A Bibliometric Analysis of mTOR Expression in Breast Cancer

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Abstract. The mTOR (mechanistic Target of Rapamycin) pathway represents a critical focus in cancer research, playing a pivotal role in cellular growth, proliferation, and survival. This study presents a comprehensive bibliometric analysis of research publications focusing on mTOR in breast cancer from 2006 to 2023, utilizing the Scopus database. This study conducted a bibliometric analysis of publications related to mTOR in breast cancer from 2006 to 2023. Data were extracted from Scopus database using a systematic search strategy, and only English-language articles focusing on human studies were included. Analytical tools, including Harzing's Publish or Perish, VOSviewer, and CiteSpace, were employed to examine citation metrics, collaboration networks, and thematic clusters within the field, providing insights into global research trends and key areas of focus. Our analysis revealed a significant growth in publication rate, particularly between 2018 and 2022. Asia, North America and Europe, dominate reseach publications with a substansial contribution from China and the United States, Network analysis identified five primary research clusters: oncogenic pathways, therapeutic targeting, multi drug resistance mechanisms, genomic insights, and clinical biomarkers. The findings indicate that although mTOR-targeted therapies show promise, particularly in overcoming treatment resistance in hormone receptor-positive subtypes, limited understanding of the pathway's interactions remains a challenge. This bibliometric study offers a comprehensive view of mTOR research trends in breast cancer, identifying key research clusters and revealing geographical disparities in research contributions. The study suggests that expanding international collaborations and integrating multi-omics data could advance personalized therapies and promote equitable progress in breast cancer treatment globally. Future investigations should focus on bridging research gaps and fostering interdisciplinary efforts to deepen understanding of mTOR's role in breast cancer biology.

Keywords : mTOR, breast cancer, bibliometric

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INTRODUCTION

Breast cancer has emerged as the most frequently diagnosed malignancy among women, with approximately 2.3 million new cases reported in 2020 [1][2]. In 2020, breast cancer caused 685,000 deaths, making it the fourth most common cause of cancer death worldwide [2][3]. Breast cancer incidence has risen in regions with historically low rates, including South America, Africa, and Asia, mainly due to Western lifestyle adoption [2]. Despite significant advances in diagnosis and treatment, the increasing global burden of breast cancer highlights the need for continued research and therapeutic innovation.

The complex pathophysiology of breast cancer necessitates a deeper understanding of molecular pathways contributing to its development and progression. Among the key pathways, the mechanistic target of rapamycin (mTOR) has garnered significant attention for its critical role in regulating cellular processes such as proliferation, growth, and survival, which are often dysregulated in malignancies [4][5]. The mTOR pathway, a central component of the PI3K/AKT signaling axis, serves as a pivotal regulator of oncogenic transformation, particularly in breast cancer, influencing tumorigenesis and therapy resistance[6][7][8].

A deep understanding of mTOR and its mechanisms in breast cancer could pave the way for the development of new therapies and more effective treatment strategies [9]. Despite advancements in understanding the role of mTOR in breast cancer, numerous gaps persist, particularly concerning its interaction with other molecular targets and its contribution to the heterogeneity of the disease. Targeted therapies aimed at inhibiting mTOR, such as the use of everolimus, have shown promise in enhancing treatment efficacy, especially in hormone receptor-positive breast cancer subtypes [10][11]. Yet, these interventions face limitations due to incomplete knowledge of the pathway's detailed mechanisms and interactions with the broader oncogenic landscape.

While numerous studies have investigated mTOR in breast cancer, a comprehensive bibliometric analysis of this field has not been conducted, limiting our understanding of research trends and potential gaps in the literature. Bibliometric analysis has proven to be a valuable tool for mapping research landscapes and identifying emerging trends, as demonstrated by recent studies in other cancer domains [12][13]. This methodological approach can provide unique insights into the evolution and current state of mTOR research in breast cancer, which is crucial for directing future investigations. Bibliometric analysis is an important tool for mapping the development of research in specific fields, including breast cancer and the mTOR pathway. By analyzing published works, we can identify research trends, international collaborations, and gaps in existing research [14]. This study aims to explore publications related to mTOR and breast cancer from geographical and temporal perspectives, as well as to provide insights into the concentration of research across different regions of the world.

SUBJECT AND METHODS

Study Design

We conducted a bibliometric analysis of research articles focusing on the role of mechanistic target of rapamycin (mTOR) in breast cancer published between 2006 and 2023. The data were retrieved from Scopus databases using a systematic search strategy. The search query was structured to capture the intersection of mTOR and breast cancer research using the following combination: (("mTOR*" OR "mammalian target of rapamycin" OR "mechanistic target of rapamycin") AND ("breast cancer*" OR "breast carcinoma*" OR "breast neoplasm*")). The search query is retricted by the following conditions: (a) the article published during the period 2006-2023; (b) article of “ARTICLE” type; (c) article written in English; and (d) the study only on human species. According to the above restrictions, a total of 544 are retrieved.

The bibliometric analysis employed multiple complementary tools to ensure a comprehensive evaluation of the research landscape. Primary citation analysis was conducted using Harzing's Publish or Perish software (version 8.0), which provided detailed metrics including citation counts, h-index, and g-index for individual publications and authors. For deeper analysis of collaboration networks and research themes, we utilized the R package "bibliometrix" (version 4.0). This package enabled us to generate co-authorship networks, analyze country collaboration patterns, and create thematic maps through multiple correspondence analysis, providing insights into the global research dynamics in the field.

Network visualization and clustering were performed using a combination of VOSviewer (version 1.6.19) and CiteSpace (version 6.1), each chosen for their specific strengths in bibliometric analysis. VOSviewer was particularly valuable for creating and visualizing bibliometric networks, including co-authorship patterns, keyword co-occurrence, and journal co-citation relationships. These visualizations helped identify clusters of related research and revealed the interconnections between different aspects of mTOR research in breast cancer. CiteSpace complemented this analysis by enabling temporal examination of emerging topics and identification of research fronts, allowing us to track the evolution of research themes over the twenty-year period.

Data Analysis

The analysis encompassed multiple dimensions of the research landscape, including publication patterns, citation impacts, geographical distribution of research, institutional collaboration networks, journal impact patterns, author productivity, and keyword evolution. Time-series analyses and basic statistical calculations were performed using Microsoft Excel, which also served to create visualizations of publication trends and citation patterns. Through the integration of results from these various analytical tools, we were able to construct a comprehensive understanding of the mTOR research landscape in breast cancer, identifying key contributors, emerging

trends, and potential areas for future investigation. This multi-faceted approach allowed us to not only quantify research output and impact but also to understand the qualitative aspects of how the field has evolved over time.

RESULTS

3.1 Publication Trends in Breast Cancer Research

Our bibliometric analysis of breast cancer research from 2006 to 2023 revealed a robust and growing research landscape, encompassing 544 publications. The publication output showed a steady increase, with an 8.3% compound annual growth rate (CAGR). From 2018 to 2022, annual publications doubled, rising from 45 to 90. This acceleration suggests an intensifying research focus on breast cancer and potentially reflects increased funding and research capacity in this critical area (Fig. 1).

The geographic distribution of research output reveals interesting patterns of global scientific activity in breast cancer research. Our analysis identified significant contributions from various regions, with particularly strong representation from Asia, North America, and Europe. China and the United States emerge as the dominant forces in this research domain, collectively accounting for nearly 60% of all publications. This geographical distribution suggests a significant emphasis on breast cancer research in these areas, potentially driven by advanced research capabilities, higher funding allocations, and the regional prevalence of breast cancer (Table 1).

Table 1: Top Contributing Countries in Breast Cancer Research (2006-2023)

Country	TP	%
China	164	30.15%
United States	162	29.78%
United Kingdom	37	6.80%
South Korea	27	4.96%
Canada	21	3.86%
Italy	21	3.86%
France	20	3.68%
Spain	18	3.31%
India	17	3.13%
Japan	17	3.13%

A visual representation through a geographical map highlights these patterns, showing concentrated research outputs in regions like North America, East Asia, and parts of Europe. In contrast, regions such as Africa and Latin America, excluding Brazil, exhibit significantly lower publication volumes, likely reflecting disparities in research funding, infrastructure, and awareness of breast cancer. However, emerging

countries like India and Brazil are demonstrating increased research activitie suggesting a positive trend toward greater global participation in this domain (Fig.1).

Thematic Analysis of mTOR in Breast Cancer using VOSviewer

Our network analysis, conducted using VOSviewer, provides crucial insights into the thematic structure of breast cancer research. A network visualization identified several distinct research clusters, each represented by specific colors and focused on various subthemes within the overarching topic (Table 2).

The blue cluster focuses on the mechanistic pathways involved in breast cancer, particularly highlighting the role of the PI3K/Akt signaling pathway in relation to mTOR. Studies within this cluster emphasize the interaction between these oncogenic pathways and their impact on tumor progression and drug resistance, as illustrated by Prvanović et al. (2021) in their work on triple-negative breast cancer (TNBC). This research underscores the complexity of oncogenic signaling and the need for integrated therapeutic approaches [15].

The green cluster delves into the therapeutic potential of mTOR inhibitors. Research has shown that targeting the mTOR pathway can significantly enhance treatment outcomes in breast cancer patients, particularly those who have developed resistance to standard therapies. For instance, Hare et al. (2017) provide a comprehensive overview of the clinical implications of mTOR inhibition, advocating for its inclusion in treatment protocols [16].

The red cluster addresses the relationship between mTOR signaling and multidrug resistance (MDR) in breast cancer. Dong et al. (2021) highlight how the activation of the mTOR pathway contributes to MDR, complicating the effectiveness of conventional treatments. This research is vital for developing innovative approaches that circumvent resistance mechanisms [17].

Studies in the yellow cluster emphasize the genetic and proteomic landscape associated with mTOR signaling. Integrative analyses, like those conducted by Stemke-Hale et al. (2008), reveal crucial mutations and expression patterns that can guide prognosis and treatment decisions. The complexity of these molecular interactions indicates a need for more detailed investigations to refine treatment personalization [18].

The purple cluster focuses on the identification of potential prognostic biomarkers within the mTOR pathway, particularly relevant to aggressive subtypes like TNBC. Nedeljkovic et al. (2019) discuss how specific alterations in mTOR components can serve as indicators of clinical outcomes, paving the way for more targeted treatment approaches and personalized therapy [19].

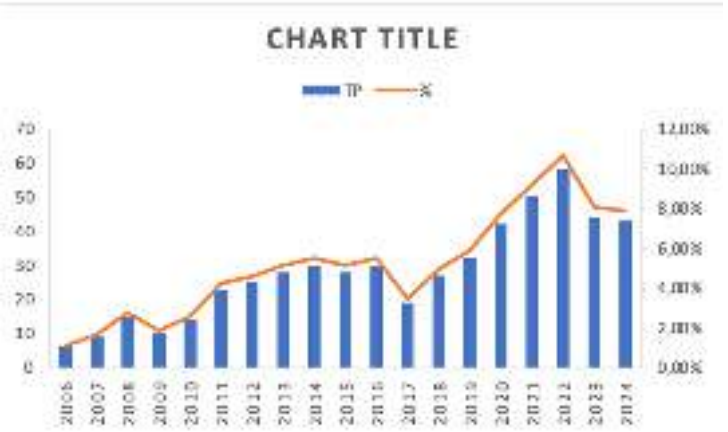

Fig 1. Annual publication trend of breast cancer research from 2006 to 2023

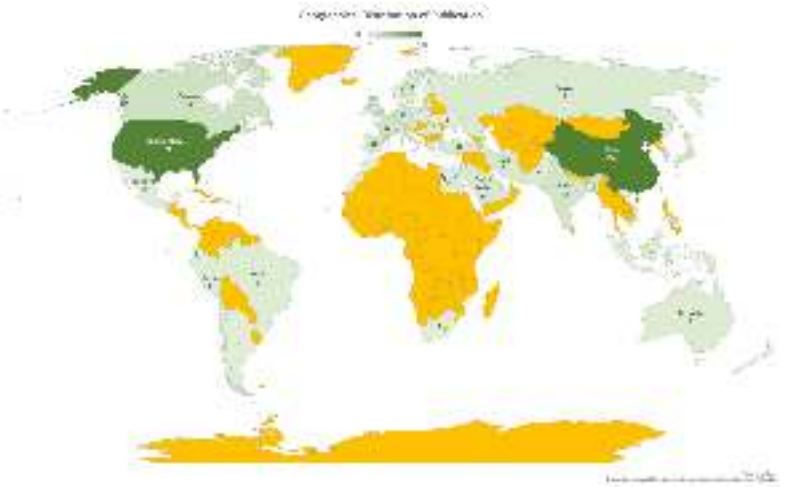

Fig 2. Global Distribution of Breast Cancer Research Publications (2006-2023)

DISCUSSION

The growing trend in publications related to mTOR research in breast cancer, observed from 2006 to 2023, underscores the increasing recognition of mTOR's pivotal role in breast cancer pathophysiology. This surge in interest is closely tied to advancements in molecular biology and targeted cancer therapies, reflecting a shift towards precision medicine in oncology [20]. Countries such as China and the United States dominate in research output, which mirrors trends seen in other areas of cancer

research, where advanced infrastructure and substantial funding drive research activities [20]. However, disparities in publication frequencies across regions suggest the need for more inclusive global collaborations, particularly in emerging economies experiencing a rise in breast cancer incidence.

Table 2: Key Research Themes Identified by Cluster Colors in mTOR Analysis

Cluster Color	Theme Description	Key Finding
Blue	Oncogenic Pathways and Mechanisms	Involves studies on the PI3K/Akt pathway's role in tumor progression and drug resistance, with a focus on interactions with the mTOR pathway.
Green	Therapeutic Targeting of mTOR	Explores the potential of mTOR inhibitors in enhancing treatment efficacy, especially in overcoming traditional therapy resistance.
Red	Multidrug Resistance Mechanisms	Investigates how mTOR activation contributes to multidrug resistance in breast cancer, impacting therapeutic strategies.
Yellow	Genomic and Proteomic Insights	Focuses on genetic mutations and proteomic alterations linked to mTOR signaling, informing personalized treatment strategies.
Purple	Clinical Implications and Prognostic Markers	Identifies biomarkers within the mTOR pathway as indicators for prognosis and treatment responses, especially in aggressive breast cancer subtypes.

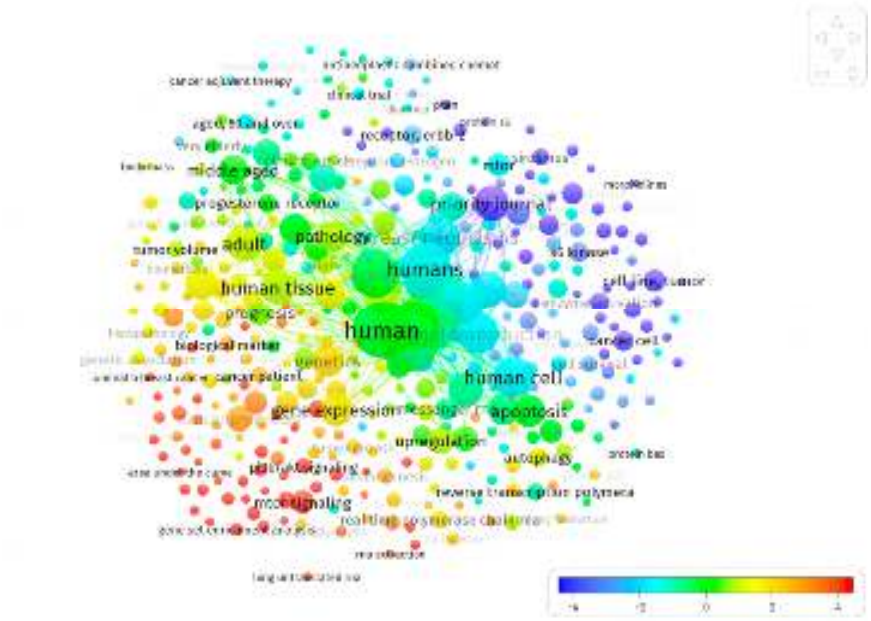

Figure 3. Network Visualization of mTOR Research Themes in Breast Cancer

The thematic analysis conducted using VOSviewer identified five primary research clusters, emphasizing oncogenic pathways and mechanisms, particularly the PI3K/Akt/mTOR axis. This focus highlights the central role of mTOR in cancer cell proliferation and survival, consistent with other bibliometric studies that underscore the significance of the PI3K/Akt pathway in oncogenic research. These insights are crucial for identifying biomarkers and therapeutic targets, especially for aggressive subtypes like Triple-Negative Breast Cancer (TNBC) [15]

The findings highlight the clinical potential of targeting the mTOR pathway, particularly through mTOR inhibitors used in combination with other treatments to overcome resistance. This aligns with studies suggesting that mTOR inhibitors can significantly improve the effectiveness of endocrine therapies in hormone receptor-positive breast cancer [16]. The increased focus on drug resistance, particularly Multidrug Resistance (MDR), underscores the challenges faced in clinical settings, emphasizing the need for innovative approaches, potentially involving multi-target inhibitors [17].

Furthermore, the integration of genomic and proteomic insights has enhanced the understanding of mTOR signaling complexities in breast cancer. These comprehensive data contribute to a deeper comprehension of tumor heterogeneity, which is vital for advancing precision oncology. The identification of molecular subtypes, based on mTOR-related mutations, aligns with findings that emphasize the importance of molecular profiling for personalized treatment strategies [18]. This molecular focus is

also mirrored in the clinical relevance of prognostic markers within the mTOR pathway, suggesting that alterations in mTOR components could serve as key indicators for prognosis and treatment response. The use of biomarkers is increasingly guiding treatment plans, reflecting the broader trend toward personalized medicine [19]

Despite providing valuable insights, this study has several limitations. First, the reliance on specific databases for bibliometric analysis could result in incomplete coverage, potentially missing relevant studies outside the selected sources. This limitation was also noted by Lin et al. (2023), who emphasized that database constraints could impact the validity of findings in bibliometric analyses [20]. Additionally, the focus on citation metrics might introduce bias, as high citation counts do not necessarily equate to clinical relevance. Future research should include multiple data sources and consider alternative evaluation metrics to obtain a more nuanced understanding of the research landscape.

Future studies should expand data sources to encompass a broader range of publications, enhancing the representativeness of research findings. Moreover, prospective studies exploring the interplay between the mTOR pathway and other molecular factors are recommended. This aligns with Zhang et al. (2023), who highlighted the significance of genetic correlations in breast cancer research [22]. Multi-omics integration—including genomic, proteomic, and epigenetic analyses—remains crucial for unraveling the complexities of breast cancer biology and for refining therapeutic interventions. Additionally, collaborative efforts involving underrepresented regions are necessary to develop a more holistic understanding of breast cancer and to ensure equitable advancements in this global health challenge.

CONCLUSIONS

The outcomes of this bibliometric analysis provide a comprehensive overview of the research trends, challenges, and opportunities within the field of mTOR research in breast cancer. Identifying knowledge gaps and emerging areas of interest guides future investigations aimed at advancing targeted therapies and improving patient outcomes. A concerted effort toward international collaborations, especially in regions with rising breast cancer cases, is essential to broaden our understanding of breast cancer biology and to promote equitable progress in cancer treatment.

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