Bibliometric

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UNVEILING THE CRITICAL ROLE OF CYP2C19 GENE IN PRECISION MEDICINE THROUGH BIBLIOMETRIC ANALYSIS

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ABSTRACT

The CYP2C19 gene is pivotal in precision medicine, influencing the efficacy of therapeutic approaches, particularly in pharmacokinetics and pharmacogenomics. This study aims to extensively chart the research landscape of the CYP2C19 gene, delineating crucial interconnections among various research themes, and identifying significant studies and future research directions in precision medicine, with a focus on CYP2C19. An extensive literature review was conducted, adhering to PRISMA guidelines for reference curation and employing bibliometric analysis for research mapping. A total of 2,293 documents were retrieved from the Scopus database using 'precision' as the keyword. After meticulous refinement and data preparation, 1,829 of these publications were deemed suitable for in-depth analysis. The study reveals a notable increase in CYP2C19-related research from 2019 to 2022. The bibliometric analysis identified four primary clusters: Clopidogrel, Pharmacogenomics-Pharmacokinetics, Cytochrome P450, and Voriconazole. The Voriconazole cluster exhibited a unique divergence, indicating opportunities for collaborative research. Key strategic areas identified include valproic acid, antidepressants, and herb-drug interactions. Our findings provide valuable insights into the CYP2C19 gene research, offering a foundation for guiding future research in precision medicine.

Keywords: *Science Mapping, CYP2C19, Precision Medicine, Bibliometric Analysis*

INTRODUCTION

The CYP2C19 gene plays a critical role in the field of precision medicine, significantly influencing the effectiveness of therapeutic strategies, particularly in pharmacokinetics (1), (2). Despite the extensive research conducted in this area, the dynamism of findings necessitates ongoing mapping, as traditional systematic literature reviews (SLRs) and meta-analyses (MAs) may not fully capture the complexity and nuances of this field. Mapping the CYP2C19 gene research provides an extensive overview of the ways that this field's research has developed. It enables in-depth analysis of related topics and reproducible research at the country level. Bibliometric analysis, in particular, can highlight strategic studies and reveal relationships between research areas more efficiently than examining individual publications (3).

The CYP2 family of genes holds significant importance in medical science, especially in pharmacokinetics and pharmacodynamics. Genes like CYP2C9 and CYP2C16 affect how drugs are metabolized in the body (pharmacokinetics), influencing the efficacy of drugs in interacting with their biological targets (pharmacodynamics) (4). For example, genetic variations in these genes can impact the effectiveness of medications like warfarin, with some genetic variants increasing the risk of side effects (5). Although research has deepened our understanding of these genes, there remains a need to assess the overall research landscape and identify areas not fully explored.

Furthermore, with the increasing number of scientific publications, particularly in the study of CYP2C19 gene's role in drug therapy, it is crucial to have a comprehensive understanding of how research related to the CYP2 gene family has evolved. The 'mapping of science' in this field will not only reveal current trends but also identify knowledge gaps that may have been overlooked, which will be essential for maximizing the efficiency of research efforts and directing resources toward the most needed or strategic areas. Bibliometric analysis, with its ability to systematically map and interpret publication data, offers a solution to this challenge.

The main objectives of this study are to explore the CYP2C19 gene research landscape in greater detail, find connections between topics, and identify possible directions for future precision medicine research and strategic studies.

MATERIAL & METHODS

This study was conducted by adopting the principles of bibliometric research as formulated by Donthu (3). We meticulously followed a series of steps to ensure the quality of data and comprehensive reporting of results.

The research involved several crucial stages: it began with the synthesis of the research question, followed by the formation of control vocabulary and keywords. The next steps involved searching for references in databases using specified filters, preparing and cleaning the data, conducting mathematical calculations and visualizations, and finally, interpreting the results (3).

The search strategy was designed to capture the most relevant and precise documents. We employed the following keywords and search query:

TITLE-ABS-KEY (cyp2c19) AND gene AND PUBYEAR > 2011 AND PUBYEAR < 2024 AND (LIMIT-TO (SRCTYPE, "j")) AND (LIMIT-TO (PUBSTAGE, "final")) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (SUBJAREA, "MEDI") OR LIMIT-TO (SUBJAREA, "PHAR") OR LIMIT-TO (SUBJAREA, "BIOC") OR LIMIT-TO (SUBJAREA, "CHEM") OR LIMIT-TO (SUBJAREA, "NEUR") OR LIMIT-TO (SUBJAREA, "IMMU") OR LIMIT-TO (SUBJAREA, "NURS") OR LIMIT-TO (SUBJAREA, "HEAL") OR LIMIT-TO (SUBJAREA, "DENT") OR LIMIT-TO (SUBJAREA, "MATH") OR LIMIT-TO (SUBJAREA, "VETE") OR LIMIT-TO (SUBJAREA, "COMP")) AND (LIMIT-TO (LANGUAGE, "English")).

The article search was conducted on October 25, 2023, using the Scopus database. Specific filters were applied during the search to ensure the retrieval of relevant and precise documents. The following diagram illustrates the scheme and limitations of the filters used in the search process.

Research Question

The research questions for this study have been formulated to explore various facets of the CYP2C19 gene research. These questions aim to uncover the depth and breadth of the research landscape in this domain. The questions are as follows:

RQ1: How many major clusters exist within the CYP2C19 gene studies? This question seeks to identify and quantify the main research clusters, providing insights into the primary areas of focus within the field.

RQ2: What is the nature of the relationships between the clusters in the CYP2C19 gene family?

This question aims to explore the interconnections and dynamics between different research clusters, shedding light on how various aspects of CYP2C19 research are interrelated.

RQ3: What are the strategic topics of research within the CYP2C19 gene family? The focus here is to identify key topics that are currently at the forefront of CYP2C19 research, which may guide future research directions and priorities.

RQ4: Is there a discernible dynamic in the publication trends within the CYP2C19 gene family?

This question intends to analyze the temporal trends in research publications, looking for patterns, growth, or shifts in focus over time.

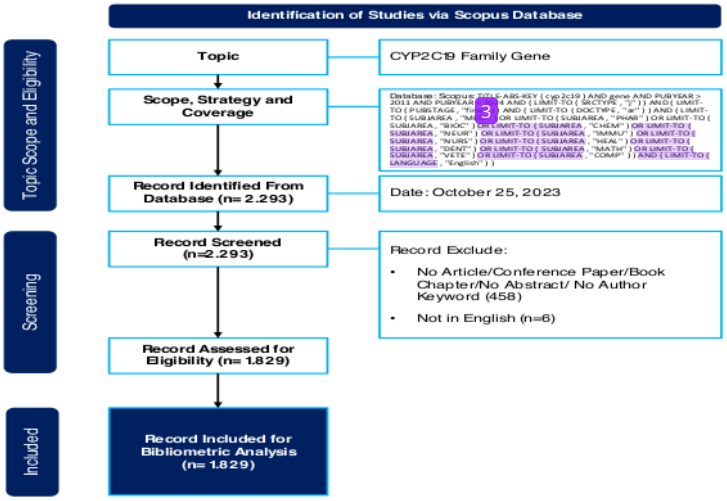


Figure 1. Document selection stages adapted from the PRISMA flow diagram (4)

RESULT & DISCUSSION

Research Productivity

Research productivity can be benchmarked by two key indicators: the number of publications and the number of citations. Higher publication output typically signifies greater productivity in the respective field of study. Our analysis of the CYP2C19 gene family research reveals a significant increase in research outputs. A notable publication momentum was observed during the period of 2019-2022, where the publication frequency exceeded the average of the previous decade (see Figure 2).

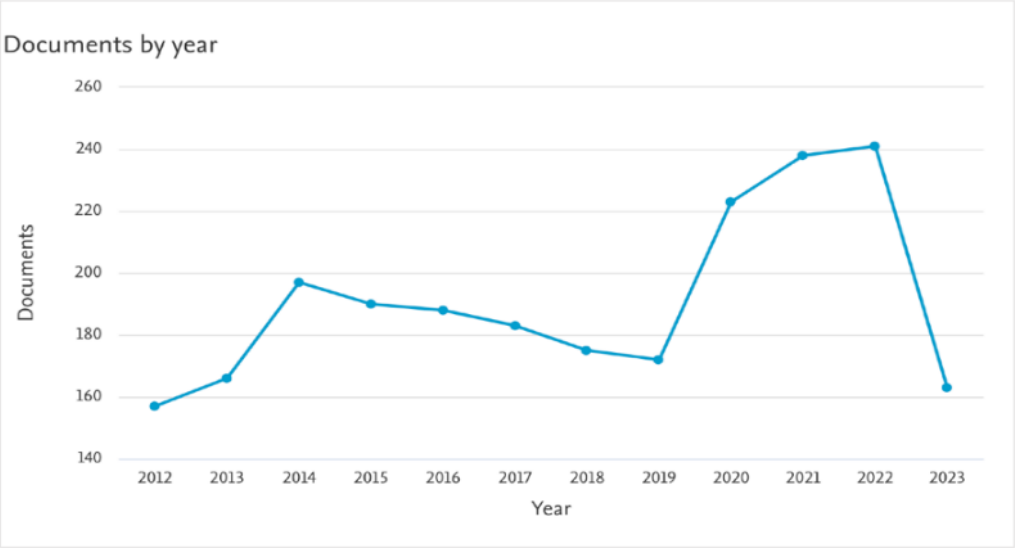


Figure 2. Publication productivity of CYP2C19 gene research. Source: Scopus, data extracted on October 25th, 2023.

A critical finding of this study involves the identification of 54 documents that discuss drug interaction between tacrolimus and voriconazole. This drug combination requires a thorough understanding to achieve optimal therapeutic effects. The outcomes of publications have a significant impact on Country Research Performance (CRP). Our data analysis revealed the top five countries with commendable CRP in CYP2C19 research, namely the

United States, China, Japan, Germany, and South Korea. These countries' success in this research area can be rationally attributed to the support of adequate research facilities and funding.



Figure 3. Country Research Performance (CRP), author, and subject area based on Scopus data extracted on October 25th, 2023. Data source: Scopus.

Clusters Study of CYP2C19 Research

In bibliometric analysis, it is crucial to consider several key aspects. Clusters are represented by closely situated nodes, often marked with identical colors, signifying their interrelatedness. The size of each node is indicative of the frequency of the associated terminology, providing insights into the prominence of certain topics within the research landscape. Additionally, lines connecting the nodes represent the relationships between terms, particularly highlighting their proximity and interconnectedness. This visual representation aids in comprehensively understanding the network of terms and their relevance in the broader context of the study

The CYP2C19 gene study area has shown notable development, as evidenced by the diversity and interaction of centroids and nodes within the research field. A meticulous examination reveals variations in the number of members within each study point, and interestingly, there is an overlap in cluster mapping.

Based on our mapping, four major clusters were identified, distinguished by different colors: red, blue, yellow, and green. The largest cluster is represented in red, with clopidogrel as its central node, followed by the yellow cluster with a central node of pharmacogenetics, the blue cluster focused on drug metabolism, and the green cluster centered around CYP2C9 (see Figure 4). This mapping has revealed numerous relationships within and between these clusters. An example of this is the polarization observed in voriconazole studies, indicated by the blue cluster's intersection with the red, yellow, and green clusters. This polarization offers insights into strong interconnections between different research areas. For instance, the study by Gong in 2023 on physiologically based pharmacokinetic (PBPK) modeling, considering CYP3A5 and CYP2C19 polymorphisms, provides deeper understanding of the drug interactions between tacrolimus and voriconazole (6). This contributes to guiding the clinical use of tacrolimus, offering crucial information on how individual genetic differences can affect the interaction and efficacy of these drugs.

This finding is significant as, to our knowledge, no bibliometric mapping of the CYP2C19 gene has been conducted previously. The clusters formed in this mapping are Clopidogrel, Pharmacogenetics, Cytochrome P450, and Voriconazole. The spectrum formed in this study's mapping aligns with data from Clinical Pharmacogenetics Implementation Consortium (CPIC), which lists 27 drug items correlated with CYP2C19 activity.

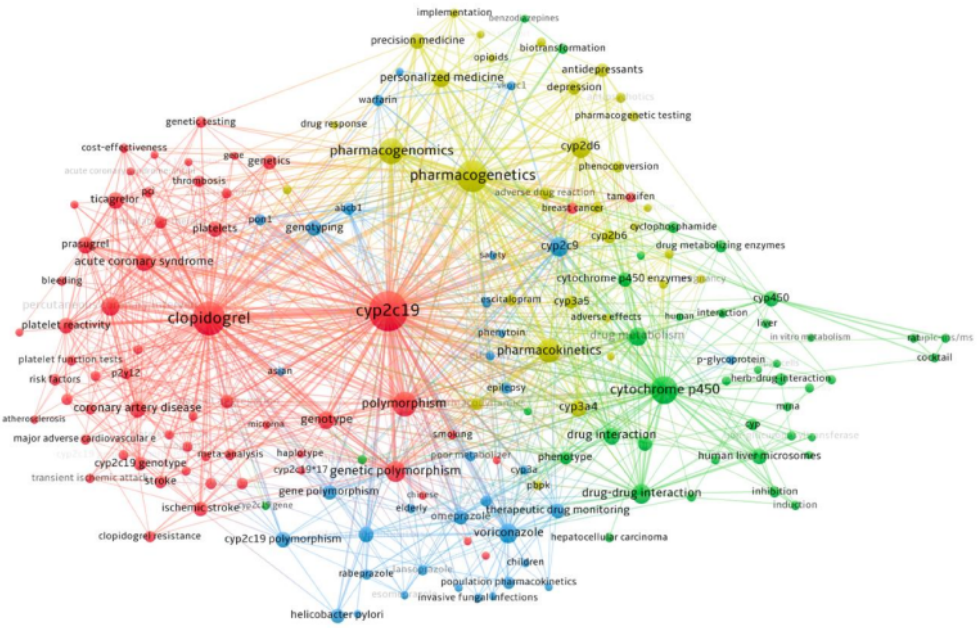


Figure 4. Visualization of Co-occurrence Analysis on Global CYP2C19 Topics Using *Author Keywords* Data.

CYP2C19 and Clopidogrel

The study of the CYP2C19 gene shows a strong conceptual connection to clopidogrel in mapping analyses (Figure 5). This relationship is evidenced by the proximity of nodes and their positioning within the same cluster, color-coded as "red". Numerous studies have explored the role of the CYP2C19 gene in relation to clopidogrel. A noteworthy study by Sung et al. (2023) investigated the implications of Clopidogrel in East Asian patients undergoing antiplatelet therapy based on clopidogrel following DES implantation. The study found that CYP2C19 genotype determination can categorize patients who may have a high risk of atherothrombotic events (7). In the mapping, it is observed that Clopidogrel and CYP2C19 are situated within the same cluster, indicating a strong relational linkage. The size of both nodes signifies a higher frequency compared to others, highlighting the prominence of these terms in the research context

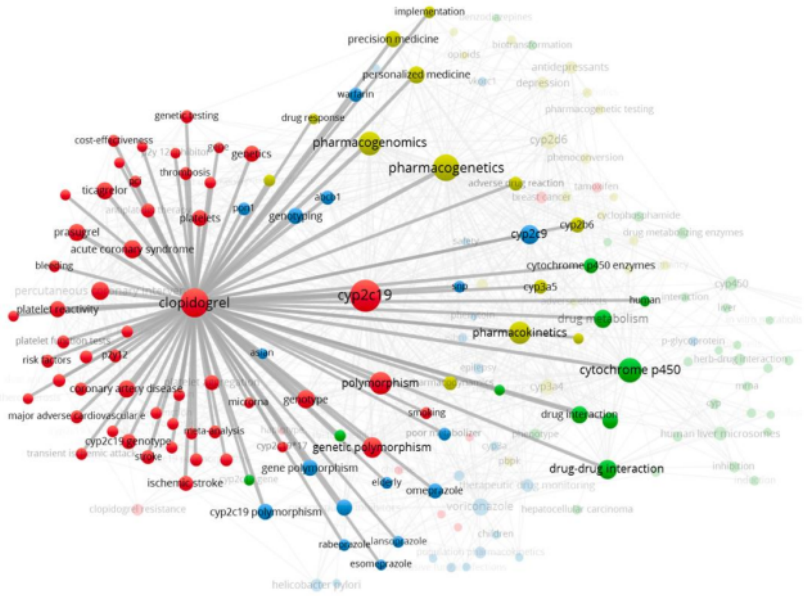


Figure 5. Relationship Between Clopidogrel and CYP2C19.

CYP2C19, Diabetes, and Cardiovascular Disease

Diabetes, a complex disease often associated with genetic factors, shows a significant correlation with the CYP2C19 gene (Figure 6). In this study, we identified 15 documents addressing this issue. Recent research indicates that CYP2C19 not only contributes to the development of diabetes but also influences the success of the therapies used. As a major enzyme in drug metabolism, CYP2C19 plays a crucial role in determining the effectiveness of diabetes treatments, with genetic variations in this enzyme affecting the drug breakdown process. Furthermore, there is evidence suggesting CYP2C19's involvement in insulin resistance, a hallmark of type 2 diabetes. The function of CYP2C19 is also significant in the context of treating cardiovascular diseases (8), which often co-occur with diabetes, where its genetic variations could influence the body's response to certain medications. In conclusion, a deeper understanding of CYP2C19's role is essential for developing more personalized and effective therapy strategies for diabetes.

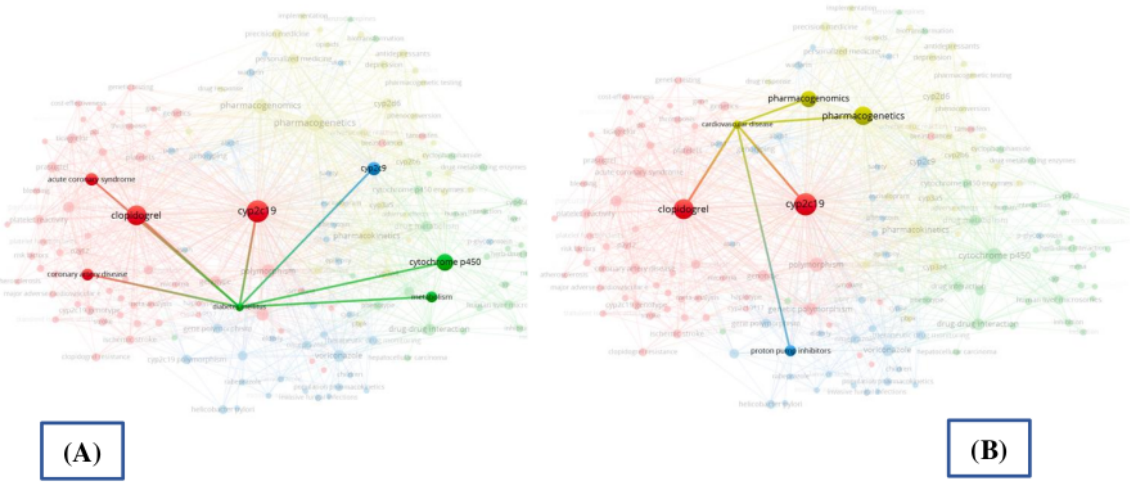


Figure 6. Relationship between Diabetes and CYP2C19 (A) and Cardiovascular Disease and CYP2C19 (B).

CYP2C19 Research Trends

The field of CYP2C19 research has shown significant advancements. The trend in CYP2C19 research is distinctly visible in the mapping visualization, especially in nodes colored yellow (Figure 7). Notably, there are more than 20 nodes post-2019, indicating a robust increase in related studies. In the mapping, topics like antidepressants, drug response, and transient ischemic attacks appear as trending areas of study. For instance, research by Minderhoud in 2022 demonstrated a correlation between the presence of CYP2C19 LoF alleles in patients treated with clopidogrel and an increased risk of recurrent cerebral ischemia (9).

This trend is further supported by other studies, particularly in "pharmacogenetics" and "pharmacogenomics". These fields involve the study of how an individual's genetics affect their response to drugs, which is central to the customization of drug therapies like clopidogrel. "Genetic testing" in this context may relate to assessing CYP2C19 genotypes to

predict the efficacy and safety of clopidogrel use, while "drug response" signifies the outcomes of such interactions (10). "Personalized medicine" indicates the ultimate goal of all these studies: to adapt and optimize medical care based on a patient's genetic profile for better clinical outcomes. The presence of these yellow nodes underscores the importance of a deep understanding of genetic factors in developing more effective and personalized therapies.

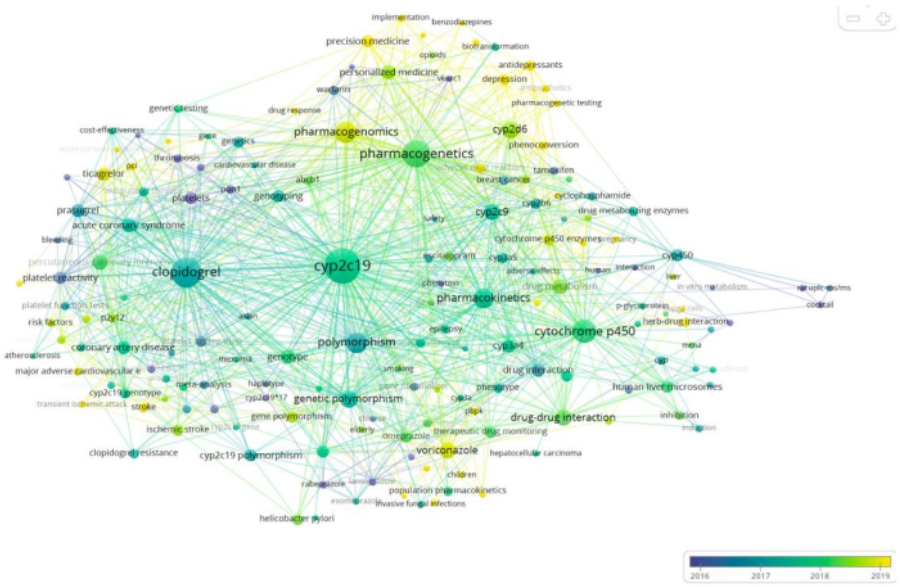


Figure 7. Mapping of Research Trends in CYP2C19 Global Studies.

These findings provide crucial information for researchers delving into the field of CYP2C19. There are many aspects that are the focus of interest in this field, as illustrated in Figure 8. The study by Xie on CYP2C19 and ticagrelor, explained in this qualitative and quantitative research, suggests that Asian patients with CYP2C19 LOF alleles might have a lower bleeding risk compared to those without LOF alleles when treated with ticagrelor (1).

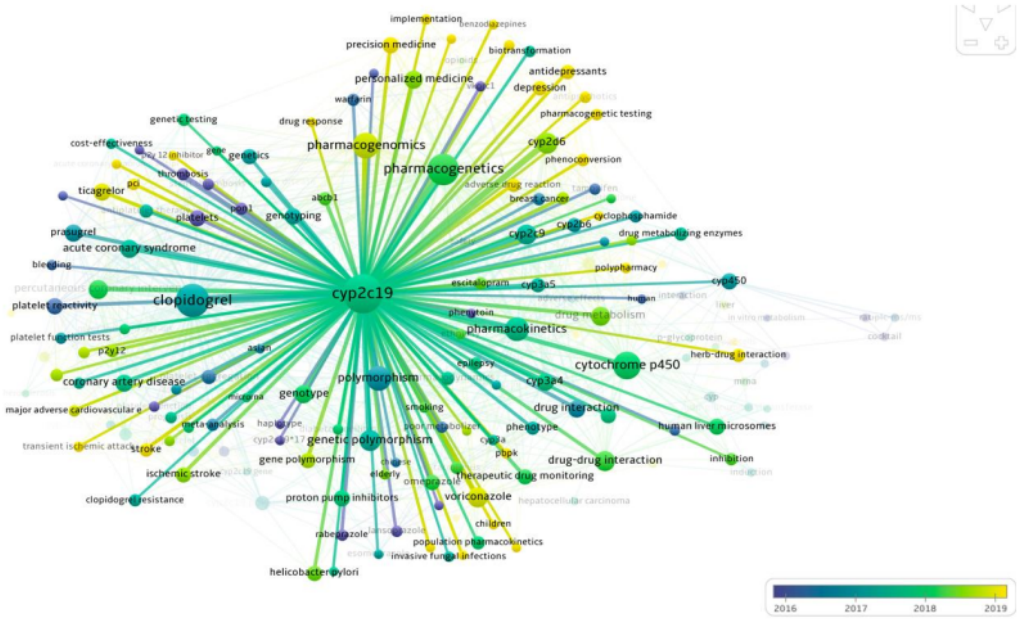


Figure 8. Recent Research on CYP2C19 (highlighted in yellow).

CONCLUSION

Bibliometric analysis of CYP2C19 research revealed 1,829 articles from the Scopus database, showing a significant annual increase in publications. This analysis provided insight into the most frequently researched areas, identifying four major clusters: Clopidogrel, Pharmacodynamic-Pharmacokinetic, Cytochrome P450, and Voriconazole. The genetic variations of CYP2C19 are closely related to the efficacy of clopidogrel and are also linked to diabetes and cardiovascular diseases.

Limitations and Suggestions

While this study provides important insights, there are several limitations that should be noted. Firstly, despite the significant increase in publications and citations, this analysis is limited to data available on Scopus, which may not encompass all relevant literature. Therefore, further exploration with a broader data scope is required. Secondly, this study

relies on cluster visualization methods that may not fully reflect the complexity and interconnections among topics in the CYP2C19 gene study, being limited to author keywords. Additional visualizations using alternative approaches are necessary to enhance accuracy and interpretation.

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REFERENCE

1. Effect of CYP2C19 genetic polymorphism on the pharmacodynamics and clinical outcomes for patients treated with ticagrelor: a systematic review with qualitative and quantitative meta-analysis | BMC Cardiovascular Disorders | Full Text [Internet]. [dikutip 18 Desember 2023]. Tersedia pada: https://bmccardiovascdisord.biomedcentral.com/articles/10.1186/s12872-022-02547-3
2. Tornio A, Backman JT. Chapter One - Cytochrome P450 in Pharmacogenetics: An Update. Dalam: Brøsen K, Damkier P, editor. Advances in Pharmacology [Internet]. Academic Press; 2018 [dikutip 18 Desember 2023]. hlm. 3–32. (Pharmacogenetics; vol. 83). Tersedia pada: https://www.sciencedirect.com/science/article/pii/S1054358918300267
3. Donthu N, Kumar S, Mukherjee D, Pandey N, Lim WM. How to conduct a bibliometric analysis: An overview and guidelines. J Bus Res. 1 September 2021;133:285–96.
4. Miftahussurur M, Doohan D, Syam AF, Nusi IA, Subsomwong P, Waskito LA, dkk. CYP2C19 Polymorphisms in Indonesia: Comparison among Ethnicities and the Association with Clinical Outcomes. Biology. April 2021;10(4):300.
5. Lee SJ. Clinical Application of CYP2C19 Pharmacogenetics Toward More Personalized Medicine. Front Genet [Internet]. 2013 [dikutip 18 Desember 2023];3. Tersedia pada: https://www.frontiersin.org/articles/10.3389/fgene.2012.00318
6. Gong F, Hu H, Ouyang Y, Liao ZZ, Kong Y, Hu JF, dkk. Physiologically-based pharmacokinetic modeling-guided rational combination of tacrolimus and voriconazole in patients with different CYP3A5 and CYP2C19 alleles. Toxicol Appl Pharmacol. 1 Mei 2023;466:116475.
7. Lee SH, Jeong YH, Hong D, Choi KH, Lee JM, Park TK, dkk. Clinical Impact of CYP2C19 Genotype on Clopidogrel-Based Antiplatelet Therapy After Percutaneous Coronary Intervention. JACC Cardiovasc Interv. 10 April 2023;16(7):829–43.
8. CYP2C19 Polymorphism in Ischemic Heart Disease Patients Taking Clopidogrel After Percutaneous Coronary Intervention in Egypt - PubMed [Internet]. [dikutip 18 Desember 2023]. Tersedia pada: https://pubmed.ncbi.nlm.nih.gov/37202608/
9. Minderhoud C, Otten LS, Hilkens PHE, van den Broek MPH, Harmsze AM. Increased frequency of CYP2C19 loss-of-function alleles in clopidogrel-treated patients with recurrent cerebral ischemia. Br J Clin Pharmacol. Juli 2022;88(7):3335–40.
10. Galli M, Franchi F, Rollini F, Cavallari LH, Capodanno D, Crea F, dkk. Genetic testing in patients undergoing percutaneous coronary intervention: rationale, evidence and practical recommendations. Expert Rev Clin Pharmacol. 3 Agustus 2021;14(8):963–78.

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