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# Patent Foramen Ovale and Migraine: A Bibliometric and Knowledge Mapping Analysis Based on the Web of Science

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Abstract: Objective: To evaluate research trends, collaborative networks, and thematic evolution in studies on patent foramen ovale (PFO) and migraine from 2005 to 2025 using bibliometric methods. Methods: The study searched the Web of Science Core Collection for 2005–2025 publications on PFO and migraine, including only English-language articles and reviews. After screening, 737 records were identified. Bibliometric analysis using VOSviewer mapped annual publication trends, co-authorship and institutional networks, co-citation patterns, and keyword co-occurrence. Results: Publication output increased overall, with an initial rise followed by a plateau (2011–2017) and renewed growth after 2018. The United States, Europe, and China were the leading contributors, forming a global network. Top institutions and prolific authors led the co-authorship network, and publications spanned cardiology and neurology journals, reflecting the field's interdisciplinary nature. Keyword co-occurrence revealed major themes (e.g., PFO closure, migraine with aura, stroke risk) spanning mechanisms to clinical management. Reference co-citation analysis highlighted foundational studies and clinical trials that established the field's knowledge base. Conclusion: Research on the PFO-migraine connection expanded over two decades. After early growth followed by a mid-period lull (amid inconclusive trials), the field resurged after 2018 with new advances and evidence of benefit in select patients. Ongoing interdisciplinary collaboration and increasing output suggest this field will continue to grow, providing new insights for potential clinical application.

Keywords: Patent foramen ovale; Migraine; Bibliometric analysis; Collaboration; Co-citation; Keyword co-occurrence

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#### 1. Introduction

Migraine is a common neurological disorder, while patent foramen ovale (PFO) is a congenital cardiac opening present in roughly 25% of adults. Studies have observed a higher prevalence of PFO among migraine patients-particularly those with aura-suggesting a potential pathophysiological link [1]. The hypothesized mechanism

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involves right-to-left shunting of microemboli or vasoactive agents through the PFO, which could trigger migraine attacks. Early clinical trials investigating PFO closure for migraine yielded mixed results, but interest in this potential therapy has persisted. Recent evidence, including a 2024 meta-analysis, indicates that PFO closure can modestly reduce migraine frequency in selected patients [2]. Nevertheless, PFO closure is not currently recommended as a routine migraine treatment, and research continues to focus on identifying which patients may truly benefit from this intervention. Consequently, the past two decades have seen a growing volume of literature exploring the PFO-migraine relationship. To elucidate the trajectory of this interdisciplinary field, the study conducted a bibliometric analysis of PFO-migraine research (2005–2025) to characterize publication trends, collaboration networks, and emerging themes.

#### 2. Methods

#### 2.1. Data source and search strategy

The authors searched the Web of Science Core Collection (2005–2025) for publications addressing the relationship between patent foramen ovale (PFO) and migraine. The search strategy used a topic-based query:TS = (("patent foramen ovale" OR PFO OR "foramen ovale, patent") AND (migraine OR "migraine with aura" OR "migraine without aura")). Only English articles and reviews were included. After screening, 737 records (570 articles, 167 reviews) were analyzed.

#### 2.2. Data analysis tools

Bibliometric indicators were evaluated using VOSviewer 1.6.20. Annual publication trends, co-authorship and institutional collaborations, co-citation patterns, and keyword co-occurrence networks were generated. Prolific authors, institutions, journals, and high-frequency keywords were identified to assess research productivity, collaboration, and thematic evolution in this field.

# 3. Results

# 3.1. Annual publication trends

As shown in **Figure 1**, the annual number of publications in this field exhibited a clear upward trend from 2005 to 2025. During the initial exploration stage (2005–2010), the annual output increased from 24 articles in 2005 to 52 articles in 2010, indicating growing academic attention to this emerging interdisciplinary topic. Between 2011 and 2017, publication output fluctuated, with slight declines in some years, likely reflecting controversies over clinical trial results and methodological adjustments, suggesting a period of validation and refinement. Since 2018, publication numbers have steadily rebounded, peaking in 2021 (40 articles) and 2024 (62 articles), marking renewed research interest in the relationship between PFO and migraine. Cumulative publications followed an exponential growth pattern (R<sup>2</sup>=0.8715), highlighting the sustained expansion of research productivity. This resurgence is closely associated with advances in diagnostic techniques, improvements in closure devices, and the application of interdisciplinary approaches, attracting more researchers to the field. Given this trajectory, the field is expected to remain active with broad potential for further development.

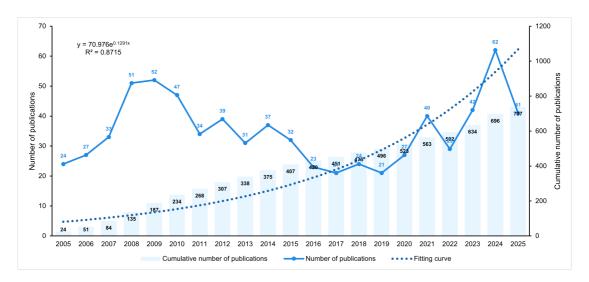


Figure 1. Annual publication trends (2005–2025) in PFO-migraine research

#### 3.2. National and institutional collaboration networks

The global country collaboration map (**Figure 2**) revealed the structural characteristics and academic influence of international research networks. The United States, Italy, Germany, the United Kingdom, and China emerged as primary research centers, with high output and frequent collaborations. The United States, leveraging strong research capacity and interdisciplinary resources, established a wide-reaching network, collaborating closely with the UK, the Netherlands, and Canada, and extending partnerships to Middle Eastern countries such as Saudi Arabia, the UAE, and Egypt. European nations showed intensive intra-regional collaborations, with Italy, Germany, France, and Spain forming concentrated clusters, reflecting strong academic traditions. In Asia, China and Japan ranked among the leading contributors and gradually integrated into the global core through collaborations with Western countries. Particularly, China demonstrated a rapidly increasing influence supported by large research teams and expanding international ties. Overall, the field displayed cross-regional concentration, with core research power clustered in Europe, North America, and East Asia, while emerging regions such as the Middle East and South America mainly entered the network via collaboration with core countries.

At the institutional level (**Figure 3**), U.S. institutions dominated the collaboration network, with the University of California, Los Angeles (UCLA), Mayo Clinic, and Harvard University positioned at the core. UCLA produced the largest output (33 articles, 2007 citations), highlighting both productivity and impact (**Table 1**). University Hospital Bern and Mayo Clinic (16 articles each) and Harvard University (15 articles) also ranked among the leading institutions. In China, Sichuan University (15 articles) and other universities such as Capital Medical University and Jilin University have gained increasing visibility, though their citation averages remain comparatively low (e.g., Sichuan University, 5.6 citations per paper). In Europe, the Frankfurt Cardiovascular Center and the University of Bologna, together with clinical hospitals, formed active clusters with strong contributions to multicenter trials and clinical studies. Notably, cross-continental collaborations, particularly U.S.—China and U.S.—Europe partnerships, were frequent, reflecting the shift toward a multi-institutional, international research model.

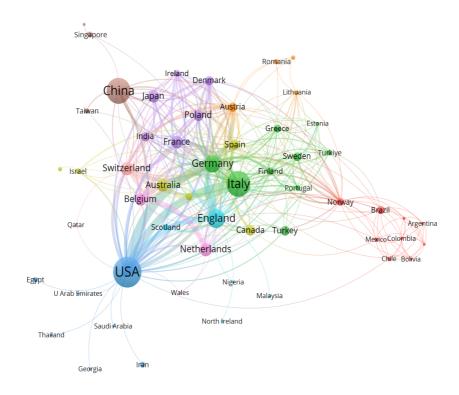


Figure 2. International collaboration network of countries in PFO-migraine research

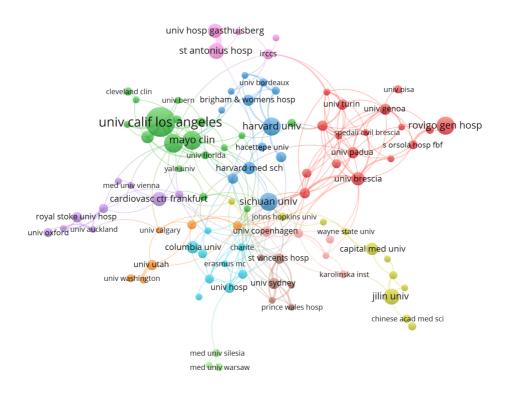


Figure 3. Institutional collaboration network in PFO-migraine research

**Table 1.** Top 10 institutions by publication output and citation impact

Institution name	<b>Total number of articles</b>	<b>Total citations</b>	Average citations
Univ Calif Los Angeles	33	2007	60.8182
Univ Hosp Bern	16	661	41.3125
Mayo Clin	16	549	34.3125
Sichuan Univ	15	84	5.6
Rovigo Gen Hosp	15	219	14.6
Harvard Univ	15	1327	88.4667
St Antonius Hosp	12	313	26.0833
Jilin Univ	12	170	14.1667
Univ Hosp Gasthuisberg	10	286	28.6
Cardiovasc Ctr Frankfurt	10	228	22.8

# 3.3. Prolific authors and collaboration patterns

Author productivity analysis (**Table 2**) showed that research output was concentrated among several leading scholars. Jonathan M. Tobis ranked first (18 articles, 992 citations), followed by Bernhard Meier (16 articles, 486 citations). Both played pioneering roles in studies on PFO closure and its relationship with migraine. Other highly productive authors included Horst Sievert (11 articles, 260 citations), Rubine Gevorgyan (9 articles, 444 citations), and Tobias Kurth (9 articles, 661 citations). Notably, Kurth's relatively few publications achieved high influence, with an average of 73 citations per article. The co-authorship network (**Figure 4**) further highlighted the central roles of Tobis, Meier, and Kurth, who formed a core group driving research directions. Team-based clusters were evident: Meier's network reflected broad international collaborations; Alessandro Padovani's group represented Italian contributions in clinical and pathophysiological studies; and Kurth's team emphasized combining mechanistic exploration with epidemiology. Authors such as Peter Wilmshurst and Horst Sievert contributed notably to methodological and technical innovations. Collectively, the author network exhibited a "core team + peripheral collaborators" structure, supporting knowledge diffusion and suggesting future growth through more cross-regional and interdisciplinary cooperation.

**Table 2.** Top 10 authors by publication output and citation impact

Author name	Total number of articles	Total citations	Average citations
Tobis, Jonathan M.	18	992	55.1111
Meier, Bernhard	16	486	30.375
Sievert, Horst	11	260	23.6364
Gevorgyan, Rubine	9	444	49.3333
Kurth, Tobias	9	661	73.4444
Wunderlich, Nina	9	228	25.3333
Sacco, Simona	8	188	23.5
Windecker, Stephan	7	293	41.8571
Tobis, Jonathan	7	249	35.5714
Post, Martijn C.	6	110	18.3333

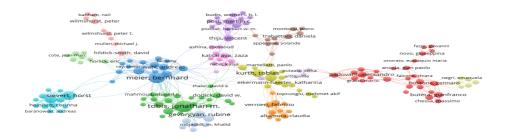


Figure 4. Author collaboration network in PFO-migraine research

#### 3.4. Journal distribution

Analysis of publication venues (**Table 3**) showed that research outputs were distributed across both cardiology and neurology journals. Catheterization and Cardiovascular Interventions published the most articles (33), while neurology-focused journals such as Headache (29) and Cephalalgia (25) also ranked highly, reflecting the cross-disciplinary nature of the field. Impact varied: although Catheterization and Cardiovascular Interventions led in volume, their average citations were modest (22.9 per article). In contrast, Neurology published fewer papers (16) but achieved higher impact (848 total citations, 53 per article). The stroke-focused journal Stroke had 13 related articles, collectively cited 1796 times (138 per article), representing the highest influence. Other key journals included Journal of Headache and Pain, European Journal of Neurology, and International Journal of Cardiology. Overall, publication patterns emphasized the interdisciplinary position of PFO-migraine research, bridging interventional cardiology and neurology.

**Table 3.** Top 10 journals by publication output and citation metrics

Journal Name	Total Number of Articles	Total Citations	Average Citations
Catheterization And Cardiovascular Interventions	33	757	22.9394
Headache	29	681	23.4828
Cephalalgia	25	932	37.28
Frontiers In Neurology	22	158	7.1818
Neurological Sciences	21	217	10.3333
Neurology	16	848	53
Journal Of Headache And Pain	15	467	31.1333
Stroke	13	1796	138.1538
European Journal Of Neurology	10	158	15.8
International Journal Of Cardiology	10	171	17.1

#### 3.5. Keyword co-occurrence and thematic evolution

Figure 5 and Table 4 highlighted central themes. "Patent foramen ovale" and "migraine" were the most frequent terms, with "percutaneous closure" and "ischemic stroke" also ranking highly, reflecting dual focuses on mechanisms and interventions. The network revealed four major thematic clusters: (1) diagnostic and detection techniques, represented by "transcranial Doppler" and "right-to-left shunt"; (2) interventional and medical treatments, centered on "percutaneous closure" and "medical therapy"; (3) cerebrovascular complications, including "ischemic stroke", "risk factors", and "cerebral infarction"; and (4) pathophysiological mechanisms, focused on "migraine with aura", "cerebral blood flow", and "serotonin." These clusters were interconnected, forming a comprehensive research chain spanning mechanisms, diagnosis, interventions, and complications. Emerging terms such as "percutaneous closure", appearing more frequently after 2015, indicated the evolution of research focus in line with technological advances. Collectively, the analysis demonstrated a multidirectional and interdisciplinary structure, delineating the trajectory from mechanistic exploration to clinical application.

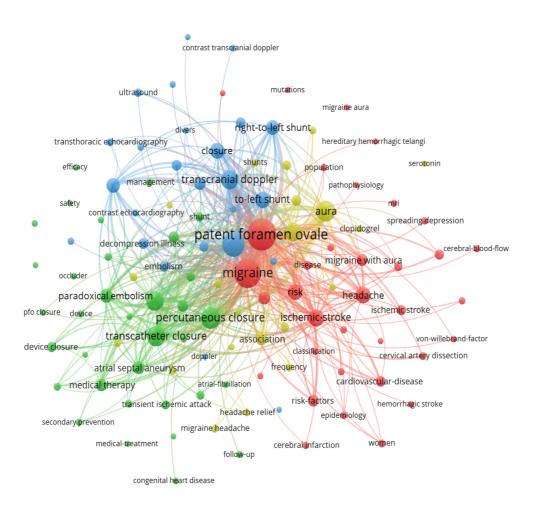


Figure 5. Keyword co-occurrence network illustrating research hotspots and thematic evolution

**Table 4.** Top 10 keywords by co-occurrence frequency

Rank	Frequency	Centrality	Time	Keyword
1	554	1.002	2015	Patent Foramen Ovale
2	441	0.8894	2015	Migraine
3	276	1.039	2014	Stroke
4	208	0.9501	2017	Percutaneous Closure
5	187	1.0867	2014	Aura
6	154	0.9079	2014	Closure
7	139	0.8552	2015	Cryptogenic Stroke
8	138	1.0242	2015	Risk
9	134	1.0937	2015	Headache
10	124	1.1924	2015	Ischemic Stroke

# 3.6. Reference co-citation analysis

The reference co-citation analysis (**Figure 6**) revealed the intellectual structure and knowledge base of PFO—migraine research. Key studies, such as Goldstein (2011), Dowson (2008), and Tobis (2017), were positioned at the core of the network, underscoring their pivotal roles in establishing theoretical frameworks and methodological foundations for subsequent investigations. These highly cited works primarily focused on the pathological links between patent foramen ovale (PFO) and migraine, diagnostic approaches, and interventional strategies. For instance, Goldstein (2011) provided critical clinical evidence and mechanistic insights, serving as a cornerstone reference for later research.

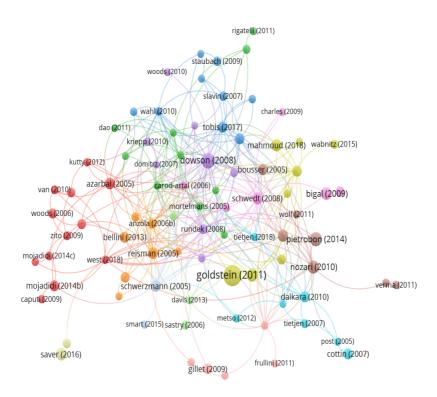


Figure 6. Co-citation network of references in PFO-migraine research

The network exhibited multiple clustered structures, each corresponding to distinct research directions. The cluster led by Dowson (2008) emphasized clinical trials and interventional studies, particularly on the efficacy of PFO closure for migraine relief. Another cluster, represented by Schwedt (2008) and Bigal (2009), focused on the epidemiology and pathophysiological mechanisms of migraine. Additional clusters highlighted the development and application of diagnostic techniques such as ultrasound and transcranial Doppler imaging. Node size indicated citation frequency, while the thickness of links reflected the strength of intellectual connections between references. The dense interconnections across clusters demonstrated the integrative nature of the field, bridging clinical practice with mechanistic and diagnostic research.

# 4. Discussion

This bibliometric analysis demonstrates that research on the patent foramen ovale (PFO)—migraine connection has expanded markedly over the past two decades, reflecting the interplay of clinical trial outcomes, technological advances, and interdisciplinary collaboration. After an initial phase of growth (2005–2010), publication activity plateaued between 2011 and 2017, largely due to inconclusive or negative findings from early randomized controlled trials such as MIST, which tempered initial enthusiasm despite anecdotal successes <sup>[3]</sup>. This period of fluctuating output reflected a "validation and refinement" stage as investigators improved study designs and clarified methodological limitations. Since 2018, however, research has resurged, with peaks in 2021 and 2024, coinciding with emerging evidence that selected patients—particularly those with migraine with aura—may benefit from PFO closure. A pivotal pooled analysis of two RCTs demonstrated significant reductions in monthly migraine days and attacks compared with medical therapy alone <sup>[4]</sup>. Such findings reinvigorated academic interest, and new trials like RELIEF are now refining patient selection criteria. The analysis of cumulative publications, showing an exponential growth pattern (R<sup>2</sup>≈0.87), indicates that the hypothesis remains a dynamic research domain, now driven by better selection strategies and interdisciplinary approaches.

The trajectory of this field underscores how evidence and research activity mutually influence one another. Early enthusiasm gave way to skepticism following equivocal trial results, yet instead of stagnating, the field adapted—adopting refined endpoints, improved imaging, and novel closure devices. Recent meta-analyses and systematic reviews now suggest that closure provides modest but clinically meaningful reductions in migraine frequency, particularly for migraine with aura <sup>[2, 5]</sup>. This evolving evidence base has prompted cautiously optimistic perspectives in the literature and even guidelines. For example, the 2022 Society for Cardiovascular Angiography and Interventions (SCAI) guidelines acknowledged migraine as a potential indication for closure in highly selected cases, while cautioning that routine closure is not yet standard practice <sup>[6]</sup>. The bibliometric results echo this narrative: after years of controversy, consensus is gradually emerging.

International collaboration has been central to progress. The United States and major European countries (Italy, Germany, UK) formed the core hubs of the collaboration network, consistent with their early involvement in PFO closure trials and robust clinical research infrastructure. These nations not only produced high output but also engaged in extensive cross-border collaborations, as exemplified by pooled patient-level meta-analyses that included investigators from multiple continents [3]. Meanwhile, China has risen rapidly in publication output, though citation impact remains lower on average, likely due to its more recent entry. Nonetheless, Chinese groups, often through collaborations with Western centers, are becoming integral contributors,

signaling a broader global commitment. The network also highlights emerging contributions from the Middle East and South America, usually through partnerships with core countries, reflecting the increasing global relevance of PFO–migraine research. The fact that migraine is a worldwide condition and PFO occurs in roughly a quarter of adults underscores the universal importance of this interdisciplinary question <sup>[6]</sup>.

At the institutional level, influential centers such as UCLA, Mayo Clinic, Harvard, and University Hospital Bern have shaped much of the evidence base, driven by senior investigators including Jonathan Tobis and Bernhard Meier. These institutions not only generated high productivity but also led pivotal trials such as PREMIUM and PRIMA [3-4]. Their prominence reflects both leadership and capacity for large-scale, multicenter studies, which are essential when outcomes hinge on enrolling appropriate subgroups such as patients with migraine aura or large right-to-left shunts. The strong U.S.–Europe links, and more recently U.S.–China partnerships, highlight the increasingly multi-institutional character of research in this field. This trend mirrors a broader pattern in medicine where complex problems require multidisciplinary expertise and multicenter collaboration to generate adequately powered results.

The analysis also shows that research output is concentrated among a relatively small group of prolific authors, such as Tobis, Meier, and Tobias Kurth, who have driven progress across both interventional and epidemiological dimensions. These leaders have acted as bridges between cardiology and neurology, ensuring that both clinical procedure data and neurological outcomes were rigorously evaluated. Co-authorship clusters centered on European, U.S., or Italian teams reflect national strengths, but the interconnectedness of these clusters underscores the importance of knowledge diffusion across borders. Emerging researchers often collaborate with these core leaders, accelerating interdisciplinary learning and hypothesis testing. This network structure has helped unify what could otherwise remain fragmented fields of cardiology and neurology into a more integrated research community.

Journal distribution further underscores the interdisciplinary nature of the field. While cardiology journals such as Catheterization and Cardiovascular Interventions lead in volume, neurology journals like Headache and Cephalalgia also rank highly, ensuring findings reach both specialties. Some of the most influential studies appeared in high-impact outlets such as Neurology and Stroke, where a few pivotal articles accrued disproportionate citations—e.g., Schwerzmann et al. (2005, Neurology) and West et al. (2018, Stroke) [7-8]. This reflects the cross-disciplinary importance of major breakthroughs, which attract a broad readership. However, the wide dispersion across journals risks siloing knowledge, underscoring the value of systematic reviews and meta-analyses in integrating findings for both audiences, as demonstrated in the 2024 review by Silalahi, which pooled RCTs and observational studies and found that PFO closure reduces monthly migraine days and attacks with a favorable safety profile [2]. Recent pooled analyses highlight consistent though nuanced benefits of closure, particularly in aura patients, helping clinicians reconcile disparate findings and offering guidance on patient selection.

Thematic analysis of keywords revealed an evolution from pathophysiological exploration to clinical application. Early focus on cerebral blood flow, serotonin, and right-to-left shunts laid the mechanistic groundwork, while recent terms emphasize closure devices, therapy, and migraine outcomes. These clusters form an interconnected research chain, from mechanism to diagnosis to intervention. This aligns with recent hypotheses suggesting platelet activation as a unifying mechanism, potentially linking microembolic phenomena and serotonin release to migraine pathogenesis, as supported by the LEARNER study, which demonstrated increased prothrombotic platelet activation and microvesicles in migraine with aura patients—changes that reverted after

PFO closure <sup>[9]</sup>. Migraine with aura has emerged as a key theme, not only associated with higher PFO prevalence but also with a greater likelihood of benefit from closure <sup>[3, 6]</sup>. The overlap between migraine and stroke further demonstrates how PFO-related research transcends disease categories, often integrating outcomes relevant to both conditions.

The co-citation analysis highlights the intellectual foundation of the field, centered on landmark studies such as Dowson's MIST trial, observational analyses by Wilmshurst, and subsequent early interventional trials. Although many of these early studies were inconclusive, they remain heavily cited as reference points for subsequent work. Despite progress, critical uncertainties remain regarding the precise mechanism by which PFO contributes to migraine and the identification of responders to closure. Current research increasingly embraces a multifactorial model, suggesting that no single explanation suffices.

#### 5. Conclusion

In summary, PFO-migraine research has evolved from initial enthusiasm, through controversy, to a renewed evidence-based trajectory. The findings illustrate how global collaboration, interdisciplinary integration, and iterative refinement of methodology have advanced the field. While closure is not yet routine therapy for migraine, accumulating evidence suggests that in carefully selected patients—particularly those with aura—meaningful benefit is achievable. Ongoing randomized trials, mechanistic studies, and advances in biomarkers and imaging are likely to further refine patient selection and therapeutic strategies. With sustained collaboration across cardiology, neurology, and imaging, what began as a clinical observation may yet translate into tangible, individualized treatments for patients living with migraine linked to a "hole in the heart."

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#### Disclosure statement

The authors declare no conflict of interest.

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