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Global Research Trends in Paroxysmal Nocturnal Hemoglobinuria: A Bibliometric and Scientometric Analysis (2015-2025)

Zeynep Tuğba Karabulut

University of Health Science Türkiye, Adana City Training and Research Hospital, Clinic of Hematology, Adana, Türkiye

ABSTRACT

Aim: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired hematologic disorder characterized by complement-mediated intravascular hemolysis, thrombosis, and bone marrow failure. Over the past decade, advances in complement- inhibition therapies have significantly transformed disease management. This study aimed to provide a comprehensive bibliometric and scientometric analysis of global PNH research published between 2015 and 2025 and to identify research trends, thematic evolution, and collaborative networks.

Methods: Publications indexed in the Web of Science Core Collection between 2015 and 2025 were retrieved using a topic-based search strategy. After manual screening of records, 1,352 English language articles and reviews were included. VOSviewer and CiteSpace were used to perform collaboration, keyword co-occurrence, and temporal cluster analyses.

Results: Annual PNH-related publications generally demonstrated an increasing trend, particularly after 2018, coinciding with the clinical expansion of complement-inhibition strategies. Keyword analysis revealed four principal thematic clusters: (1) complement-mediated hemolysis and therapy; (2) bone marrow failure syndromes; (3) diagnostics and molecular biology; and (4) clinical outcomes and complications. A temporal analysis demonstrated a shift from mechanistic and diagnostic studies (2015-2018) to therapeutic innovation and long-term outcomes research (2022-2025). The United States emerged as the leading contributor and central hub of international collaboration, followed by Japan, England, and Italy. Research activity from Asian countries has increased in recent years.

Conclusion: PNH research over the past decade has shifted from foundational disease characterization toward therapeutic optimization and personalized management strategies. Complement inhibition remains the central focus of investigation. Continued international collaboration and research on emerging therapies and real-world outcomes are essential to address unmet clinical needs.

Keywords: Paroxysmal nocturnal hemoglobinuria, bibliometric analysis, scientometrics, VOSviewer, complement inhibitors

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired hematologic disorder characterized primarily by complement-mediated intravascular hemolysis, thrombosis, and bone marrow failure. The disease arises from a somatic mutation in the *PIGA* gene, which leads to the loss of glycosylphosphatidylinositol-anchored proteins on hematopoietic cells, rendering red blood cells highly susceptible to complement-mediated lysis. PNH can present with fatigue, hemoglobinuria, abdominal pain, thrombosis, and varying degrees of anemia, which contribute to significant morbidity and mortality if untreated [1].

The discovery and implementation of complement inhibition therapies have transformed the clinical management of PNH. The first targeted therapy, eculizumab, is a humanized monoclonal antibody directed against complement protein C5. Eculizumab has been shown to dramatically reduce intravascular hemolysis, decrease transfusion requirements,

Address for Correspondence: Assoc. Prof. Zeynep Tuğba Karabulut, University of Health Science Türkiye, Adana City Training and Research Hospital, Clinic of Hematology, Adana, Türkiye

E-mail: drzeyneptk@gmail.com **ORCID ID:** orcid.org/0000-0003-1600-9731

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improve quality of life, and markedly reduce the risk of thrombotic events, which historically were the leading cause of death in untreated PNH patients [2].

Building upon the success of eculizumab, second-generation C5 inhibitors such as ravulizumab have been developed, offering extended dosing intervals and improved pharmacokinetics, thereby enhancing treatment convenience without compromising efficacy [3]. In addition, more recent advances include the development of proximal complement inhibitors such as pegcetacoplan (targeting C3), and oral inhibitors targeting complement factors B and D, which aim to address both intravascular and extravascular hemolysis and further improve patient outcomes [4].

Despite significant therapeutic advancements, PNH remains an ultra-rare and clinically heterogeneous condition, with ongoing research addressing unmet needs such as breakthrough hemolysis, suboptimal responses to existing therapies, and optimal long-term disease management strategies [5]. Over the past decade, the volume of scientific literature on PNH has increased substantially, encompassing mechanistic insights, therapeutic developments, clinical outcomes, and real-world treatment experiences.

Bibliometric and scientometric analyses provide quantitative and visual insights into research trends, influential authors, institutional collaborations, and thematic focuses within a scientific field. These methods are especially valuable in rare diseases like PNH, where a comprehensive understanding of research activity can guide future investigations and identify knowledge gaps. Therefore, this study aims to conduct a bibliometric and scientometric analysis of PNH research published between 2015 and 2025, using data from the Web of Science database and performing network visualization with VOSviewer. To our knowledge, no previous study has comprehensively evaluated the global intellectual structure, thematic evolution, and collaboration patterns of PNH research using combined bibliometric and scientometric approaches.

Methods

Data Source and Search Strategy

The bibliometric dataset was retrieved from the Web of Science Core Collection on 18 December 2025. The search was conducted within the Science Citation Index Expanded and the Emerging Sources Citation Index.

Publications related to PNH published between 2015 and 2025 were identified using the following topic-based search strategy:

TS=("paroxysmal nocturnal hemoglobinuria" or "PNH")

Both the full disease name and its commonly used abbreviation were included in the search strategy to maximize retrieval sensitivity. Only English language articles and reviews were included in the analysis. Editorials, meeting abstracts, corrections, letters, and non-English publications were excluded.

Because searches using the isolated abbreviation "PNH" may retrieve unrelated publications, all retrieved records were manually screened by title and abstract to ensure relevance to PNH. Irrelevant records were excluded from the final dataset.

All records were exported in plain text (.txt) format, including full records and cited references, for bibliometric and scientometric analyses. Duplicate records were identified and removed prior to bibliometric analysis. Data from 2025 represent a partial year and should therefore be interpreted cautiously.

Ethical Considerations

This study did not involve human participants or animal subjects and was based exclusively on publicly available bibliographic data; therefore, ethical approval was not required.

Bibliometric Network Analysis

VOSviewer (version 1.6.20) was used to construct keyword co-occurrence, country collaboration, and author collaboration networks. Full counting was applied. The minimum keyword occurrence threshold was set at 5. Node size represented publication or keyword frequency, whereas link thickness reflected the total link strength.

Country- and author-level collaboration analyses were performed to identify the most productive countries, institutions, and influential researchers in PNH research.

Temporal and Cluster Analysis

Temporal evolution and cluster analyses were conducted using CiteSpace (version 6.3.R1). The analysis was performed using time slicing with one-year intervals from 2015 to 2025. The node selection criterion was set to the top 25 most-cited or most frequently occurring items per slice. Pathfinder pruning was applied to simplify the network structure and improve visualization clarity.

Network quality and clustering validity were evaluated using modularity (Q) and mean silhouette (S) scores. Higher Q and S values indicated robust and well-defined thematic clusters.

Visualization and Data Interpretation

All visualizations were generated using the default layout and clustering algorithms of VOSviewer and CiteSpace. Network maps were interpreted according to node size, color distribution, and link strength. Results obtained from both software tools were compared to improve thematic consistency and interpretability.

Results

Global Publication Trends

A total of 1,352 publications related to PNH, published between 2015 and 2025, were retrieved from the Web of Science Core Collection and were included in the analysis. The annual number of publications increased over the study period,

particularly after 2018, coinciding with the introduction and broader clinical adoption of novel complement inhibitors such as ravulizumab and pegcetacoplan. However, modest year-to-year fluctuations were observed (Figure 1).

Keyword Co-occurrence Analysis

The keyword co-occurrence network generated using VOSviewer revealed a well-organized and interconnected thematic structure. The most frequent keyword, PNH formed the central node of the network and was surrounded by closely related concepts such as hemolysis, aplastic anemia, complement system, and flow cytometry (Figure 2).

Several major thematic clusters were identified:

• Cluster 1: Complement-mediated hemolysis and therapy: Included terms such as eculizumab, ravulizumab, complement inhibitor, pegcetacoplan, and extravascular hemolysis.

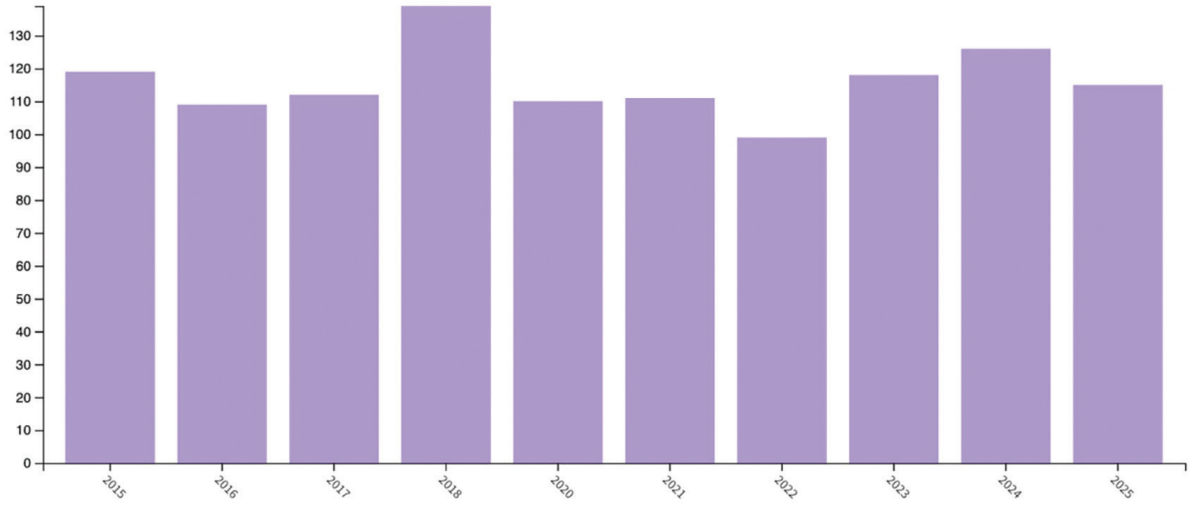

Figure 1. Annual number of publications on paroxysmal nocturnal hemoglobinuria between 2015 and 2025, illustrating the temporal trend and growth in research activity

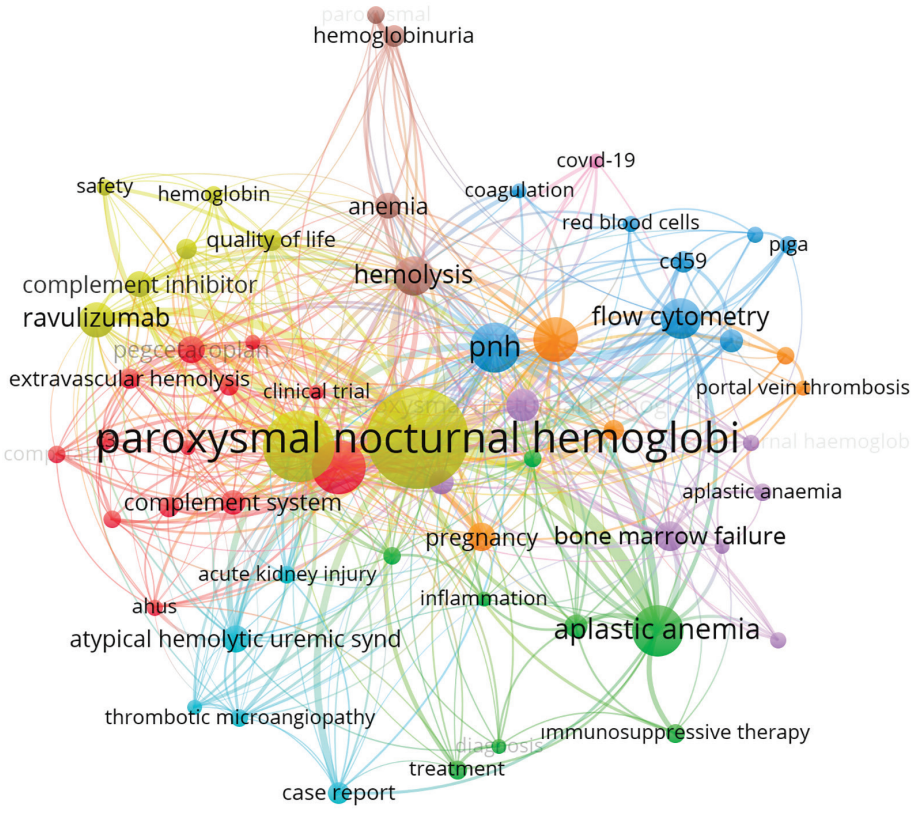

Figure 2. Keyword co-occurrence network visualization of paroxysmal nocturnal hemoglobinuria research generated using VOSviewer. Node size reflects keyword frequency, while link thickness indicates co-occurrence strength between keywords. Different colors represent thematic clusters related to complement inhibition, bone marrow failure syndromes, diagnostics, and clinical outcomes

This cluster reflects the dominance of therapeutic research centered on complement inhibition strategies.

• Cluster 2: Bone marrow failure syndromes contained aplastic anemia, bone marrow failure, and stem cell transplantation, underscoring the biological overlap between PNH and immune-mediated marrow disorders.

• Cluster 3: Diagnostics and molecular biology included flow cytometry, CD55, CD59, PIGA mutation, and biomarkers, highlighting sustained attention to diagnostic advancements and pathogenesis.

• Cluster 4: Clinical outcomes and complications: contains thrombosis, quality of life, and safety, emphasizing patient-centered research directions.

Overall, the keyword network demonstrates that recent PNH research integrates pathophysiology, diagnostics, and therapeutic innovation into a cohesive, multidisciplinary field.

Temporal Evolution of Research Themes

CiteSpace analysis demonstrated a well-structured temporal progression of research themes from 2015 to 2025 (modularity Q=0.584; mean silhouette=0.918) (Figure 3).

• 2015-2018: Early studies focused on disease mechanisms, diagnostic confirmation, and hemolysis-related concepts.

• 2019-2021: Research attention shifted toward complement-targeted therapies, particularly eculizumab and ravulizumab, and toward the intersection between PNH and aplastic anemia.

• 2022-2025: New clusters emerged around complement-mediated hemolysis, narrative reviews, novel complement inhibitors, and real-world clinical data, indicating the maturation of clinical research and the expansion of therapeutic options.

Country Collaboration Analysis

The country co-authorship network demonstrated that PNH research is globally distributed but concentrated in a limited number of highly productive countries (Table 1, Figure 4). The United States emerged as the principal hub for international collaboration, demonstrating the highest publication volume and the strongest collaborative linkages.

Other leading contributors included Japan, England, and Italy, which formed a major triad of transcontinental research partnerships. China, South Korea, and India have shown rapid growth in publication output since 2020, reflecting expanding global participation and access to complement inhibitors.

Peripheral yet notable contributions were observed from Germany, France, and Brazil, suggesting a gradual diversification of PNH-related research beyond traditional centers.

The institutional productivity analysis demonstrated that major contributions originated from specialized hematology and complement research centers, located primarily in Europe and North America (Table 4). Assistance Publique-Hôpitaux de Paris, Université Paris Cité, and Johns Hopkins University were among the most productive institutions in the field.

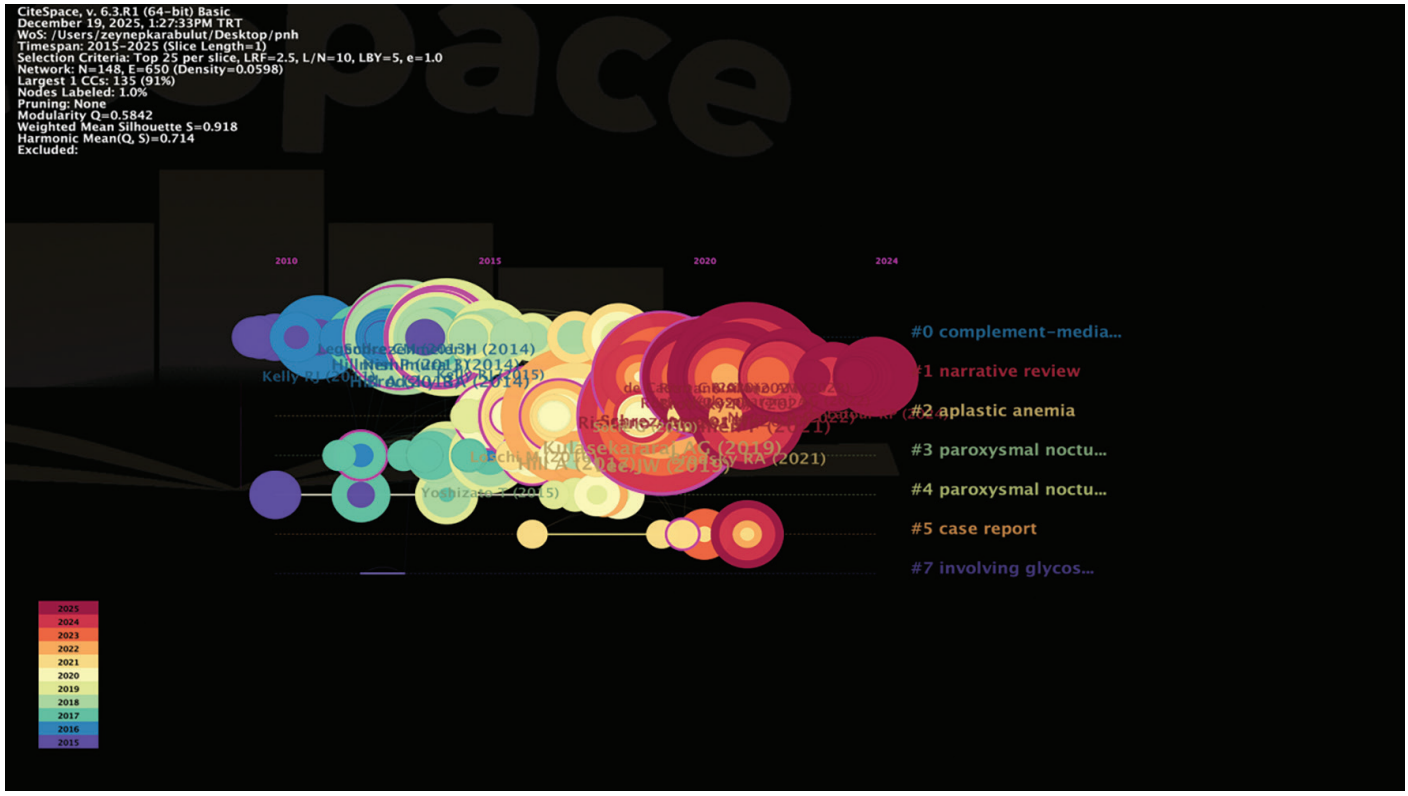

Figure 3. Timeline visualization of thematic evolution in paroxysmal nocturnal hemoglobinuria research between 2015 and 2025 generated using CiteSpace. Node size represents keyword frequency, and color gradients indicate publication year. The figure demonstrates the temporal transition from mechanistic and diagnostic studies toward complement inhibition therapies, real-world clinical outcomes, and personalized treatment strategies

Table 1. Top contributing countries in paroxysmal nocturnal hemoglobinuria research

Rank	Country	Publications
1	United States	520
2	Italy	156
3	China	153
4	Japan	147
5	England	144
6	Germany	136
7	France	101
8	Canada	69
9	Netherlands	66
10	Switzerland	66

Author Collaboration Network

The author co-authorship network analysis identified several influential researchers who serve as central nodes in the field (Table 2, Figure 5). Key contributors included de Latour et al. [6], Kulasekararaj et al. [7], Brodsky [8], Lambris et al.[9], and Obara N. [10], who represent core nodes with dense interconnections.

Distinct author clusters corresponded to subfields such as:

- clinical trial design and complement therapy (de Latour et al. [6], Brodsky [8]),
- immunopathogenesis (Lambris et al. [9]),
- and long-term patient management (Kulasekararaj et al. [7], Obara et al. [10]).

This demonstrates a highly collaborative, multidisciplinary research structure that combines clinical and translational expertise.

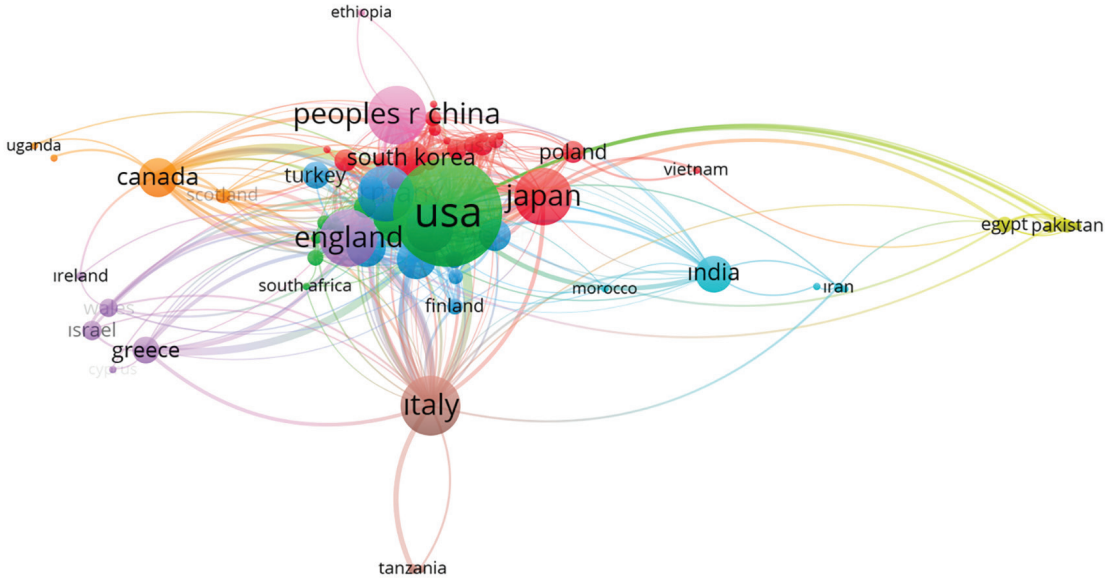

Figure 4. International country collaboration network in paroxysmal nocturnal hemoglobinuria research generated using VOSviewer. Node size reflects publication output, while link thickness represents collaboration strength between countries. The United States occupies the central position within the global collaboration network, with strong connections to major research contributors including Japan, England, Italy, and China

Table 2. Most influential authors in paroxysmal nocturnal hemoglobinuria research

Rank	Author	Publications
1	de Latour et al. [6]	43
2	Brodsky [8]	39
3	Kulasekararaj et al. [7]	38
4	Schrezenmeier et al. [11]	36
5	Lee et al. [12]	33
6	Risitano et al. [13]	31
7	Kulasekararaj et al. [14]	30
8	Fattizzo et al. [15]	26
9	Schrezenmeier et al. [11]	26
10	Höchsmann et al. [16]	25

Network Characteristics

The global keyword co-occurrence network comprised 148 nodes and 650 links, with a network density of 0.0598. The largest connected component contained 91% of items, which confirms a well-integrated and cohesive field. The high silhouette score indicates that thematic clusters are internally consistent and conceptually meaningful. The relatively high proportion of interconnected nodes suggests that PNH research has evolved into a highly collaborative and interdisciplinary field that integrates hematology, immunology, molecular biology, and translational therapeutics. Citation analysis identified several landmark publications that substantially shaped the contemporary understanding and therapeutic management of PNH (Table 3).

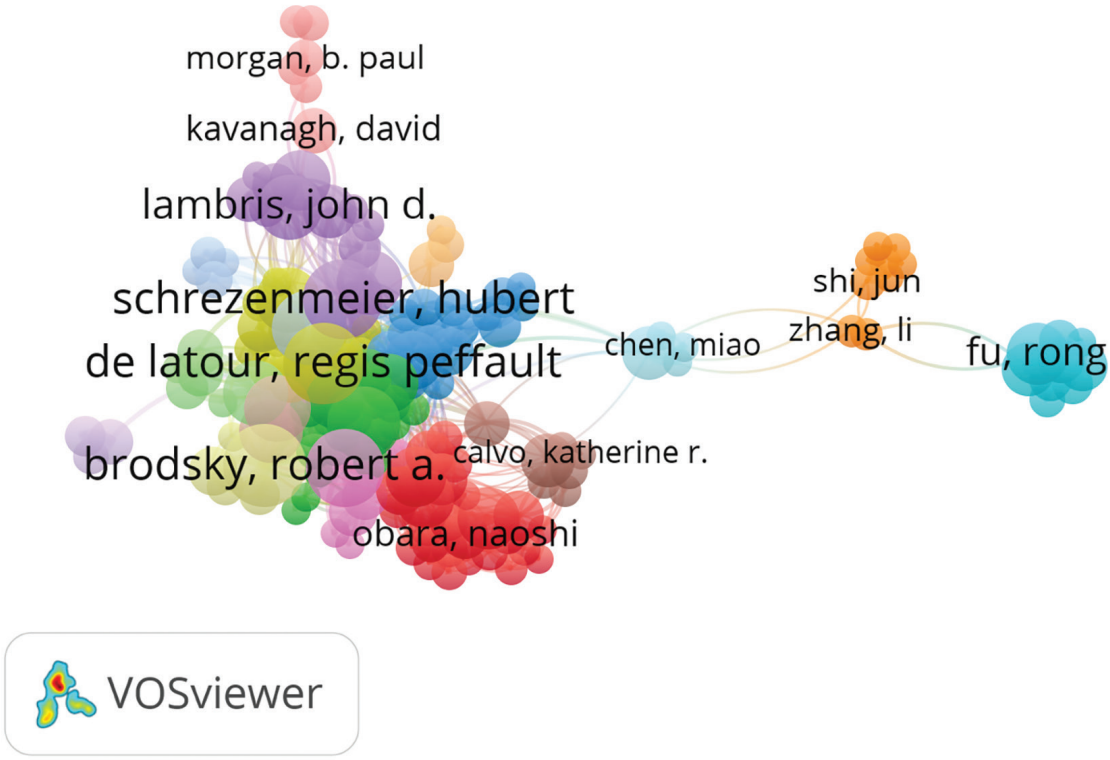

Figure 5. Author collaboration network in PNH research (2015-2025) generated by VOSviewer. Node size represents publication volume, and link thickness indicates collaboration strength. Prominent hubs include de Latour et al. [6], Kulasekararaj et al. [7], Brodsky [8], Lambris et al. [9], and Obara et al. [10], forming distinct but interconnected research clusters

Table 3. Most influential PNH-related publications identified in the bibliometric analysis (2015-2025)

Rank	First Author	Year	Journal	Citations
1	Hill et al. [17]	2017	Nature Reviews Disease Primers	367
2	Lee et al. [12]	2019	Blood	340
3	Hillmen et al. [18]	2021	New England Journal of Medicine	329
4	Kulasekararaj et al. [14]	2019	Blood	311
5	Kelly et al. [19]	2015	New England Journal of Medicine	221

PNH: Paroxysmal nocturnal hemoglobinuria

Table 4. Leading institutions contributing to PNH research

Rank	Institution	Publications
1	Assistance Publique Hôpitaux Paris	75
2	Université Paris Cité	75
3	Hospital Universitaire Saint Louis APHP	57
4	Johns Hopkins University	54
5	King's College Hospital NHS foundation trust	53

PNH: Paroxysmal nocturnal hemoglobinuria, APHP: Assistance Publique-Hôpitaux de Paris

Discussion

This bibliometric and scientometric analysis provides a comprehensive overview of the intellectual structure and temporal evolution of PNH research between 2015 and 2025. By integrating keyword co-occurrence, temporal clustering, and collaboration networks, this study highlights how research priorities have progressively shifted from foundational disease mechanisms toward therapeutic innovation and long-term clinical management.

Our results indicate that complement-mediated hemolysis and complement-inhibition therapies are a central research theme in contemporary PNH literature. This finding is consistent with the pivotal role of complement dysregulation in PNH pathophysiology and the transformative clinical impact of complement inhibitors. Since the introduction of eculizumab, a monoclonal antibody targeting complement component C5, multiple studies have demonstrated significant reductions in intravascular hemolysis, thromboembolic events, and transfusion requirements, along with improved survival outcomes [6,7]. These therapeutic advances are clearly reflected in the prominence of keywords related to complement inhibition in our co-occurrence network.

The temporal analysis further revealed a transition in research focus. Early studies primarily emphasized diagnostic confirmation, hemolytic mechanisms, and disease characterization, whereas later publications increasingly concentrated on long-acting and next-generation complement inhibitors, including ravulizumab and pegcetacoplan. Ravulizumab, engineered to allow extended dosing intervals while maintaining sustained complement inhibition, has been shown to provide efficacy comparable to eculizumab with improved treatment convenience [8,9]. The emergence of ravulizumab-related keywords in recent years underscores the growing emphasis on optimizing long-term disease control and patient quality of life.

Importantly, recent literature has expanded beyond terminal complement blockade to explore proximal complement inhibition, particularly targeting C3 and factor B. Pegcetacoplan, a C3 inhibitor, has demonstrated superior hemoglobin stabilization and reduced transfusion dependence in selected patient populations, especially those with persistent extravascular hemolysis despite C5 inhibition [2,10]. The increasing visibility of terms related to extravascular hemolysis and proximal complement inhibition in our analysis reflects this evolving therapeutic paradigm.

Another prominent theme identified in this study is the close association between PNH and bone marrow failure syndromes, particularly aplastic anemia. This relationship has long been recognized, with immune-mediated bone marrow injury playing a central role in the clonal expansion of PNH cells [11,12]. The persistence of aplastic anemia-related keywords across multiple time slices suggests that this overlap remains a critical area of investigation, particularly regarding treatment sequencing and hematopoietic stem cell transplantation.

Our findings demonstrate that, geographically, PNH research is dominated by a small number of highly productive countries: the United States, followed by Japan and several European countries. These regions have historically hosted major clinical trials and centers of excellence in complement biology and rare hematologic diseases [7,13]. The increasing contribution from Asian countries, such as China and South Korea, in recent years likely reflects broader access to complement inhibitors and growing participation in multinational clinical studies.

The author collaboration network further highlights the importance of multidisciplinary and multicenter cooperation in advancing PNH research. Influential researchers identified in our analysis have contributed substantially to clinical trials, translational studies, and consensus guidelines, reinforcing the collaborative nature of progress in this rare disease field [13,14].

Despite these advances, unmet clinical needs remain. Breakthrough hemolysis, residual anemia, and long-term treatment burden continue to affect a subset of patients receiving complement inhibitors [6,15]. The recent focus on novel therapeutic targets and real-world outcome studies, as reflected in our temporal clusters, suggests that future research will increasingly address treatment personalization, long-term safety, and cost-effectiveness. The growing visibility of real-world outcome studies in recent years suggests an increasing emphasis on long-term treatment safety, healthcare utilization, and patient-reported outcomes beyond controlled clinical trial settings.

Research Gaps and Future Directions

Despite substantial advances in complement inhibition therapies, several important research gaps remain in the PNH literature. Our analysis demonstrated that current research is heavily concentrated in North America, Europe, and selected Asian countries, whereas data from low- and middle-income regions remain limited. Although therapeutic studies dominate recent publications, relatively few studies focus on long-term real-world outcomes, pediatric PNH populations, quality-of-life measures, and cost-effectiveness analyses.

The emergence of keywords related to proximal complement inhibition and personalized treatment strategies suggests that future research will increasingly focus on individualized disease management. Further integration of genomic profiling, biomarker-driven approaches, and real-world registry data may improve long-term therapeutic optimization. Expanded international collaboration will also be essential to address disparities in access to novel complement inhibitors and to improve global understanding of rare hematologic disorders such as PNH.

Overall, this bibliometric analysis mirrors the clinical evolution of PNH management, underscores the central role of complement inhibition, and highlights emerging therapeutic strategies. By mapping the development of research themes and collaborations, this study provides valuable insights into past achievements and future directions in PNH research.

Study Limitations

This study has several limitations. First, the analysis was limited to the Web of Science Core Collection database and English-language publications, which may have excluded relevant studies indexed in other databases or published in other languages. Second, bibliometric analyses are inherently influenced by database coverage, citation practices, and temporal citation bias. Third, because data for 2025 cover only a partial year, recent publication trends should be interpreted with caution. Despite these limitations, the present study provides a comprehensive overview of the global research landscape and thematic evolution of PNH research.

Conclusion

This bibliometric and scientometric analysis provides a comprehensive overview of global research trends in PNH from 2015 to 2025. Complement-mediated hemolysis and complement inhibition therapies remain the central focus, reflecting their pivotal role in PNH pathophysiology and management. Temporal trends highlight a shift from foundational mechanistic studies toward next-generation complement inhibitors, real-world outcomes, and personalized treatment strategies. The study also emphasizes the importance of international and multidisciplinary collaborations in advancing PNH research. These insights not only map past achievements but also guide future directions, particularly in optimizing long-term patient outcomes, addressing unmet clinical needs, and evaluating cost-effectiveness of emerging therapies. The findings of this study may help guide future collaborative research efforts and support strategic prioritization in the rapidly evolving field of complement-mediated hematologic disorders.

Ethics

Ethics Committee Approval: This study did not involve human participants or animal subjects and was based exclusively on publicly available bibliographic data; therefore, ethical approval was not required.

Informed Consent: The requirement for informed consent has been removed.

Footnotes

Financial Disclosure: The authors declared that this study received no financial support.

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