,325        | 76      | 567           | 0.030380968 | 0.04489327  |
| India        | 8205           | 47      | 515           | 0.027594706 | 0.01214672  |
| Canada       | 19,212         | 73      | 496           | 0.026576649 | 0.02841534  |
| South Korea  | 14,240         | 59      | 459           | 0.024594117 | 0.021080962 |
| Spain        | 19,244         | 66      | 422           | 0.022611584 | 0.028488907 |

4.4. Most Frequent Terms

4.4.1. Authors

Professor G.A. Calin came in first with the most publications (161) and citations (h-index) of all of the researchers. With 46,117 citations and an h-index of 79, Professor Croce, C.M., came in first. Both came from the United States. Table 5 lists the top ten writers in terms of the number of publications. Figure 4 shows the total number of citations and articles by writers, as well as their h-indices and C/A values.
4.4.2. Frequently Cited Articles

“MicroRNA expression profiles identify human cancers”, by Lu et al., was published in Nature in 2005 and received the most citations. As of the time of data collection, the article had 6712 citations. Table 6 lists the top ten most cited papers on miRNA in cancer. Eight of the ten documents were original papers, with only two being reviews.
Table 6. Top 10 cited articles on miRNA in cancer (2003–2019).

| Authors                              | Title                                                                 | Year | Source Title                        | Document Type | Cited by |
|--------------------------------------|-----------------------------------------------------------------------|------|-------------------------------------|---------------|----------|
| Lu, J. et al. [1]                    | MicroRNA expression profiles classify human cancers                  | 2005 | Nature                              | Article       | 6712     |
| Calin, G.A. and Croce, C.M. [4]      | MicroRNA signatures in human cancers                                  | 2006 | Nature Reviews Cancer                | Review        | 5205     |
| Esquela-Kerscher, A. and Slack, F.J. [20] | Oncomirs—MicroRNAs with a role in cancer                             | 2006 | Nature Reviews Cancer                | Review        | 5058     |
| Mitchell, P.S. et al. [15]           | Circulating microRNAs as stable blood-based markers for cancer detection | 2008 | Proceedings of the National Academy of Sciences of the United States of America | Article       | 4606     |
| Volinia, S. et al. [71]              | A microRNA expression signature of human solid tumours defines cancer gene targets | 2006 | Proceedings of the National Academy of Sciences of the United States of America | Article       | 4193     |
| Iorio, M.V. et al. [72]              | MicroRNA gene expression deregulation in human breast cancer         | 2005 | Cancer Research                     | Article       | 2928     |
| Johnson, S.M. et al. [73]            | RAS is regulated by the let-7 microRNA family                        | 2005 | Cell                                | Article       | 2729     |
| Landgraf, P. et al. [74]             | A Mammalian microRNA Expression Atlas Based on Small RNA Library Sequencing | 2007 | Cell                                | Article       | 2417     |
| Yanaihara, N. et al. [75]            | Unique microRNA molecular profiles in lung cancer diagnosis and prognosis | 2006 | Cancer Cell                         | Article       | 2329     |
| Skog, J. et al. [76]                 | Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers | 2008 | Nature Cell Biology                 | Article       | 2298     |

4.4.3. Journals

Table 7 lists the top ten journals that published papers about miRNA in cancer from 2003 to 2019. These ten publications accounted for roughly 20% of all papers retrieved. With 4.44 per cent (n = 829) of the total retrieved publications, the journal Oncotarget has the highest percentage of Article publications. The journal Cancer Research had the most citations (n = 41,876), with 6.20 per cent (n = 41,876). It had the highest h-index of 106 as well. Figure 4 depicts a source-by-source review of papers and citations, as well as the h-index. Seven of the top ten publications are dedicated to cancer and tumour biology.

4.4.4. Subject Area

Biochemistry, Genetics, and Molecular Biology (n = 12,906; 42.2 percent) had the most publications (n = 10,193; 33.3 percent), led by Medicine (n = 10,193; 33.3 percent), Pharmacology, Toxicology, and Pharmaceutics (n = 1510; 4.9%), Agricultural and Biological Sciences (n = 1045; 3.4%), Chemistry (n = 780; 2.5%), Immunology and Microbiology (n = 777; 2.5%), Computer Science (n = 527; 1.7%), Chemical Engineering (n = 476; 1.6%), Engineering (n = 448; 1.5%), Neuroscience (n = 414; 1.4%), Others (n = 1527; 5.0%).

Funding sponsor Table 8 shows the top 10 funding agencies for articles on miRNA in cancer.
Table 7. Top 10 journals.

| Journal Name                  | Total Citation | h Index | Total Articles | % Citation | % Articles |
|-------------------------------|----------------|---------|----------------|------------|------------|
| Oncotarget                    | 15,560         | 54      | 829            | 2.30%      | 4.44%      |
| Plos One                      | 33,313         | 86      | 777            | 4.93%      | 4.16%      |
| Oncology Reports              | 5462           | 37      | 326            | 0.81%      | 1.75%      |
| Oncology Letters              | 2783           | 26      | 324            | 0.41%      | 1.74%      |
| Tumour Biology                | 5916           | 17      | 303            | 0.88%      | 1.62%      |
| Molecular Medicine Reports    | 2454           | 23      | 291            | 0.36%      | 1.56%      |
| Cancer Research               | 41,876         | 106     | 280            | 6.20%      | 1.50%      |
| Scientific Reports            | 3945           | 32      | 265            | 0.58%      | 1.42%      |
| Oncogene                      | 21,939         | 84      | 213            | 3.25%      | 1.14%      |
| International Journal Of Oncology | 5918       | 44      | 203            | 0.88%      | 1.09%      |

Table 8. Top 10 funding sponsors for articles on miRNA in cancer (2003–2019).

| Rank | Founding Sponsor                               | Number |
|------|-----------------------------------------------|--------|
| 1    | National Natural Science Foundation of China  | 1440   |
| 2    | National Natural Science Foundation of China (NSFC) | 1205  |
| 3    | National Institutes of Health (NIH)           | 521    |
| 4    | National Institutes of Health                 | 433    |
| 5    | National Cancer Institute                     | 235    |
| 6    | National Cancer Institute (NCI)               | 169    |
| 7    | National Research Foundation of Korea (NRF)   | 160    |
| 8    | National Basic Research Program of China (973 Program) | 149    |
| 9    | Natural Science Foundation of Jiangsu Province | 146    |
| 10   | Associazione Italiana per la Ricerca sul Cancro | 122    |

5. Discussion

5.1. Key Findings

Bibliometric assessment was used to illustrate various aspects of global scientific evidence on miRNA and its vital role in cancer, as well as the ongoing development of publications in this area from 2003 to 2019. Scopus was used to examine the research papers published in the title related to miRNA and its function in cancer research. A total of 14,572 articles were reported and published between 2003 and 2019. From 2012 until 2019, the second half of the time period, the number of retrieved research papers expanded by about six times as compared to the first half of the time period from 2003–2011. China and the United States accounted for almost two-thirds (68%) of all written papers, while Italy, Japan, Germany, the United Kingdom, India, Canada, South Korea, and Spain each contributed about a fifth (29%).

5.2. Journals That Published the Most Articles

According to our findings, the journal “Oncotarget” was the most productive in terms of publishing papers about miRNA in cancer, whereas Plos One, Oncology Reports, Oncology Letters, Tumor Biology, Molecular Medicine Reports, Cancer Research, Scientific Reports, Oncogene, and International Journal of Oncology were actively involved in publishing work related to miRNA in cancer. The journal “Cancer Research” had the highest number of citations and h-index when compared to the other nine journals mentioned above.
5.3. Good Quality Publication Output

The rising number of high-quality studies validates the role of miRNA in cancer. Using bibliographic and density visualising analysis of publications indexed in Scopus, the global research output on research that investigates the relationship between miRNA and cancer was calculated using three indices of qualitative research outputs: total citations, h index, and average citation (45). These vital bibliometric indices were calculated for the top ten productive authors, journals, countries, and institutions in this present study. Professor Croce, C.M., from the United States, has total citation numbers of 46,117 and an h-index of 79, whereas Lu et al., from the United States, had received the highest number of citations for the article entitled “MicroRNA expression profiles classify human cancers”.

5.4. Strengths

The study is novel for its comprehensive extraction and evaluation of research outputs from the available global data and for establishing the clinical ramifications of miRNAs in cancer diagnosis and prognosis.

5.5. Limitations

The limitation of our exploratory search is the exclusion of publications from non-Scopus bibliographic sources like PubMed, Google Scholar, and Web of Science. The extraction of data from Scopus encompasses vital bibliometric and visual density processing indicators and can provide a credible and precise impression of the output of publications.

In addition, the global data analysis of total citations and citations per article may be confounded with self-citations by authors. Furthermore, this bibliometric study did not collect distinct institutional affiliations as well as single and multiple country publications as specific information was not available for all articles, and miRNA-Cancer research is primarily led by research groups affiliated with one institution.

6. Conclusions

This study was a comprehensive bibliometric analysis of studies contemplating the role of miRNAs in cancer. Scopus database was exclusively used to collect papers relevant to the study, articles from various journals in Scopus were scanned, and relevant data were retrieved. During the time period from 2003 to 2019, it was noted that the number of papers published in the time span of the years 2012 to 2019 had increased by six times in contrast to the number of papers published from 2003 to 2011, while the number of citations increased sevenfold in the same pattern.

The bibliometric indicators validate the vital clinical information on performance assessment of research productivity and quality of research output. Hence, this study ascertains a valuable reference for clinical oncologists, cancer scientists, policy decision-makers and clinical data researchers.

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