Bibliometric Study

Evolution and Emerging Trends in Liposomal Bupivacaine Research: A Comprehensive Bibliometric Study (1993-2024)

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Background: Liposomal bupivacaine has become a significant advancement in postsurgical pain management.

Objectives: Our study aimed to describe liposomal bupivacaine's current research landscape and its evolution from 1993 through 2024.

Study Design: Bibliometric analysis.

Methods: Publications related to liposomal bupivacaine were sourced from the Web of Science Core Collection. The analysis employed VOSviewer, CiteSpace, and R4.3.3 to examine publication trends, collaborations, and emerging research themes.

Results: A total of 580 publications were identified, showing an annual growth rate of 13.59%. The United States led the field with 457 publications and 8,880 citations, followed by the People's Republic of China and the State of Israel. The Mayo Clinic, Harvard University, and the University of Texas System were the top institutions. The Journal of Arthroplasty published the most articles—33—and garnered the highest citations—957. Key authors such as Daniel S. Kohane and Michael A. Mont were prominent. A cluster analysis highlighted 5 major research hotspots: pain management and recovery; regional anesthesia techniques; surgical innovation and drug delivery; pharmacological safety; and clinical/regulatory issues. Notably, citation bursts around terms like "placebo controlled trial," "total knee arthroplasty," and "enhanced recovery after surgery" indicate shifting research priorities toward optimizing perioperative protocols.

Limitations: Our analysis was limited to publications indexed in the Web of Science Core Collection, potentially excluding relevant studies from other databases or non-English publications; this limitation may have introduced language and database biases.

Conclusion: Our bibliometric study highlights 5 major hotspots in liposomal bupivacaine research and reveals a temporal shift from basic pharmaceutical development to clinical integration within enhanced recovery protocols. These findings underscore the need for future investigations focusing on comparative effectiveness, cost–benefit evaluation, and protocol standardization across surgical specialties.

Key words: Liposomal bupivacaine, postoperative analgesia, bibliometric analysis, pain management, surgical outcomes

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Postoperative pain management remains a major clinical challenge, affecting approximately 80% of patients undergoing surgery and contributing to prolonged hospitalization, increased costs, and decreased patient satisfaction (1,2). Effective analgesia is crucial for recovery, early mobilization, and improved surgical outcomes. While local anesthetics are integral to pain control, their utility is often constrained by a short duration of action, necessitating repeated dosing or continuous infusion (3). Liposomal bupivacaine—a sustained-release formulation in which bupivacaine is encapsulated within multivesicular liposomes—

has emerged as a promising solution, providing analgesia for up to 72 hours (4). This sustained-release characteristic may offer prolonged pain relief, reduced opioid use, and enhanced patient comfort (5).

Since its US Food and Drug Administration approval in 2011 for single-injection peripheral nerve blockade, liposomal bupivacaine has been widely investigated across various surgical procedures, including orthopedic surgery, hemorrhoidectomy, and thoracic surgery (5,6). Recent years have seen growing research and clinical adoption, with numerous randomized controlled trials assessing its safety and efficacy in diverse surgical settings (7-9). Its inclusion in Enhanced Recovery After Surgery protocols further highlights its potential to improve postoperative recovery. Nonetheless, evidence remains conflicting. For example, a meta-analysis of 16 randomized controlled trials by Chen et al found no significant benefit of liposomal bupivacaine over conventional periarticular injection after total knee arthroplasty in terms of pain scores, nausea and vomiting, or hospital stay (10). Other studies report comparable efficacy to plain local anesthetics in abdominal fascial plane blocks (11) and no superior analgesic effect within the surgical plane (12). These inconsistencies underscore the need for critical reappraisal of its clinical value amid rapidly expanding literature. Although a substantial body of evidence—spanning basic science, clinical trials, systematic reviews, and real-world data—has accumulated (6), the research landscape lacks comprehensive mapping of trends, hotspots, and evolutionary trajectories.

Bibliometrics provides a quantitative approach to analyze large volumes of scientific literature (13). While bibliometric studies have been applied to pain and anesthesia research (14-16), none have focused specifically on liposomal bupivacaine. We conducted a bibliometric analysis of relevant publications about liposomal bupivacaine published from January 1, 1993 through October 16, 2024. We used advanced tools to visualize the global research landscape; identify leading contributors and institutions; trace thematic shifts; and highlight emerging research directions.

Methods

Search Strategy

We conducted a literature search on the Web of Science Core Collection (WoSCC) database on October 16, 2024. The specific search formula was TS = ("Liposomal bupivacaine"), which comprehensively captured relevant publications by searching titles, abstracts, author keywords, and Keywords Plus fields. The inclusion criteria were: 1) English language; 2) published from January 1, 1993 through October 16, 2024; 3) and articles related to liposomal bupivacaine meeting the search formula. Additionally, records—such as reviews, editorial materials, letters, and meeting abstracts—were excluded. Data extraction was performed systematically using a standardized protocol. Literature information was exported from WoSCC using the "Full record and cited references" option in "plain text" format to ensure comprehensive capture of all bibliographic fields. The dataset—including titles, authors, keywords, abstracts, institutions, countries, languages, and cited references—was retrieved using the "export" feature with the "record content" option configured to "full record and cited references."

Bibliometric Analysis

VOSviewer 1.6.20 (www.vosviewer.com) (17), CiteSpace 6.3.R1 (https://citespace.podia.com) (18), and R 4.3.3 (The R Foundation) (19) were used to perform the bibliometric analysis and visualization. R-bibliometrix (www.bibliometrix.org) was used for the country collaboration analysis. VOSviewer was used to visualize the institutional cooperation map, author cooperation map, author co-citation network, and keyword co-occurrence network.

In the network visualizations, node size represents the frequency or volume of the corresponding element (publications, citations, or co-occurrences), with larger nodes indicating higher values. Node colors typically represent different clusters or time periods, with similar colors indicating elements belonging to the same thematic group or temporal range. Connection lines represent relationships between elements, with line thickness indicating the strength of association or collaboration intensity. CiteSpace was used for temporal analysis and citation burst detection, with parameters set to time slicing from January 1, 1993 through October 16, 2024 with one-year intervals, node types configured for keywords, and thresholds set to the top 5 items per time slice. Pruning methods included pathfinder and pruning merged networks to optimize network clarity. R-bibliometrix was used for comprehensive statistical analysis, including calculation of bibliometric indicators, trend analysis, and generation of descriptive visualizations. We used the h-index to quantify the academic influence of individuals and journals, respectively. The h-index is an important tool

for evaluating the academic contribution of researchers and is useful for predicting their future scientific achievements (20,21). In our study, the h-index of each author was obtained from the WoSCC.

Results

Quantitative Analysis of Publication

A total of 580 publications about liposomal bupivacaine published from January 1, 1993 through October 16, 2024 were identified in the WoSCC database. Of the 1,020 publications initially identified, 440 were excluded and 580 were included in the analyses (Fig.1). Based on the data analysis, the field shows a total of 3,150 authors from 1,723 institutions across 350 countries/regions contributed to these 580 manuscripts. These works were published in 223 journals, citing 11,338 references. The annual growth rate was 13.59%, with an average of 18.14 citations per document (Fig. 2A).

Annual publication trends demonstrate a distinctive growth trajectory characterized by 3 distinct phases of research development (Fig. 2B). The initial phase from 1993 through 2010 shows minimal research activity, with sporadic publications averaging one or 2 articles per year and one year—2000—producing no publications. The transitional phase from 2013 through 2015 marks the beginning of sustained research interest, with annual publications increasing from 2 to 16 articles. The exponential growth phase commencing in 2016 demonstrates dramatic research expansion, with publications surging from 35 in 2016 to a peak of 76 in 2021.

Analysis of the Countries

Publications came from 48 countries, with the United States dominating the field (457 articles, 78.8%), followed by the People's Republic of China (50 articles, 8.6%) and the State of Israel (8 articles, 1.4%) (Fig. 3A). Regarding citations, the United States led with 8,880 citations (average 19.4 per paper), followed by China (291 citations, 5.8 per paper) and Israel (193 citations, 24.1 per paper). Countries like the Kingdom of Belgium, the Kingdom of Denmark, and Canada showed high citation effects despite fewer publications, with average citations of 54.0, 24.0, and 31.6 per paper respectively (Table S1). Among the 30 countries involved in international collaborations with a minimum of one article, the United States had the highest number of collaborations with other countries (link strength [LS] = 57), followed by Belgium (LS =12) and Israel (LS =10) (Fig. 3B).

Analysis of Institutions

Our institutional analysis revealed that the Mayo Clinic (92 publications), Harvard University (73 publications), and the University of Texas System (69 publications) were the most productive institutions (Fig. 3C). The Cleveland Clinic Foundation (58 publications) and University of California System (39 publications) rounded out the top 5. Harvard Medical School and the University of Texas MD Anderson Cancer Center each contributed 38 publications. Among the 216 institutions involved in international collaborations with a minimum of 2 articles, Pacira BioSciences Inc. (LS = 34) had the highest number of collaborations with other

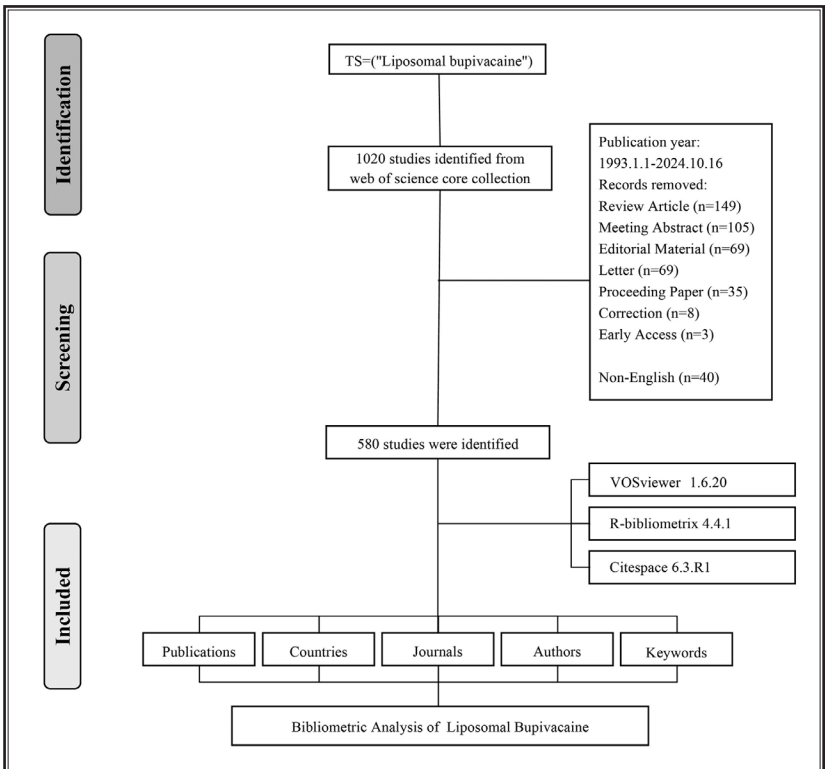


Fig. 1. *Flowchart of the literature screening process.*

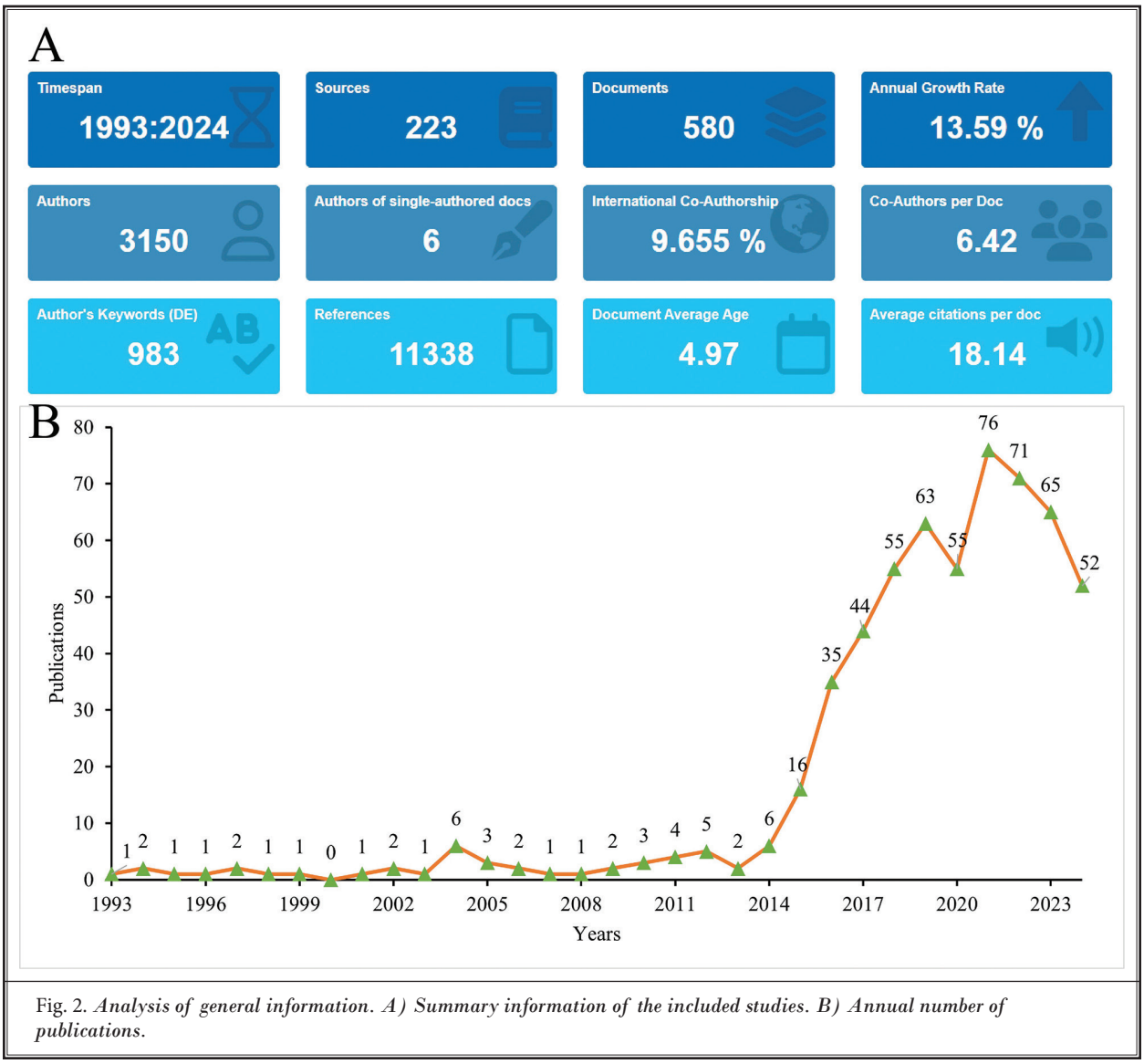


Fig. 2. *Analysis of general information. A) Summary information of the included studies. B) Annual number of publications.*

countries, followed by Duke University (LS = 29) and Harvard Medical School (LS = 27) (Fig. 3D).

Analysis of Journals

The Journal of Arthroplasty was the leading journal with the highest h-index—20—and the most citations—957—, followed by the Journal of Shoulder and Elbow Surgery (h-index 12, 366 citations). Anesthesia and Analgesia, despite fewer publications, had substantial citations—913—and maintained a high impact in the field. The journal with the highest impact factor (IF) was Anesthesiology (IF = 9.1) and the British Journal of Anaesthesia (IF = 9.1) (Table S2). The co-occurrence networks of journals contain 103 with at least 2 occurrences. The 3 key journals with the highest total link strength in co-occurrence networks were the Journal of Arthroplasty with 350, Anesthesiology with 216, and the Journal of Shoulder and Elbow Surgery with 150 (Fig. 4A). The coupling networks of journals contain 103 with at least 2 couples. The 3 key journals with the highest total link strength in co-occurrence networks were the Journal of Arthroplasty with 8,447, the Journal of Knee Surgery with 4,412, and the Journal of Shoulder and Elbow Surgery with 4,333 (Fig. 4B).

Analysis of Authors

Our analysis of author contributions showed that Daniel S. Kohane led with an h-index of 8 and the high-

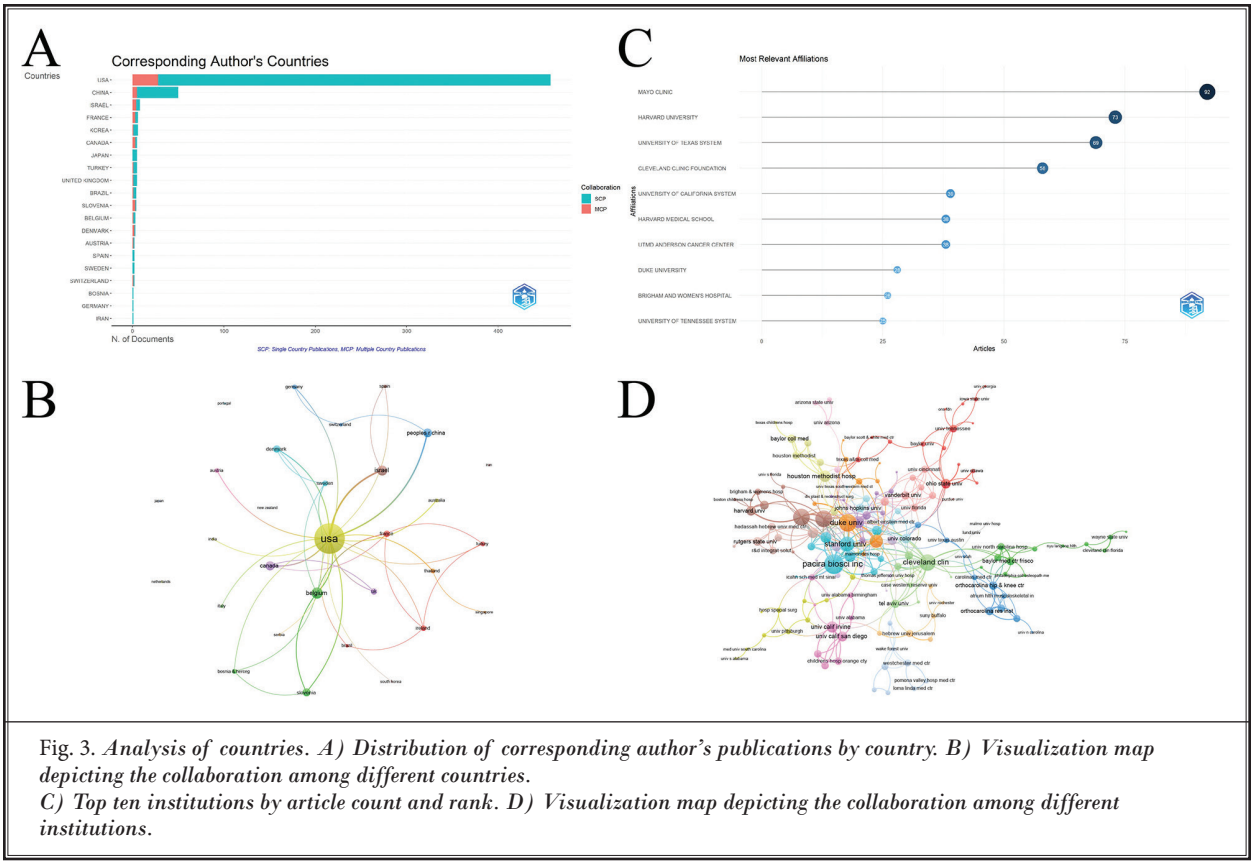


Fig. 3. *Analysis of countries. A) Distribution of corresponding author's publications by country. B) Visualization map depicting the collaboration among different countries. C) Top ten institutions by article count and rank. D) Visualization map depicting the collaboration among different institutions.*

est citation count (515 citations), followed by Michael A. Mont (h-index 7, 295 citations) and John W. Barrington (h-index 6, 258 citations). Notable authors Alparslan Turan and Michael Y. Wang made significant contributions with h-indices of 6 and 5 respectively (Table S3). Among the 402 authors involved in international collaborations with a minimum of 2 articles, Alparslan Turan had the highest number of collaborations with other authors with 39 collaborations, followed by Boris Sepesi with 33 collaborations, and Daniel I. Sessler with 30 collaborations (Fig. 5).

Most Cited Articles

The most cited article (243 citations) was published in Diseases of the Colon & Rectum in 2011 (22). This article focused on multicenter, randomized, double-blind, placebo-controlled trials for hemorrhoidectomy pain treatment (22). The second most cited paper (224 citations) appeared in The Knee in 2012 (23). It was a dose-ranging study of wound infiltration for post total knee arthroplasty analgesia (23). The third most cited work (200 citations) was published in Regional Anesthesia and Pain Medicine in 2018 (24). This article was a practice advisory about local anesthetic systemic toxicity (24). Other highly cited works include Golf, et al's (25) 2011 study (184 citations) and Wang, et al's (26) 2017 paper (131 citations) focusing on neurosurgical applications (Table S4).

Key Words Analysis

A total of 90 high-frequency key words were identified and categorized into 5 thematic clusters, each reflecting a critical aspect of liposomal bupivacaine research (Fig. 6A). The largest cluster (Cluster One, red, 26 items) centered on comprehensive pain management and enhanced recovery, highlighting the core clinical applications in postoperative care. Key terms included "analgesia", "arthroplasty", "enhanced recovery", "epidural analgesia", "pain management", "postoperative analgesia", and "opioid use". The second cluster (Cluster 2, green, 24 items) focused on advanced regional anesthesia techniques, particularly nerve blocks and multimodal approaches. Key words in this category included "abdominis plane block", "brachial-plexus block", "interscalene block", "multimodal analgesia", "peripheral-nerve block", and "total joint arthroplasty".

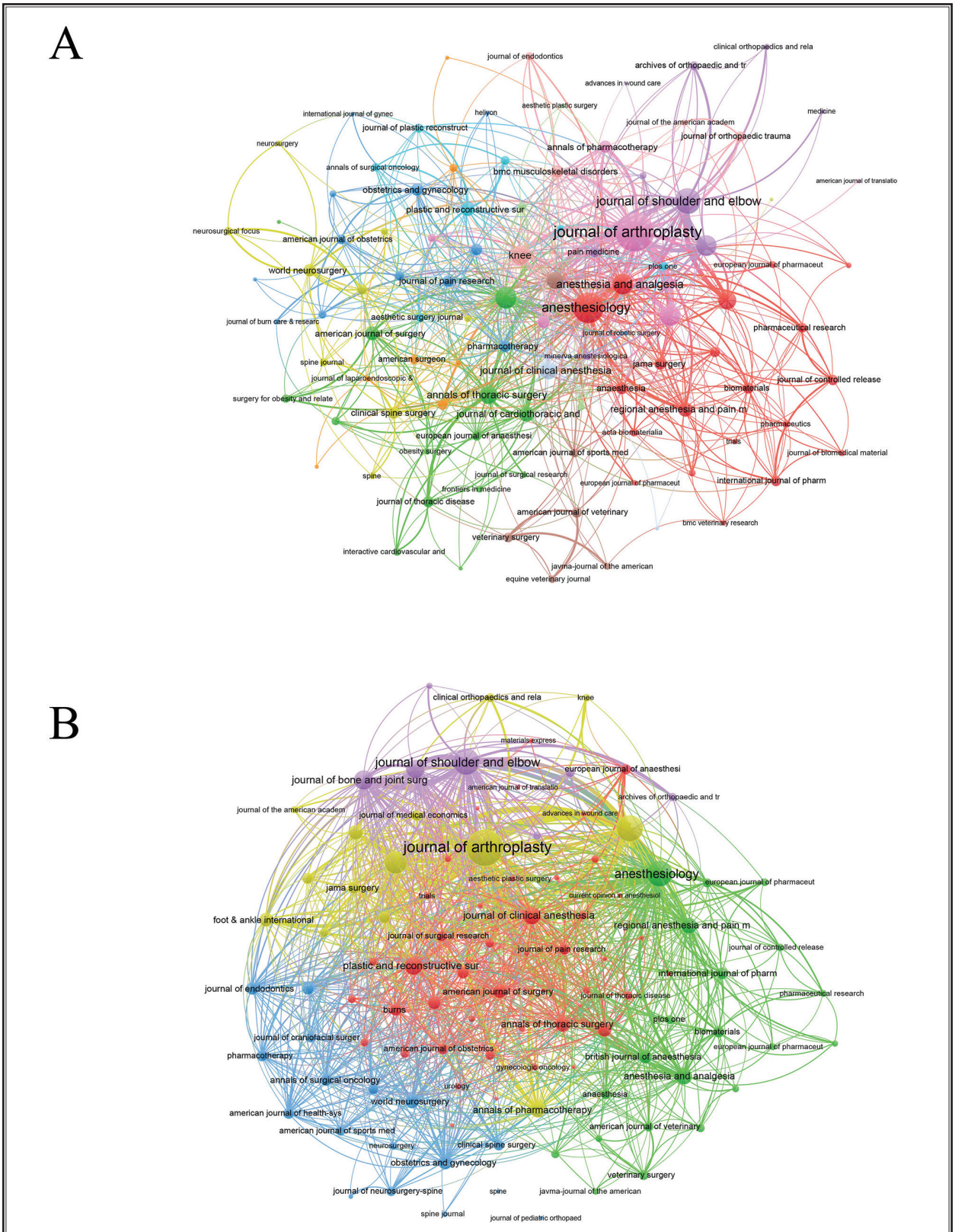


Fig. 4. *Analysis of journals. A) Co-occurrence network of journals. B) Coupling network of journals.*

The third cluster (Cluster 3, blue, 18 items) emphasized surgical technique innovation and drug delivery systems, featuring terms such as "adductor canal block", "depo-foam bupivacaine", "periarticular injection", "wound infiltration", and "placebo-controlled trial". The fourth cluster (Cluster 4, yellow, 15 items) pertained to pharmacological optimization and safety considerations, with key terms including "dexamethasone", "drug-delivery", "ropivacaine", "local-anesthetics", and "microspheres". The smallest cluster (Cluster 5, purple, 7 items) addressed clinical safety and regulatory aspects, featuring terms such as "regional anesthesia", "morphine", "infusion", and "safety".

Our analysis of the top 20 key words with the strongest citation bursts from 1993 through 2024 found evolving research priorities in liposomal bupivacaine development (Fig. 6B). The key word with the highest burst strength was "placebo controlled trial" (8.45, 2012–2017), followed by "periarticular injection" (7.50, 2018–2019). Early bursts primarily focused on basic drug development and formulation science, as reflected by key words such as "local anesthetics" (5.43, 1996–2004), "microspheres" (4.55, 2002–2011), and "release" (3.04, 2004–2018). The middle period emphasized clinical validation and surgical applications, demonstrated by key words like "total knee arthroplasty" (5.58, 2015–2017), "trial" (5.04, 2015–2016), and "local infiltration analgesia" (4.53, 2016–2018). In more recent years, the research focus has shifted toward advanced pain management strategies and enhanced recovery protocols,

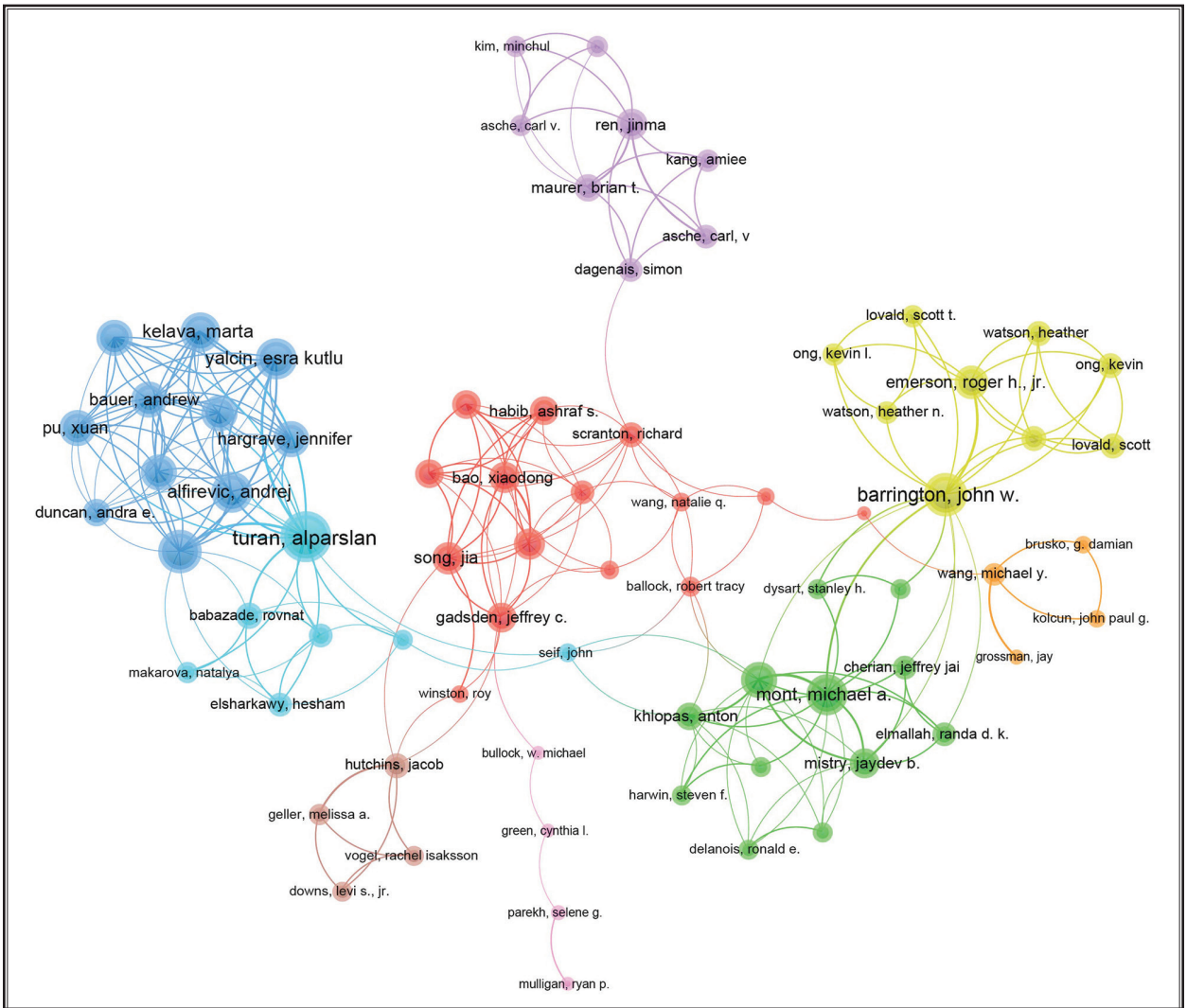
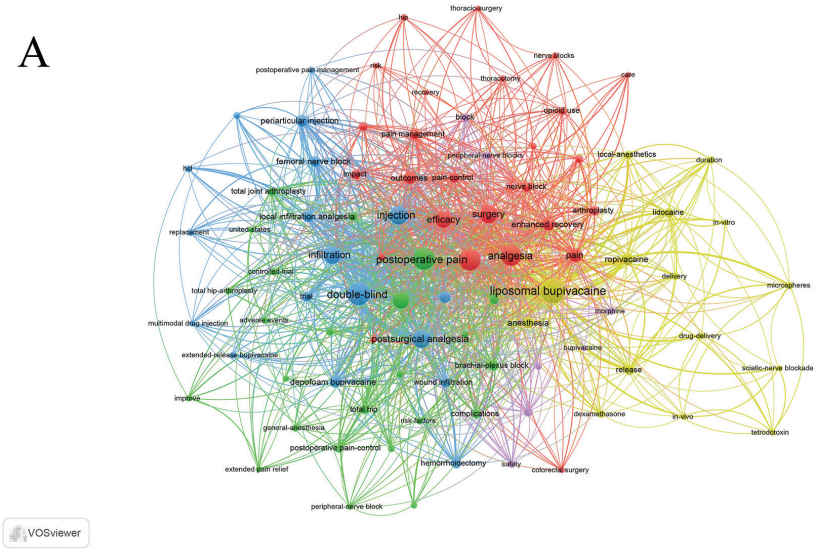


Fig. 5. *Visualization map depicting the collaboration among different authors.*

A



2024/10/23 11:55 View Citation Burst History

B

Top 20 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	1993 - 2024
local anesthetics	1996	5.43	**1996**	2004	
microspheres	2002	4.55	**2002**	2011	
release	2004	3.04	**2004**	2018	
placebo controlled trial	2012	8.45	**2012**	2017	
augmentation mammaplasty	2012	3.47	**2012**	2016	
postsurgical pain	2012	3.04	**2012**	2018	
double blind	2014	3.83	**2014**	2016	
wound infiltration	2014	3.55	**2014**	2017	
block	2014	3	**2014**	2015	
total knee arthroplasty	2015	5.58	**2015**	2017	
trial	2015	5.04	**2015**	2016	
local infiltration analgesia	2016	4.53	**2016**	2018	
femoral nerve block	2016	4.04	**2016**	2018	
total joint arthroplasty	2016	3	**2016**	2020	
randomized controlled trial	2017	3.98	**2017**	2018	
periarticular injection	2017	7.5	**2018**	2019	
morphine	2019	3.64	**2019**	2021	
epidural analgesia	2017	3.07	**2020**	2022	
enhanced recovery after surgery	2019	3.7	**2021**	2024	
abdominis plane block	2019	3.7	**2021**	2024	

Fig. 6. *A) Visual analysis of key word co-occurrence network analysis. B) Top 20 Key words with the strongest citation bursts.*

as demonstrated by emerging keywords such as "enhanced recovery after surgery" (3.70, 2021–2024), "abdominis plane block" (3.70, 2021–2024), and "epidural analgesia" (3.07, 2020–2022), all of which continue to show strong bursts through 2024.

Discussion

General Information

Our bibliometric analysis reveals significant growth in liposomal bupivacaine research from 1993 through 2024, characterized by 3 central, interconnected themes: its strategic integration within Enhanced Recovery After Surgery protocols, its role in refining multimodal analgesia combined with regional techniques, and the development of sophisticated, procedure-specific protocols aided by outcome prediction modeling. The field is advancing toward personalized pain management, presenting key opportunities for standardizing protocols across specialties, conducting comprehensive economic analyses, and creating predictive frameworks for tailored treatments.

Beginning in 2016, liposomal bupivacaine research entered a phase of rapid expansion, with its publication growth rate significantly surpassing that of conventional anesthetics or general postoperative analgesia, underscoring its rising scientific and clinical priority (16,27). The United States dominates the field, contributing 457 publications and receiving 8,880 citations, a leadership position likely attributable to the technology's early development and first regulatory approval there (28). The People's Republic of China's emergence as the second most productive nation, despite a later entry, indicates a growing interest in advanced pain management within its expanding health care system (10). The concentration of leading institutions (e.g., Mayo Clinic, Harvard University) in the United States reflects their established research programs and clinical expertise in this area (29).

Our analysis found a pronounced geographic disparity, with minimal contributions from low- and middle-income countries. This imbalance stems from interconnected barriers, primarily the substantial cost of liposomal bupivacaine—often 20-30 times higher than conventional bupivacaine—making it prohibitive for resource-constrained settings (30). Furthermore, low- and middle-income countries often lack the advanced research infrastructure, specialized equipment, and regulatory frameworks required to conduct clinical trials with such sophisticated formulations (31).

The journal landscape mirrors clinical applications: The Journal of Arthroplasty leads in publication volume, highlighting the drug's significance in orthopedic surgery, while high-impact anesthesia journals attest to its broad relevance (32). Key opinion leaders include Daniel S. Kohane (h-index 8, 515 citations) and Michael A. Mont (h-index 7, 295 citations). Landmark studies, such as the efficacy trials by Gorfine, et al (22) and Bramlett, et al (23), along with Neal, et al's (24) safety advisory, have collectively shaped the foundation of current clinical practice.

Emerging Research Hotspots

Based on the key word clustering analysis, we identified 5 distinct research hotspots and frontier trends in liposomal bupivacaine research; each hotspot represents a specific area of clinical application and scientific investigation.

Cluster 1 (Red, 26 items): Comprehensive Pain Management and Enhanced Recovery

This cluster highlights the core clinical applications of liposomal bupivacaine, underscoring its fundamental role in modern perioperative care. Evidence confirms that it significantly reduces postoperative pain scores and opioid consumption across various procedures, with pronounced benefits in orthopedic surgeries like total knee and hip arthroplasty (33). Its integration into Enhanced Recovery After Surgery protocols has been shown to shorten hospital stays and improve patient satisfaction (34). In pediatric populations, it provides prolonged analgesia for up to 72 hours with a favorable safety profile (35). Furthermore, its use in colorectal surgery, as part of a multimodal approach, accelerates the return of bowel function and reduces postoperative ileus (36). These opioid-sparing effects, confirmed by recent meta-analyses, contribute significantly to efforts aimed at mitigating the opioid crisis in patients who had surgery (34).

Cluster 2 (Green, 24 items): Advanced Regional Anesthesia Techniques

This cluster centers on advanced regional anesthesia techniques that utilize liposomal bupivacaine as a foundational agent. Evidence confirms its superior performance. When used in transversus abdominis plane blocks, it provides analgesia for up to 96 hours postsurgery, which is significantly longer than conventional anesthetics (37). Similarly, its application in brachial plexus and other peripheral nerve blocks delivers prolonged

pain control for upper extremity procedures without increasing neurological risk (38,39). Systematic reviews and meta-analyses consistently affirm that these techniques yield sustained reductions in pain scores and opioid consumption, while also maintaining a safety profile comparable to traditional local anesthetics (40). Consequently, its integration into multimodal analgesic regimens, where it acts synergistically with nonopioid adjuncts, has become a standard of care.

Cluster 3 (Blue, 18 items): Surgical Technique Innovation and Drug Delivery

This cluster details the pharmaceutical innovation of liposomal bupivacaine's DepoFoam® technology (Pacira Pharmaceuticals), which enables sustained drug release for 72–96 hours, and its effect on refining surgical techniques such as periarticular injection and wound infiltration (41-43). Its clinical superiority, validated by double-blind trials across specialties like hemorrhoidectomy, has secured its role in practice (8,44). However, meta-analyses have highlighted considerable heterogeneity among trials, which is attributed to variable methodologies and patient factors (10,11). A key methodological challenge is the drug's distinct physical properties, which complicate effective blinding despite countermeasures like opaque syringes (45,46). Therefore, refining experimental protocols—particularly through improved blinding and stricter control of confounders—is a critical imperative for future trials.

Cluster 4 (Yellow, 15 items): Pharmacological Optimization and Safety

This cluster describes the pharmacological and safety profile underpinning bupivacaine's development and optimization. The liposomal formulation's unique pharmacokinetics—characterized by predictable sustained release and lower peak plasma concentrations than conventional anesthetics—have been clearly explained, contributing to its favorable efficacy and safety profile (47). In vivo studies have further explained tissue distribution and cellular uptake, which helps to determine optimal dosing and injection strategies (48). Clinically, liposomal bupivacaine has a longer duration of action than ropivacaine while maintaining a comparable safety margin in peripheral nerve blocks (39). Its combination with adjuvants, such as dexamethasone, has synergistic effects, further extending analgesia without additional risk (49). These attributes position it as a leading option among long-acting local anesthetics, offering an optimal balance of efficacy, duration, and safety. Exploratory research into novel combinations, including with tetrodotoxin, suggests the potential for ultra-long-duration anesthesia, though such applications remain investigational (50).

Cluster 5 (Purple, 7 items): Clinical Safety and Regulatory Considerations

Although the smallest cluster, this one addresses the critical transition of liposomal bupivacaine from clinical validation to routine practice, focusing on safety monitoring and regulatory integration. Postmarketing surveillance has confirmed its favorable safety profile in real-world use, aligning with pre-approval trial data (51). Clinically, it has been shown to provide analgesia equivalent to continuous nerve blocks while avoiding catheter-related complications (52), and its significant opioid-sparing effect is well-documented (53). All of this evidence have directly informed clinical practice, leading to its inclusion in updated regional anesthesia guidelines as a standard option for prolonged analgesia (39) and prompting the development of specific safety protocols for dosing and patient selection (54).

Evolution of Study Trends

Our citation bursts analysis describes liposomal bupivacaine research's evolution, transitioning from basic pharmaceutical development to clinical application optimization and, more recently, a focus on advanced pain management strategies and enhanced recovery after surgery protocols.

From 1996 through 2004, research primarily concentrated on fundamental drug development and basic local anesthetic science. The keyword "local anesthetics" (from 1996 through 2004) highlighted the foundational work on understanding sustained-release formulations and their potential clinical applications (55). During this period, studies focused on developing novel drug delivery systems and establishing the theoretical framework for extended-duration local anesthesia (56).

The period from 2005 through 2011 marked the transition to pharmaceutical innovation and formulation development. Citation bursts for "microspheres" (from 2002 through 2011) and "release" (from 2004 through 2018) indicate intensive research into liposomal encapsulation technology and controlled drug release mechanisms (57). This era was characterized by the development of DepoFoam technology and early preclinical studies demonstrating the feasibility of prolonged local anesthetic action (58).

From 2012 to 2017, research focus shifted toward clinical validation and efficacy demonstration. Keywords such as "placebo controlled trial" (from 2012 through 2017), "postsurgical pain" (from 2012 through 2018), and "total knee arthroplasty" (from 2015 through 2017) reflect pivotal clinical trials establishing therapeutic superiority over conventional local anesthetics (23). This period established the evidence base for regulatory approval and clinical adoption across multiple surgical specialties.

Since 2018, the emphasis has evolved toward optimization of clinical protocols and integration with comprehensive perioperative care. The prominence of "periarticular injection" (from 2018 through 2019), "enhanced recovery after surgery" (from 2021 through 2024), and "abdominis plane block" (from 2021 through 2024) reflects efforts to refine application techniques and incorporate liposomal bupivacaine into multimodal analgesia protocols (59). It holds particular promise for bridging the analgesic gap between single-injection peripheral nerve blocks and prolonged neuraxial opioids for managing post cesarean delivery pain (60). Thus, current research emphasizes opioid-sparing strategies and patient-centered outcomes in the context of enhanced recovery pathways.

The high cost of liposomal bupivacaine, a result of its complex manufacturing process, necessitates thorough pharmacoeconomic evaluations to inform future health care policies. A real-world study by Tran, et al (61) reported its cost-effectiveness for colorectal surgery pain, primarily due to reduced hospitalization and postoperative ileus management costs. However, its clinical application faces several limitations: a defined maximum dose often requires supplemental analgesia, complicating protocols; mild local reactions, though uncommon, warrant monitoring (62); and concomitant use with other local anesthetics raises concerns about cumulative toxicity. These findings underscore the need for large-scale, multicenter randomized controlled trials to rigorously evaluate its efficacy and long-term safety across diverse surgical environments, which is essential for establishing evidence-based guidelines on optimal dosing, timing, and patient selection.

Limitations

Our study has several limitations. Firstly, our analysis was limited to publications indexed in the WoSCC, potentially excluding relevant studies from other databases or non-English publications, which may have introduced language and database bias. Secondly, the focus on citation-based metrics (e.g., total citations and h-index) may favor older publications and potentially underestimate the effect of recent innovations that have clinical significance. Thirdly, the key word analysis relies on author-defined terms, which may not fully capture emerging terminologies or interdisciplinary applications. Finally, our study does not assess the clinical translation or real-world implementation of research findings, limiting insights into practical application.

Conclusions

The evolution of liposomal bupivacaine research reflects its transition from an experimental formulation to a clinically relevant tool for multimodal analgesia. Future research should address unresolved questions regarding cost-effectiveness, patient-specific tailoring, and integration into global perioperative care pathways, particularly in resource-limited settings.

Authors' Contributions

Jiangang Hu carried out the studies, participated in collecting data, and drafted the manuscript. Xinhong Wan performed the statistical analysis and participated in its design. Xinhong Wan and Jiangang Hu participated in acquisition, analysis, or interpretation of data and drafted the manuscript. Both authors read and approved the final manuscript.

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Table S1 *Publication and Citation Profiles of Leading Countries*

Country	Articles	Freq	SCP	MCP	MCP_Ratio	TP	TP_rank	TC	TC_rank	Average Citations
USA	457	0.788	429	28	0.061	1446	1	8880	1	19.4
CHINA	50	0.086	45	5	0.1	140	2	291	2	5.8
ISRAEL	8	0.014	4	4	0.5	27	3	193	3	24.1
FRANCE	6	0.01	3	3	0.5	20	6	123	6	20.5
KOREA	6	0.01	5	1	0.167	16	12	30	13	5
CANADA	5	0.009	2	3	0.6	20	5	158	5	31.6
JAPAN	5	0.009	5	0	0	17	9	69	10	13.8
TURKEY	5	0.009	4	1	0.2	20	7	25	14	5
UNITED KINGDOM	5	0.009	4	1	0.2	25	4	121	7	24.2
BRAZIL	4	0.007	3	1	0.25	16	10	86	8	21.5
SLOVENIA	4	0.007	1	3	0.75	16	11	62	11	15.5
BELGIUM	3	0.005	2	1	0.333	17	8	162	4	54
DENMARK	3	0.005	1	2	0.667	14	13	72	9	24
AUSTRIA	2	0.003	1	1	0.5	7	17	1	21	0.5
SPAIN	2	0.003	2	0	0	9	14	22	15	11
SWEDEN	2	0.003	2	0	0	8	15	48	12	24
SWITZERLAND	2	0.003	1	1	0.5	8	16	9	17	4.5
BOSNIA	1	0.002	1	0	0	NA	NA	0	23	0
GERMANY	1	0.002	1	0	0	7	18	14	16	14
IRAN	1	0.002	1	0	0	5	20	2	20	2

Note(s): Articles: Publications of Corresponding Authors only. Freq: Frequence of Total Publications. MCP_Ratio: Proportion of Multiple Country Publications. TP: Total Publications. TP_rank: Rank of Total Publications. TC: Total Citations. TC_rank: Rank of Total Citations. Average Citations: The average number of citations per publication.

Table S2 *Bibliometric Indicators of High-Impact Journals*

Journal	H_ index	G_index	M_ index	IF 2023	JCR 2023	TP	TP_ rank	TC	TC_ rank	PY_ start
JOURNAL OF ARTHROPLASTY	20	31	1.818	3.4	1	33	1	957	1	2014
JOURNAL OF SHOULDER AND ELBOW SURGERY	12	20	1.333	2.9	1	26	2	366	7	2016
ANESTHESIA AND ANALGESIA	10	11	0.313	4.6	1	11	8	913	2	1993
ANESTHESIOLOGY	10	16	0.345	9.1	1	16	3	813	3	1996
PLASTIC AND RECONSTRUCTIVE SURGERY	9	12	0.818	3.2	1	12	6	286	9	2014
JOURNAL OF KNEE SURGERY	8	15	0.889	1.6	3	15	4	66	51	2016
REGIONAL ANESTHESIA AND PAIN MEDICINE	8	12	0.421	5.1	1	12	7	646	4	2006
JOURNAL OF BONE AND JOINT SURGERY-AMERICAN VOLUME	7	11	0.875	4.4	1	11	9	386	6	2017
JOURNAL OF CLINICAL ANESTHESIA	7	13	0.226	5	1	13	5	162	14	1994
ANNALS OF THORACIC SURGERY	6	8	0.6	3.6	1	8	14	158	15	2015
JOURNAL OF CARDIOTHORACIC AND VASCULAR ANESTHESIA	6	7	1	2.3	2	10	10	73	49	2019
ANNALS OF SURGICAL ONCOLOGY	5	5	0.5	3.4	1	5	20	53	68	2015
BRITISH JOURNAL OF ANAESTHESIA	5	5	0.167	9.1	1	5	21	411	5	1995
INTERNATIONAL JOURNAL OF PHARMACEUTICS	5	7	0.185	5.3	1	7	16	58	59	1998
NEUROSURGICAL FOCUS	5	5	0.556	3.3	1	5	26	25	130	2016
ORTHOPEDIC CLINICS OF NORTH AMERICA	5	9	0.5	1.4	3	9	11	52	72	2015
ORTHOPEDICS	5	7	0.556	1.1	3	8	15	68	50	2016
AMERICAN JOURNAL OF SURGERY	4	8	0.5	2.7	1	8	12	77	41	2017
BMC ANESTHESIOLOGY	4	4	0.571	2.3	2	4	30	54	64	2018
DISEASES OF THE COLON & RECTUM	4	5	0.286	3.2	1	5	22	196	13	2011

Note(s): H_index: The h-index of the journal, which measures both the productivity and citation impact of the publications. IF: Impact Factor, indicating the average number of citations to recent articles published in the journal. JCR_Quartile: The quartile ranking of the journal in the Journal Citation Reports, indicating the journal's ranking relative to others in the same field (Q1: top 25%, Q2: 25%-50%, Q3: 50%-75%, Q4: bottom 25%). TP: Total Publications. TP_rank: Rank of Total Publications. TC: Total Citations. TC_rank: Rank of Total Citations. Average Citations: The average number of citations per publication. PY_start: Publication Year Start, indicating the year the journal started publication.

Table S3 *Publication and Citation Profiles of High-Impact Authors*

Author	h_index	g-index	m-index	PY_start	TP	TP_Frac	TP_rank	TC	TC_rank
KOHANE DANIEL S.	8	10	0.471	2008	10	1.91	1	515	1
MONT MICHAEL A.	7	7	0.778	2016	7	1.13	3	295	4
BARRINGTON JOHN W.	6	7	0.6	2015	7	1.28	3	258	6
TURAN ALPARSLAN	6	9	0.667	2016	9	1.48	2	104	12
CHUGHTAI MORAD	5	5	0.556	2016	5	0.65	10	138	9
GRANT GJ	5	5	0.161	1994	5	1.01	10	320	3
REN JINMA	5	5	0.556	2016	5	0.89	10	103	13
THROCKMORTON THOMAS W.	5	7	0.625	2017	7	1.49	3	96	14
WANG MICHAEL Y.	5	6	0.556	2016	6	1.68	6	492	2
AMIN NIRAV H.	4	4	0.571	2018	5	1.18	10	24	20
AZAR FREDERICK M.	4	6	0.5	2017	6	0.99	6	74	15
BROLIN TYLER J.	4	6	0.571	2018	6	1.29	6	58	16
CATA JUAN P.	4	4	0.4	2015	4	0.47	15	233	7
GIL DMITRY	4	4	0.667	2019	4	0.6	15	39	17
HUTCHINS JACOB	4	5	0.4	2015	5	1.05	10	123	11
LEGROS FJ	4	4	0.125	1993	4	0.55	15	202	8
MEMTSOUDIS STAVROS G.	4	6	0.571	2018	6	1.31	6	268	5
ORAL EBRU	4	4	0.667	2019	4	0.6	15	39	17
SANZONE ANTHONY G.	4	4	0.444	2016	4	2.17	15	29	19
AMUNDSON ADAM W.	3	4	0.375	2017	4	0.39	15	132	10

Note(s): H_index: The h-index of the journal, which measures both the productivity and citation impact of the publications. g_index: The g-index of the journal, which gives more weight to highly-cited articles. m_index: The m-index of the journal, which is the h-index divided by the number of years since the first published paper. TP: Total Publications. TP_rank: Rank of Total Publications. TC: Total Citations. TC_rank: Rank of Total Citations. Average Citations: The average number of citations per publication. PY_start: Publication Year Start, indicating the year the journal started publication.

Table S4 *List of TOP50 most cited articles.*

Paper	DOI	Total Citations	TC per Year	Normalized TC
GORFINE SR, 2011, DIS COLON RECTUM	10.1097/DCR.0b013e318232d4c1	243	17.36	2.16
BRAMLETT K, 2012, KNEE	10.1016/j.knee.2011.12.004	224	17.23	3.77
NEAL JM, 2018, REGION ANESTH PAIN M	10.1097/AAP.0000000000000720	200	28.57	7.86
GOLF M, 2011, ADV THER	10.1007/s12325-011-0052-y	184	13.14	1.64
WANG MY, 2017, J NEUROSURG-SPINE	10.3171/2016.9.SPINE16375	131	16.38	3.24
RICE DC, 2015, ANN THORAC SURG	10.1016/j.athoracsur.2015.02.074	128	12.80	3.16
GRANT GJ, 2004, ANESTHESIOLOGY	10.1097/00000542-200407000-00021	127	6.05	2.91
GAFFNEY CJ, 2017, ORTHOP CLIN N AM	10.1016/j.ocl.2017.05.001	122	15.25	3.02
EPSTEIN-BARASH H, 2009, P NATL ACAD SCI USA	10.1073/pnas.0900598106	120	7.50	1.55
MONT MA, 2018, J ARTHROPLASTY	10.1016/j.arth.2017.07.024	112	16.00	4.40
SURDAM JW, 2015, J ARTHROPLASTY	10.1016/j.arth.2014.09.004	108	10.80	2.67
BAGSBY DT, 2014, J ARTHROPLASTY	10.1016/j.arth.2014.03.034	107	9.73	2.12
WANG MY, 2016, NEUROSURG FOCUS	10.3171/2015.11.FOCUS15435	107	11.89	3.50
AFONSO A, 2017, PLAST RECONSTR SURG	10.1097/PRS.0000000000003235	101	12.63	2.50
MCALVIN JB, 2014, BIOMATERIALS	10.1016/j.biomaterials.2014.02.015	100	9.09	1.98
KOLCUN JPG, 2019, NEUROSURG FOCUS	10.3171/2018.12.FOCUS18701	100	16.67	5.19
EL-BOGHDADLY K, 2017, ANESTHESIOLOGY	10.1097/ALN.0000000000001668	98	12.25	2.43
HUSSAIN N, 2021, ANESTHESIOLOGY	10.1097/ALN.0000000000003651	95	23.75	11.07
BOOGAERTS JG, 1994, J CLIN ANESTH	10.1016/0952-8180(94)90079-5	89	2.87	1.21
SANTAMARIA CM, 2017, MATER TODAY	10.1016/j.mattod.2016.11.019	86	10.75	2.13
PADERA R, 2008, ANESTHESIOLOGY	10.1097/ALN.0b013e31816c8a48	85	5.00	1.00
HUTCHINS J, 2015, GYNECOL ONCOL	10.1016/j.ygyno.2015.06.008	81	8.10	2.00
KHALIL KG, 2015, ANN THORAC SURG	10.1016/j.athoracsur.2015.08.017	81	8.10	2.00
BRUSKO GD, 2019, NEUROSURG FOCUS	10.3171/2019.1.FOCUS18692	80	13.33	4.15
OKOROHA KR, 2016, J SHOULDER ELB SURG	10.1016/j.jse.2016.05.007	76	8.44	2.49
WANG MY, 2018, NEUROSURGERY	10.1093/neuros/nyx400	74	10.57	2.91
ELMALLAH RK, 2018, J KNEE SURG	10.1055/s-0037-1604152	73	10.43	2.87
GRASU RM, 2018, J NEUROSURG-SPINE	10.3171/2018.4.SPINE171317	72	10.29	2.83
ILFELD BM, 2013, ANESTH ANALG	10.1213/ANE.0b013e31829cc6ae	71	5.92	1.82
LAVAND'HOMME PM, 2022, EUR J ANAESTH	10.1097/EJA.0000000000001691	71	23.67	12.57
NAMDARI S, 2017, J BONE JOINT SURG AM	10.2106/JBJS.16.00296	70	8.75	1.73
AMUNDSON AW, 2017, ANESTHESIOLOGY	10.1097/ALN.0000000000001586	67	8.38	1.66
SEYMOUR RB, 2017, J BONE JOINT SURG AM	10.2106/JBJS.17.00066	67	8.38	1.66
FOLEY PL, 2019, COMPARATIVE MED	10.30802/AALAS-CM-19-000048	65	10.83	3.38
GRANT GJ, 2001, PHARM RES-DORDR	10.1023/A:1011059131348	61	2.54	1.00
LEE CY, 2019, ANN THORAC SURG	10.1016/j.athoracsur.2018.06.081	61	10.17	3.17
BOOGAERTS J, 1993, ANESTH ANALG	NA	60	1.88	1.00
SABESAN VJ, 2017, J SHOULDER ELB SURG	10.1016/j.jse.2017.06.044	60	7.50	1.48
SHIKANOV A, 2007, J CONTROL RELEASE	10.1016/j.jconrel.2006.10.014	60	3.33	1.00
HUTCHINS JL, 2016, ANAESTHESIA	10.1111/anae.13502	58	6.44	1.90
DAVIDSON EM, 2010, ANESTH ANALG	10.1213/ANE.0b013e3181d26d2a	58	3.87	1.71
GRANT GJ, 1994, REGION ANESTH	NA	58	1.87	0.79
ABILDGAARD JT, 2017, J SHOULDER ELB SURG	10.1016/j.jse.2017.03.012	58	7.25	1.44

Table S4 cont. *List of TOP50 most cited articles*.

Paper	DOI	Total Citations	TC per Year	Normalized TC
JOGERST K, 2020, ANN SURG ONCOL	10.1245/s10434-020-08386-w	58	11.60	4.72
ALIJANIPOUR P, 2017, J ARTHROPLASTY	10.1016/j.arth.2016.07.023	57	7.13	1.41
COLLIS PN, 2016, J ARTHROPLASTY	10.1016/j.arth.2015.09.025	56	6.22	1.83
KIM AJ, 2017, J LAPAROENDOSC ADV S	10.1089/lap.2017.0337	56	7.00	1.39
STOKES AL, 2017, DIS COLON RECTUM	10.1097/DCR.0000000000000747	53	6.63	1.31
JAIN RK, 2016, J ARTHROPLASTY	10.1016/j.arth.2016.03.036	52	5.78	1.70
JABLONKA EM, 2017, PLAST RECONSTR SURG	10.1097/PRS.0000000000003508	52	6.50	1.29