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Original Article

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Perioperative anaesthetic management in robotic-assisted surgery: a bibliometric and visual analysis of two decades of research

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ABSTRACT

Aims: Robotic-assisted surgery imposes a distinctive combination of physiological conditions that define a specific anaesthetic problem: prolonged carbon dioxide pneumoperitoneum, fixed steep head-down positioning, and restricted access to the patient after docking. Bibliometric analyses of robotic surgery have been organised by surgical specialty, and none has mapped its anaesthetic and perioperative dimension. This study describes the structure, growth and thematic evolution of that literature.

Methods: The Web of Science Core Collection was searched for articles and reviews published in English between 2000 and 2025 combining robotic surgery terms with anaesthetic and perioperative terms. Retracted and duplicate records were removed and both authors independently reviewed all flagged records. Analyses were performed in R with the bibliometrix package and VOSviewer, after harmonising country names, affiliations and author keywords with purpose-built thesauri.

Results: The final corpus comprised 1,528 documents from 422 journals and 8,626 authors, attracting 20,985 citations (h-index 58). Output grew at 14.6% annually between 2010 and 2025, with 55.8% of the literature published in the last five years. The United States led output (567 documents), followed by the Republic of Korea (178). Yonsei University was the most productive institution (50 documents). International collaboration was limited (11.78%). The proportion of this literature appearing in anaesthesiology journals fell from 48.5% in 2001-2008 to 21.9% in 2021-2025. Five thematic clusters emerged; telesurgery and Artificial Intelligence were present only as low-frequency emerging topics.

Conclusion: This literature is expanding rapidly but is increasingly published outside anaesthesiology journals, with limited international collaboration.

Keywords: Anesthesiology, patient positioning, head-down tilt, pneumoperitoneum, publishing

INTRODUCTION

Robotic-assisted surgery imposes a set of physiological conditions that are unusual in their combination rather than in any single element. Carbon dioxide (CO_2) pneumoperitoneum is maintained for hours while the patient is held in a steep head-down tilt fixed by the docked manipulator arms, so that positioning cannot be adjusted once the operation is under way and physical access to the patient is substantially restricted.[1] The resulting increases in intra-abdominal and intrathoracic pressure reduce pulmonary compliance and functional residual capacity, while cephalad venous congestion raises intraocular and intracranial pressure and alters cerebral perfusion.[2-4] These changes are not incidental to the surgical approach. They define the anaesthetic problem. Managing them has generated a distinct body of work on ventilation strategy, haemodynamic and fluid management, neuromuscular blockade, positioning-related injury and analgesic technique, alongside the enhanced recovery after surgery (ERAS) pathways and same-day discharge protocols that the minimally invasive approach has made feasible.[5-7]

Robotic platforms have meanwhile diffused rapidly across urology, gynaecology, general surgery and thoracic surgery, and the volume of associated publication has grown accordingly. This growth has attracted repeated bibliometric attention, but that attention has been organised almost entirely along surgical lines. Published analyses have mapped robotic surgery in obstetrics and gynaecology,[8] in spinal[9] and orthopaedic surgery,[10] in acute care and trauma settings,[11] and from a health economics perspective.[12] Each characterises productivity, collaboration and thematic structure within a surgical specialty. Bibliometric work in anaesthesiology has developed in parallel but along topic lines, addressing Artificial Intelligence in anaesthetic practice,[13] perioperative multimodal analgesia[14] and perioperative complications.[15] To our knowledge, no bibliometric analysis has been conducted at the intersection of these two literatures. None has mapped the anaesthetic and perioperative dimension of robotic surgery as a field in its own right.

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This omission matters for a reason that is itself empirical. If the perioperative agenda in robotic surgery is increasingly set outside anaesthesiology, then anaesthesiologists are contributing to a literature whose structure, leading venues and emerging directions they have not systematically examined. Bibliometric analysis is suited to this question because it describes the structure of a literature (its geography, its collaborative architecture, its journals, and the way its themes succeed one another) rather than pooling effect estimates as a systematic review would.[16] It is therefore appropriate where the object of interest is the shape of a field rather than the answer to a single clinical question.

The present study maps the global literature on perioperative anaesthetic management in robotic-assisted surgery indexed in the Web of Science Core Collection between 2001 and 2025. Its objectives were to describe the growth trajectory and model its trend; to identify the leading countries, institutions, authors and journals and characterise international collaboration; to determine the distribution of this literature between anaesthesiology and surgical journals and how that distribution has changed; and to delineate the thematic structure of the field and the topics currently emerging.

METHODS

Ethics

As the study is based solely on previously published and publicly available bibliographic records, and does not involve human participants, animals, or identifiable patient data, neither institutional review board approval nor informed consent was required. The study was conducted in accordance with the relevant ethical principles and publication ethics standards.

Study Design

This is a bibliometric and visual analysis of the scientific literature on perioperative anaesthetic management in robotic-assisted surgery. Reporting follows the BIBLIO minimum requirements for bibliometric reviews of the biomedical literature,[17] and the selection process is presented as a flow diagram (**Figure 1**).

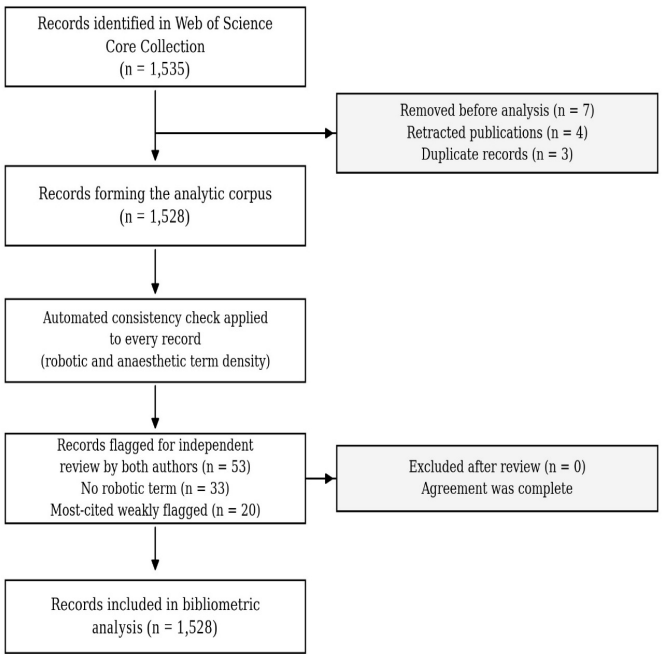

Figure 1. Flow diagram of record identification and selection

Data Source and Search Strategy

The Web of Science Core Collection (Clarivate Analytics, Philadelphia, PA, USA) was the single data source because it provides complete cited-reference data, a prerequisite for co-citation analysis. All records were retrieved on a single day, 1 August 2026, to avoid inconsistencies arising from weekly indexing updates.

A stratified search strategy was constructed. The first component captured robotic surgery through proximity operators combining the truncated term robot* with surgical procedure terms, together with named platforms (da Vinci, Hugo RAS, Versius, Senhance, Revo-i, hinotori) and the terms surgical robot*, telesurg* and telerobotic surg*. The second component captured anaesthetic and perioperative care and was deliberately stratified. Procedure-specific perioperative terms (for example pneumoperitoneum, Trendelenburg, sugammadex and erector spinae plane block) were searched in title, abstract and author keyword fields. Generic terms recurring incidentally in almost every surgical outcome report (for example an*esthe*, opioid* and postoperative pain) were restricted to title and author keyword fields. This stratification preserved sensitivity for anaesthesia-specific content while limiting retrieval of surgical papers in which anaesthesia is mentioned only in passing. A third component retrieved all robotic surgery records published in journals assigned to the Web of Science Anesthesiology category, capturing anaesthesia-focused work using none of the indexed keywords.

Results were limited to the document types Article and Review, to English, and to 2000-2025. The lower boundary corresponds to United States Food and Drug Administration approval of the da Vinci system in July 2000. The upper boundary was the last complete calendar year, avoiding an artefactual decline in the final data point.

Eligibility and Record Verification

Records were eligible if they addressed anaesthetic technique, perioperative management or the physiological consequences of the robotic operative setting in human patients. Retracted publications and duplicate records sharing a digital object identifier were removed before analysis, retaining the more highly cited copy of each duplicate pair.

Because the search was designed for specificity rather than breadth, an automated consistency check was applied to every remaining record. Records were flagged if robotic terms appeared neither in the title nor more than once across title, abstract and author keywords, or if anaesthetic terms appeared at most once. Both authors then independently reviewed all records containing no robotic mention (n=33) together with the twenty most-cited weakly flagged records. Agreement was complete and no record was excluded, so a chance-corrected agreement coefficient was not calculable.

Data Extraction and Normalisation

Records were exported as plain text including full records and cited references, and processed in R version 4.5.2 (R Foundation for Statistical Computing, Vienna, Austria)[18] with the bibliometrix package.[16] Four normalisation steps preceded analysis.

First, publication year was corrected. Web of Science filters and tabulates by Early Access date, whereas the exported

publication-year field carries the final issue year. In this corpus, 425 records carried an Early Access date and 113 of these disagreed with the issue year. The Early Access year was used when present, which reproduced the database interface counts exactly.

Second, country names were harmonised: Turkey and Turkiye were merged following the 2022 designation change, and England, Scotland, Wales and Northern Ireland were merged as the United Kingdom. Taiwan was retained as a separate entity, consistent with the database.

Third, institutional affiliations were merged, because Web of Science lists parent systems and their constituent units separately.

Fourth, author-level analyses used full author names rather than abbreviated forms, because abbreviated forms conflate distinct individuals in a corpus with substantial East Asian authorship. Author keywords were consolidated with a purpose-built thesaurus merging orthographic variants, abbreviations and synonyms.

Bibliometric Indicators and Visualisation

Annual output was modelled by exponential regression and summarised by the compound annual growth rate, defined as the ratio of the last to the first annual publication count raised to the power of the reciprocal of the number of intervening years, minus one. Two growth values are reported and they are not interchangeable. The annual growth rate given in Table 1 is the bibliometrix default, which applies this formula to the full 2001-2025 timespan and therefore takes the single document published in 2001 as its baseline; with a denominator of one document the resulting value is highly sensitive to the choice of starting year. The compound annual growth rates given in the Results were recalculated over 2010-2025 and 2015-2025, intervals in which annual output was already established, and describe recent growth more informatively. Author productivity was tested against Lotka's law,[19] its exponent estimated by ordinary least squares regression of log-transformed author counts on log-transformed document counts across all productivity levels, and journal distribution was tested against Bradford's law.[20] Country-level output is reported on two bases, which are not interchangeable. Overall country participation credits a document to every country represented among the affiliations of all its authors, so an internationally co-authored paper is counted once for each contributing country; these are the counts given in the text when total national contribution is described. Corresponding-author country assigns each document to the country of its corresponding author alone and is the basis of Table 2 and of the collaboration indices. Collaboration was described using single-country and multiple-country publication proportions, which are defined only under corresponding-author attribution. Networks were constructed in bibliometrix and visualised with the Fruchterman-Reingold layout and Louvain clustering (random seed fixed at 42 for keywords and 7 for countries); VOSviewer version 1.6.20 (Centre for Science and Technology Studies, Leiden University, Leiden, the Netherlands) was used for cross-validation.[21] Analyses were descriptive. No inferential hypothesis testing was performed.

Table 1. Main information about the corpus

Item	Value
Timespan	2001-2025
Documents	1.528
Sources (journals)	422
Original articles	1.324
Reviews	204
Annual growth rate (%)	24.52
Mean document age (years)	6.07
Total citations	20.985
Mean citations per document	13.73
Documents never cited (%)	10.3
Corpus h-Index	58
Corpus g-Index	83
Cited references	46.120
Authors	8.626
Author appearances	10.351
Single-authored documents	31
Co-authors per document	6.77
Documents per author	0.177
International co-authorship (%)	11.78
Author keywords	2.811
Keywords plus	2.306
Open access documents (%)	53.4

Author counts are based on full author names after disambiguation of abbreviated forms. The annual growth rate is the bibliometrix default compound annual growth rate, calculated across the full 2001-2025 timespan from the first and last annual counts of 1 and 193 documents. Because the 2001 baseline is a single document, this value exceeds the compound annual growth rates of 14.6% for 2010-2025 and 11.0% for 2015-2025 reported in the text

Table 2. Ten most productive countries, ranked by corresponding-author country

Country	Documents	Total citations	SCP	MCP	Mean citations	MCP ratio (%)
USA	528	8,144	467	61	15.42	11.6
Republic of Korea	171	2,507	163	8	14.66	4.7
China	128	961	123	5	7.51	3.9
Japan	123	1,125	122	1	9.15	0.8
Italy	80	1,075	65	15	13.44	18.8
India	75	552	73	2	7.36	2.7
United Kingdom	51	781	44	7	15.31	13.7
Germany	46	886	37	9	19.26	19.6
Turkiye	45	197	42	3	4.38	6.7
France	42	663	33	9	15.79	21.4

Each document is assigned to the country of its corresponding author, so these counts are lower than the overall country participation figures given in the Results, which credit a document to every country represented among its authors' affiliations. Turkey and Turkiye were merged, as were England, Scotland, Wales and Northern Ireland. SCP: Single-country publications, MCP: Multiple-country publications

RESULTS

Selection and Characteristics of the Corpus

The search retrieved 1,535 records. Four retracted publications and three duplicate records were removed, leaving 1,528 documents for analysis. Independent review of flagged records excluded none (Figure 1).

The corpus spanned 2001 to 2025 and comprised 1,324 original articles and 204 reviews published across 422 journals

by 8,626 authors (Table 1). Documents carried a mean of 6.77 co-authors and only 31 were single-authored, indicating a collaboratively produced literature. The corpus attracted 20,985 citations, a mean of 13.73 per document, with a corpus h-index of 58 and a g-index of 83. In total, 10.3% of documents had never been cited. Just over half (53.4%) were open access.

Growth Trajectory

Output was negligible for almost a decade after the first record appeared in 2001, with 33 documents published between 2001 and 2008 (Figure 2). A period of emergence between 2009 and 2016 produced 290 documents as the physiological consequences of the robotic operative setting were first characterised. Acceleration followed: annual output rose from 71 documents in 2018 to 193 in 2025, and the years 2021 to 2025 alone contributed 852 documents, or 55.8% of the corpus. The compound annual growth rate was 14.6% between 2010 and 2025 and 11.0% between 2015 and 2025. An exponential model fitted the post-2009 trajectory closely (R^2=0.951) and projects approximately 282 publications in 2026 and 391 in 2028 if current conditions persist.

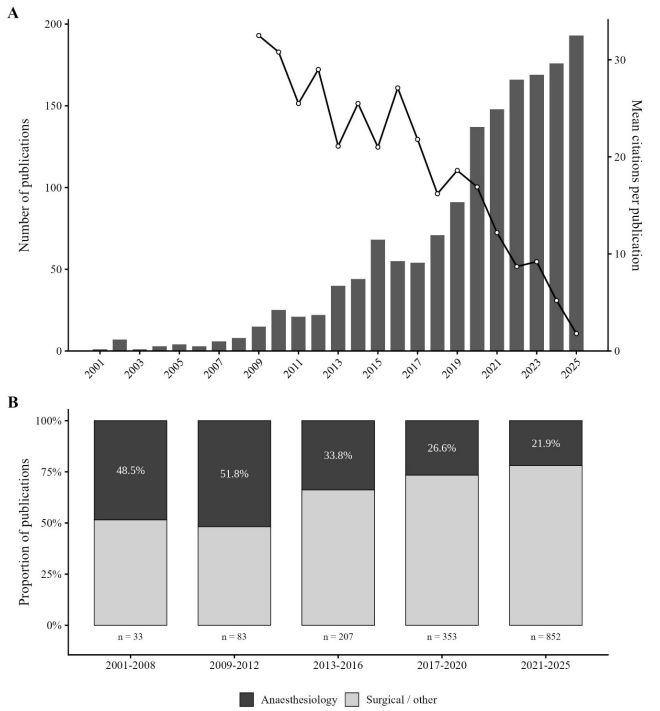

Figure 2. Growth and journal distribution of the literature, 2001-2025. (A) Annual number of publications (bars, left axis) and mean citations per publication (line, right axis). The citation line is shown only for years with at least fifteen publications; its decline in recent years reflects citation lag rather than reduced influence. (B) Proportion of publications appearing in anesthesiology versus surgical or other journals, by period. Percentages denote the anesthesiology share

Mean citations per document declined from 32.5 in 2009 to 1.8 in 2025. This gradient reflects citation lag rather than diminishing influence, since recent publications have had proportionately less time to accrue citations.

Countries, Institutions and Collaboration

Authors from 63 countries contributed. Counting every country represented among author affiliations, the United States dominated with 567 documents, more than three times the second-ranked country. The Republic of Korea followed with 178 documents, ahead of China (135), Japan (125) and Italy (111). Turkiye ranked tenth with 52 documents. The corresponding-author counts in Table 2 are lower for the same countries, at 528 documents for the United States and 171 for the Republic of Korea, because each document is there credited to a single country.

Productivity and citation impact diverged markedly (Table 2). The Netherlands produced 15 documents as corresponding-author country but attracted 59.7 citations per document. Conversely, India (7.36), China (7.51) and Japan (9.15) combined substantial output with comparatively low citation rates. Turkiye recorded the lowest mean among the twenty most productive countries, at 4.38 citations per document.

International collaboration was limited: only 11.78% of documents involved authors from more than one country. Among the ten most productive countries, multiple-country publication ratios were highest for France (21.4%), Germany (19.6%) and Italy (18.8%), and lowest for Japan (0.8%), India (2.7%), China (3.9%) and the Republic of Korea (4.7%). Ratios were higher still among several smaller contributors, including Belgium (60.0%), Brazil (36.4%), the Netherlands and Switzerland (both 33.3%) and Canada (27.8%), although each rests on between ten and eighteen documents (Table 3). Turkiye's ratio was 6.7%. The country collaboration network resolved into three communities (Figure 3): a cluster centred on the United States including the Republic of Korea, Japan, China, India, Turkiye and Brazil; a European cluster around Italy, France, Spain, Canada and Denmark; and a third grouping the United Kingdom, Germany, Austria, Switzerland, Belgium and Australia.

Yonsei University was the most productive institution with 50 documents and 23.6 citations per document, followed by the University of California System (39), the University of Texas System (37), Harvard University and the Mayo Clinic (35 each), and Ohio State University (34). Two of the ten most productive institutions were Korean (Table 4).

Author productivity was highly skewed and followed Lotka's law with a steeper exponent than the classical value of 2 (β=3.471; R^2=0.984): 7,519 authors (87.2%) contributed a single document, 778 (9.0%) two, and only 329 (3.8%) three or more (Figure 4). Chae Min Suk and Kim Young-Kug were the most prolific with twelve documents each, followed by Hong Sang Hyun, Hwang Jai-Hyun and Kim Na Young with eleven each. Productivity and influence were not equivalent: Kim Young-Kug, Hwang Jai-Hyun and Rha Koon Ho each achieved a within-corpus h-Index of 10, whereas authors with comparable document counts reached 6 or 7.

Journals and the Distribution of this Literature

Publications were dispersed across 422 journals. Bradford's law identified a core of 17 journals, with 68 in Zone 2 and 337 in Zone 3 (R^2=0.9914; Bradford multiplier k=4.48; Figure 5). Thus 4.0% of journals carried approximately one third of the literature.

The Journal of Robotic Surgery was the most productive source with 92 documents, followed by Surgical Endoscopy (49) and the Journal of Cardiothoracic and Vascular Anesthesia (41). Only three of the ten most productive journals were anaesthesiology journals (Table 5). Productivity and impact again diverged: the British Journal of Anaesthesia published 17 documents but attracted 59.9 citations per document, the highest of any core journal, while Anesthesia and Analgesia averaged 30.8 across 22 documents.

Table 3. Twenty most productive countries

Country	Documents (all affiliations)	Documents (corresponding author)	SCP	MCP	MCP ratio (%)	Total citations	Mean citations
USA	567	528	467	61	11.6	8,144	15.42
Republic of Korea	178	171	163	8	4.7	2,507	14.66
China	135	128	123	5	3.9	961	7.51
Japan	125	123	122	1	0.8	1,125	9.15
Italy	111	80	65	15	18.8	1,075	13.44
India	77	75	73	2	2.7	552	7.36
United Kingdom	73	51	44	7	13.7	781	15.31
Germany	62	46	37	9	19.6	886	19.26
Turkiye	52	45	42	3	6.7	197	4.38
France	60	42	33	9	21.4	663	15.79
Denmark	27	26	24	2	7.7	392	15.08
Canada	32	18	13	5	27.8	228	12.67
Taiwan	22	18	16	2	11.1	123	6.83
Australia	21	15	12	3	20.0	262	17.47
Netherlands	29	15	10	5	33.3	896	59.73
Spain	26	15	12	3	20.0	156	10.40
Switzerland	26	15	10	5	33.3	136	9.07
Brazil	19	11	7	4	36.4	93	8.45
Belgium	28	10	4	6	60.0	223	22.30
Singapore	11	10	9	1	10.0	202	20.20

Countries are ranked by the number of documents whose corresponding author was based in that country. Two counting bases are shown and they are not interchangeable. Documents (all affiliations) credits a document to every country represented among the affiliations of all its authors, so an internationally co-authored paper is counted once for each contributing country; these are the counts reported in the Results when total national contribution is described, and they sum to more than the 1,528 documents in the corpus. Documents (corresponding author) assigns each document to a single country and is the basis of Table 2, of the SCP and MCP counts and of the collaboration indices. Total and mean citations are given on the corresponding-author basis. Turkey and Turkiye were merged, as were England, Scotland, Wales and Northern Ireland. Mean citations for countries with few documents rest on small denominators and are correspondingly unstable. SCP: Single-country publications, MCP: Multiple-country publications

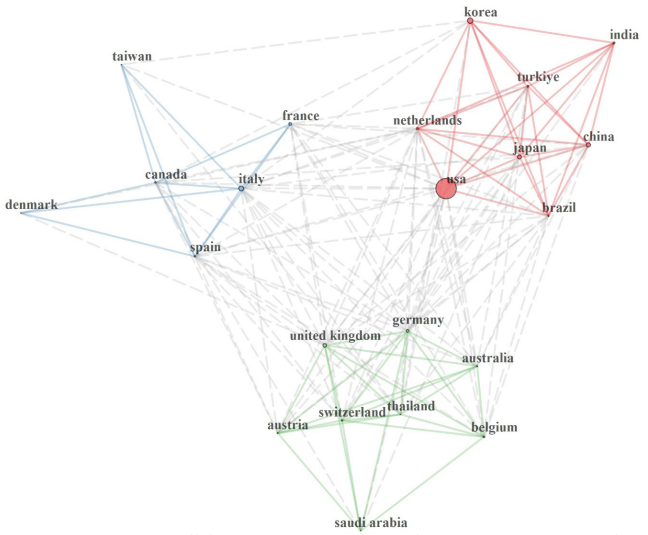

Figure 3. Country collaboration network. Node size is proportional to publication count; colour denotes cluster membership (Louvain algorithm). Top 22 countries shown

Table 4. Twenty most productive institutions

Institution	Documents	Total citations	Mean citations
Yonsei University	50	1.182	23.6
University of California System	39	849	21.8
University of Texas System	37	764	20.6
Harvard University	35	668	19.1
Mayo Clinic	35	337	9.6
Ohio State University	34	711	20.9
Cleveland Clinic Foundation	31	591	19.1
Seoul National University	31	338	10.9
Icahn School of Medicine at Mount Sinai	24	394	16.4
Pennsylvania Commonwealth System of Higher Education	23	394	17.1
State University System of Florida	23	296	12.9
Catholic University of Korea	20	125	6.2
University of Ulsan	20	345	17.2
Johns Hopkins University	19	679	35.7
University of Pittsburgh	19	320	16.8
University of Pennsylvania	17	166	9.8
Cornell University	16	130	8.1
Weill Cornell Medicine	15	119	7.9
Assistance Publique-Hôpitaux de Paris	14	183	13.1
University of California Los Angeles	14	307	21.9

Institutional names were harmonised with a purpose-built thesaurus before ranking, because Web of Science Indexes parent systems and their constituent units as separate affiliations. Some residual overlap remains where a constituent unit could not be unambiguously assigned to a listed parent system

The distribution of this literature between anaesthesiology and surgical journals changed substantially over time (Figure 2). Anaesthesiology journals carried 48.5% of documents published between 2001 and 2008 and 51.8% between 2009 and 2012, but their share fell to 33.8% in 2013-2016, 26.6% in 2017-2020 and 21.9% in 2021-2025. Across the corpus the proportion was 26.8%. Absolute output in anaesthesiology journals rose over the same period from 16 to 187 documents, so the decline is proportional rather than absolute.

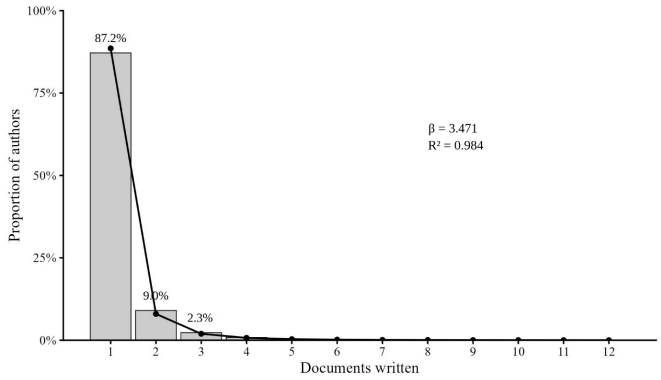

Figure 4. Author productivity distribution against Lotka's law

Bar labels give the proportion of authors at each exact level of productivity, so the label above the third bar refers to authors with exactly three documents. The 3.8% reported in the Results aggregates all authors with three or more documents and therefore corresponds to the third and all subsequent bars combined

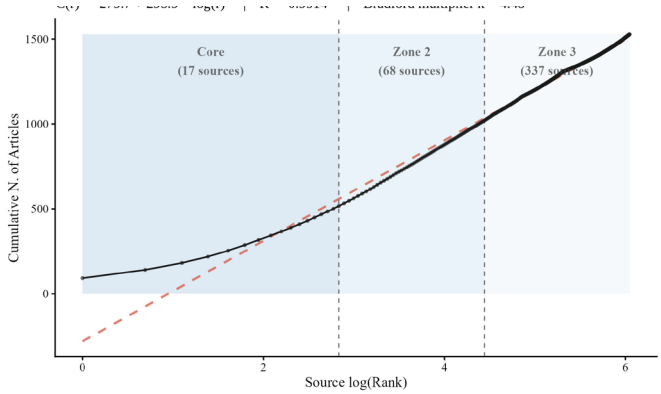

Figure 5. Bradford's law distribution of source journals

Most-cited Documents

The most-cited document was a randomised trial of multimodal prehabilitation published in JAMA Surgery in 2023 (415 citations), followed by a systematic review of enhanced recovery after urological surgery (242 citations) (Table 6). Three of the ten most-cited documents appeared in the British Journal of Anaesthesia and one in Anesthesia and Analgesia. The most-cited anaesthesia-specific investigations addressed the cardiovascular, cerebrovascular and respiratory consequences of steep Trendelenburg positioning combined with CO_2 pneumoperitoneum (189 citations),[2] intraocular pressure during steep Trendelenburg positioning (145 citations),[3] and haemodynamic perturbation during robot-assisted radical prostatectomy in 45° Trendelenburg (119 citations).[4]

Thematic Structure

Keyword co-occurrence analysis resolved into three network communities (Figure 6): a positioning-physiology community (Trendelenburg position, pneumoperitoneum, intraocular pressure, positive end-expiratory pressure, propofol, general anaesthesia, robot-assisted radical prostatectomy); an analgesia community (postoperative pain, opioids, transversus abdominis plane block, regional anaesthesia, multimodal analgesia, thoracic surgery, transoral robotic surgery); and a recovery and outcomes community (ERAS, same-day discharge, length of stay, postoperative complications, radical cystectomy, partial nephrectomy).

Table 5. Ten most productive journals

Journal	Documents	Total citations	Mean citations	Zone	Category
Journal of Robotic Surgery	92	809	8.8	1	Surgical/other
Surgical Endoscopy and Other Interventional Techniques	49	725	14.8	1	Surgical/other
Journal of Cardiothoracic and Vascular Anesthesia	41	465	11.3	1	Anaesthesiology
Journal of Clinical Medicine	37	351	9.5	1	Surgical/other
Journal of Endourology	35	580	16.6	1	Surgical/other
Asian Journal of Surgery	33	365	11.1	1	Surgical/other
BMC Anesthesiology	30	335	11.2	1	Anaesthesiology
World Journal of Urology	26	313	12.0	1	Surgical/other
Journal of Minimally Invasive Gynecology	24	420	17.5	1	Surgical/other
Anesthesia and Analgesia	22	677	30.8	1	Anaesthesiology

Zone denotes the Bradford's law zone; category denotes whether the journal is assigned to the Web of Science Anesthesiology subject category

Table 6. Ten most-cited documents

First author	Year	Journal	Citations	Citations per year	DOI
Molenaar CJL	2023	JAMA Surgery	415	103.8	10.1001/jamasurg.2023.0198
Azhar RA	2016	European Urology	242	22.0	10.1016/j.eururo.2016.02.051
Kalmar AF	2010	British Journal of Anaesthesia	189	11.1	10.1093/bja/aeq018
Finnerty DT	2020	British Journal of Anaesthesia	182	26.0	10.1016/j.bja.2020.06.020
Mitsala A	2021	Current Oncology	176	29.3	10.3390/curroncol28030149
Gandaglia G	2014	Journal of Clinical Oncology	168	12.9	10.1200/JCO.2013.53.5096
Awad H	2009	Anesthesia and Analgesia	145	8.1	10.1213/ane.0b013e3181a9098f
Ashrafian H	2017	British Journal of Anaesthesia	133	13.3	10.1093/bja/aex383
Kussman BD	2004	Pediatric Anesthesia	131	5.7	10.1046/j.1460-9592.2003.01192.x
Gainsburg DM	2012	Minerva Anestesiologica	128	8.5	PMID 22415437

Citations per year were calculated as total citations divided by the number of years since publication, inclusive of the publication year. The 2012 Minerva Anestesiologica article predates the assignment of digital object identifiers by that journal, so its PubMed identifier is given instead. DOI: Digital object identifier, PMID: PubMed identifier

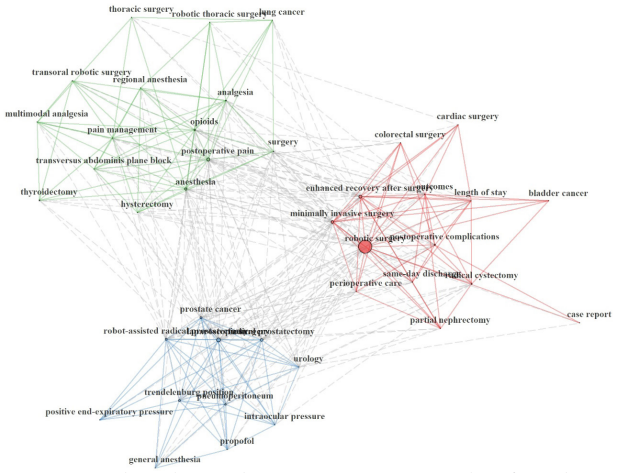

Figure 6. Author keyword co-occurrence network after thesaurus harmonisation. Node size is proportional to occurrence frequency; colour denotes cluster membership. Top 40 keywords shown

Thematic mapping identified five clusters (Table 7; Figure 7). Robotic surgery occupied the motor quadrant (966 keyword occurrences), radical prostatectomy sat on the motor-basic boundary (753) and carried the positioning-physiology terms, postoperative pain was a well-developed niche theme (490), ERAS was a basic theme (286), and thyroidectomy with transoral robotic surgery and sugammadex formed a small emerging cluster (69).

Table 7. Centrality and density values for the thematic clusters

Cluster	Terms	Occurrences	Centrality	Density
Robotic surgery	22	966	0.300	8.66
Radical prostatectomy	23	753	0.193	8.05
Postoperative pain	23	490	0.122	10.36
Enhanced recovery after surgery	10	286	0.161	6.54
Thyroidectomy	3	69	0.038	5.53

Centrality measures the strength of a cluster's links to other clusters and density its internal cohesion, both computed by the Callon method on author keywords occurring at least six times. Clusters are ordered by keyword occurrence. Quadrant assignment in Figure 7 is based on median partitions of these values and should be read as indicative, since the radical prostatectomy and enhanced recovery after surgery clusters lie close to a partition line

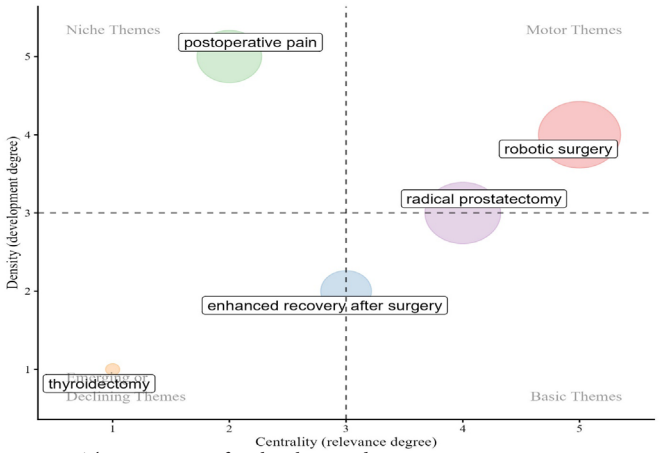

Figure 7. Thematic map of author keywords

Trend analysis showed an orderly succession (Figure 8). Cardiac surgery, intraocular pressure and Trendelenburg position peaked between 2015 and 2017; intracranial pressure, optic nerve sheath diameter, rhabdomyolysis, dexmedetomidine and transversus abdominis plane block between 2018 and 2019; pneumoperitoneum, radical cystectomy and laparoscopic surgery around 2020; and postoperative pain, opioids and postoperative complications in 2022. The most recent terms were robotic thoracic surgery, ERAS, outcomes, colorectal surgery, lung cancer and Artificial Intelligence, all peaking in 2023 or 2024. Telesurgery, telemedicine and Artificial Intelligence were also present, but at low frequency: they were carried by 14, 11 and 10 documents respectively and all fell below the display threshold of the keyword co-occurrence network shown in Figure 6 (Table 8). They are therefore best regarded as emerging signals rather than as established themes.

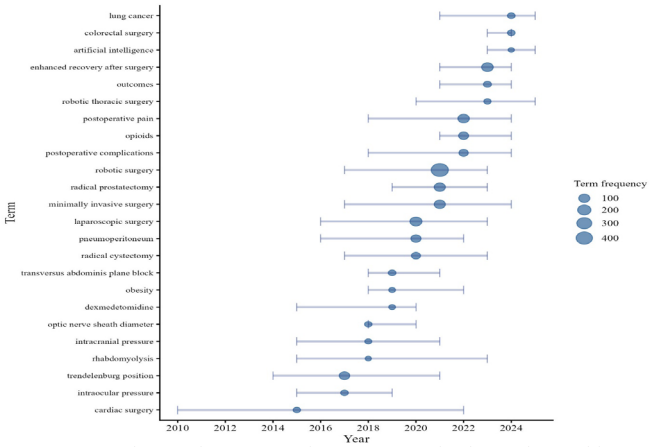

Figure 8. Trend topics by year. Circle position marks the median publication year of each term; horizontal bars span the first and third quartiles; circle size is proportional to term frequency

Table 8. Frequency and year range of terms denoting remote and computational approaches

Term	Documents	Year range
Telesurgery	14	2007-2025
Telemedicine	11	2007-2025
Artificial Intelligence	10	2021-2025
5G	3	2021-2025
Remote surgery	2	2022-2025
Machine learning	1	2025

Terms were counted where they appeared in the title, author keywords or keywords plus of a document. Counts are not mutually exclusive. All fell below the display threshold of the keyword co-occurrence network shown in Figure 6

DISCUSSION

This analysis mapped 1,528 documents on perioperative anaesthetic management in robotic-assisted surgery indexed between 2001 and 2025. Three findings stand out.

Output grew at a compound annual rate of 14.6% between 2010 and 2025, and an exponential model accounted for 95% of the variance in the post-2009 trajectory. Yet the share of this literature appearing in anaesthesiology journals fell from 48.5% in 2001-2008 to 21.9% in 2021-2025, and only three of the ten most productive journals were anaesthesiology titles. Absolute output in anaesthesiology journals rose more than tenfold over the same interval, so this is dilution rather than retreat: expansion has been driven by publication in surgical and general medical venues. The pattern is intelligible. The early literature addressed questions only anaesthesiologists were positioned to ask, such as how steep head-down positioning combined with capnoperitoneum alters cardiovascular, cerebrovascular and respiratory homeostasis, and these studies appeared in anaesthesia journals.[2-4] The recent literature is dominated by enhanced recovery pathways, opioid-sparing

protocols and same-day discharge, which are perioperative by definition but are increasingly designed, implemented and reported by surgical teams.[6,7] One interpretation of this pattern, which these descriptive data can suggest but not demonstrate, is that anaesthesiologists increasingly contribute to an agenda they do not predominantly set and are less likely to encounter its findings in their own journals. Journal distribution indicates where this literature appears; it does not identify who designed, led or funded the underlying studies, so this reading should be treated as an implication of the findings rather than as a result established by them.

Productivity and citation impact were not equivalent. The United States produced 567 documents, more than three times the second-ranked country, but the highest citation rate belonged to the Netherlands (59.7 citations per document from 15 corresponding-author publications). Conversely, several high-output countries recorded low citation rates, including India (7.36), China (7.51) and Turkiye (4.38). The same divergence appeared at journal level, where the British Journal of Anaesthesia published only 17 documents but attracted 59.9 citations per document. These are descriptive associations and should not be read causally. Citation rates are shaped by journal selection, topic and language as much as by study quality, and means derived from small denominators are unstable.

Collaboration was limited and unevenly distributed. Only 11.78% of documents involved more than one country. The lowest multiple-country ratios belonged to the four most productive Asian contributors: Japan (0.8%), India (2.7%), China (3.9%) and the Republic of Korea (4.7%). Among the larger contributors, France (21.4%) and Germany (19.6%) were the most outward-facing; several smaller ones were more so still, including Belgium (60.0%), the Netherlands and Switzerland (both 33.3%) and Canada (27.8%). The Korean case is instructive: Yonsei University was the leading institution and Korean investigators occupied most leading author positions, reflecting a concentrated national programme built substantially around transoral and transaxillary robotic thyroidectomy, an approach with distinctive anaesthetic demands and one that formed its own thematic cluster. High productivity and low external collaboration can coexist, but the combination limits the generalisability of single-centre protocols. Turkiye ranked tenth in output but recorded the lowest citation rate among the twenty most productive countries and a multiple-country ratio of 6.7%. For Turkish anaesthesia departments, international co-authorship is the more actionable of these two gaps. The steep Lotka exponent (β=3.471), with 87.2% of authors contributing a single document, points in the same direction: the field has not yet consolidated a stable core of dedicated investigators.

The thematic sequence traces a coherent maturation. Attention moved from the immediate physiological consequences of the operative setting, such as intraocular and intracranial pressure, optic nerve sheath diameter and rhabdomyolysis, through regional analgesic technique, to recovery pathways and discharge outcomes. Postoperative pain emerged as a well-developed but peripheral niche theme, indicating an internally coherent literature not yet central to the field. The most recently rising terms are robotic thoracic surgery, Artificial Intelligence and telesurgery. The last two rest on a small evidence base, comprising 10 and 14 documents respectively (**Table 8**), and are more accurately described as emerging topics, or as potential future research directions, than as established frontiers. The only Hot Paper in the corpus addressed ultra-long-distance robotic surgery. These topics raise anaesthetic questions that the current literature has barely addressed, including perioperative management when the operating surgeon is remote.

Practical Implications

Anaesthesiology departments involved in robotic programmes should recognise that much of the relevant evidence now appears outside anaesthesia journals and structure their literature surveillance accordingly. For countries combining substantial output with limited external collaboration, including Turkiye, multicentre and cross-national designs offer the clearest route to greater influence. The emerging topics identified here, and telesurgery in particular, are represented by few documents at present, but they invite anaesthetic engagement before practice patterns are established elsewhere.

Limitations

Four limitations apply. First, the analysis was confined to the Web of Science Core Collection. Work indexed only in Scopus, PubMed or regional databases was not captured, and approximately one fifth of records came from the Emerging Sources Citation Index, whose citation behaviour differs from that of the Science Citation Index Expanded. Second, restriction to English excludes non-English perioperative practice and may understate non-anglophone contributions. Third, citation counts favour older publications, so recent work is systematically under-represented in impact measures. Fourth, the corpus was defined primarily by the search strategy. Although both authors reviewed all records flagged by an automated consistency check and excluded none, the boundary between anaesthetic and surgical content is not always sharp and a different eligibility threshold would yield a somewhat different corpus.

CONCLUSION

Research on perioperative anaesthetic management in robotic-assisted surgery has grown rapidly and continuously since 2009, with more than half of the literature published in the last five years. The United States leads output, followed by the Republic of Korea, and Yonsei University is the most productive institution. The literature is dispersed across 422 journals, with a core of 17 accounting for approximately one third of output. Two findings deserve particular attention: citation impact is concentrated in countries and journals of modest output rather than in the largest producers, and the proportion of this literature published in anaesthesiology journals has fallen by more than half since the field's early period. As robotic surgery continues to expand, and as telesurgery and Artificial Intelligence appear as potential future research directions, these patterns suggest that deliberate engagement by anaesthesiologists, through international collaboration and through publication in their own specialty venues, may help to keep the perioperative dimension of this field shaped by anaesthetic expertise. This is an implication of the publication patterns described here rather than a conclusion demonstrated by them.

ETHICAL DECLARATIONS

Ethics Committee Approval

As the study is based solely on previously published and publicly available bibliographic records, ethics committee approval was not required.

Informed Consent

Since this research is a bibliometric study, it did not require informed consent.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: MNK, MTD; Design: MNK, MTD; Control: MNK, MTD; Resources: MNK, MTD; Materials: MNK, MTD; Data Collection and/or Processing: MNK, MTD; Analysis and/or Interpretation: MNK, MTD; Literature Review: MNK, MTD; Writing the Article: MNK, MTD; Critical Review: MNK, MTD.

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Journal of Comprehensive Surgery

Original Article

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Helicobacter pylori infection and acute pancreatitis severity: findings from a retrospective cohort study

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ABSTRACT

Aims: While *Helicobacter pylori* (HP) is a well-known pathogen in gastroduodenal diseases, its potential role in acute pancreatitis remains unclear. This study aimed to investigate the association between HP infection and disease severity in patients with acute pancreatitis.

Methods: In this retrospective cohort study, 143 adult patients diagnosed with acute pancreatitis between January 2014 and October 2024 were analyzed. HP status was determined via histopathological examination of gastric biopsy specimens. Patients were stratified as HP-positive or HP-negative. Clinical severity was evaluated using the Ranson score and BISAP score. Radiologic severity was assessed using the Computed Tomography Severity Index (CTSI) and the revised Atlanta classification. Laboratory parameters, intensive care unit (ICU) admission, and length of hospital stay were also compared between groups.

Results: Of the 143 patients, 55 (38.5%) were HP-positive and 88 (61.5%) were HP-negative. No statistically significant differences were observed between the two groups in terms of Atlanta classification subtypes (p=0.256), clinical severity scores, or key laboratory values. HP positivity was not associated with ICU admission or longer hospitalization. However, in subgroup analyses, HP-positive patients with biliary pancreatitis demonstrated higher clinical severity scores (Ranson and BISAP), while no differences were observed in non-biliary cases.

Conclusion: HP infection was not significantly associated with the overall clinical or radiological severity of acute pancreatitis. However, exploratory subgroup analyses suggested higher clinical severity scores in patients with biliary pancreatitis, which should be interpreted cautiously. These findings indicate that the relationship between HP infection and acute pancreatitis severity may vary depending on etiology and requires further investigation.

Keywords: *Helicobacter pylori*, acute pancreatitis, disease severity, Atlanta classification

INTRODUCTION

Acute pancreatitis is an inflammatory disorder of the pancreas characterized by sudden onset of abdominal pain, elevated pancreatic enzymes, and a variable clinical course ranging from mild, self-limiting inflammation to severe necrotizing disease with systemic complications and organ failure.[1] Acute pancreatitis has a multifactorial etiology, with gallstones (20-70%), alcohol use (up to 30%), and hypertriglyceridemia (approximately 9%) being the most common causes, while less frequent etiologies include drug-induced, autoimmune, and genetic forms of the disease.[2] *Helicobacter pylori* (HP) is a gram-negative, microaerophilic bacterium that colonizes the gastric mucosa and is well known for its association with chronic gastritis, peptic ulcer disease, and gastric malignancies.[3] In recent years, HP has also been implicated in several extragastric conditions, including cardiovascular diseases, metabolic syndrome, and autoimmune disorders.[4] Recent studies have suggested that HP infection may exert systemic effects beyond the stomach, contributing to extra-gastric inflammatory responses through mechanisms such as extracellular vesicle release and potential direct effects on pancreatic tissue.[5,6] These findings support a possible link between HP and pancreatic inflammation, although its clinical relevance remains unclear.

Several pathophysiological mechanisms have been proposed to explain a potential link between HP infection and pancreatic inflammation. These include bacterial translocation, immune-mediated injury, molecular mimicry, and alterations in the gut-pancreas axis.[4-9] Recent studies have demonstrated that HP infection can significantly influence gut microbial composition, leading to dysbiosis and altered systemic immune responses, which may contribute to systemic inflammatory amplification.[10,11] Some studies have demonstrated an increased prevalence of HP infection in patients with chronic or acute pancreatitis, suggesting a possible role in pancreatic inflammation.[12,13] However, other studies failed to show a significant association, and current evidence remains inconclusive.

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Despite these conflicting findings, the role of HP infection in acute pancreatitis severity remains poorly defined. Previous studies have often relied on serological tests, had heterogeneous patient populations, or did not systematically apply validated severity indices. Therefore, the present study aimed to specifically investigate whether histologically confirmed HP infection is associated with the clinical and radiological severity of acute pancreatitis. By employing both clinical (Ranson, BISAP) and radiological (CTSI, revised Atlanta classification) scoring systems, we sought to provide a more robust evaluation and address gaps in the existing literature.

METHODS

Ethics

This study was approved by the Ankara Training and Research Hospital Ethics Committee (Date: 09.10.2024, Decision No: 258/2024). The requirement for informed consent was waived by the ethics committee due to the retrospective nature of the study. All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki.

Study Design and Patient Selection

This retrospective cohort study was conducted at the Gastroenterology Department of Ankara Training and Research Hospital between January 2014 and October 2024. This study was conducted retrospectively by reviewing existing medical records, and no additional interventions were applied to the patients. Adult patients (≥18 years) who were diagnosed with acute pancreatitis and had undergone HP testing were included. The diagnosis of acute pancreatitis was established based on at least two of the following criteria: characteristic abdominal pain, elevated serum amylase and/or lipase levels (≥3 times the upper limit of normal), or radiologic findings consistent with pancreatitis. Patients with a history of chronic pancreatitis, active or previous gastrointestinal infections other than HP, or incomplete clinical records were excluded. A total of 160 patients with a diagnosis of acute pancreatitis were initially screened. After excluding 17 patients (7 with missing biopsy data, 6 with incomplete records, and 4 younger than 18 years), 143 patients were included in the final analysis (88 HP-negative and 55 HP-positive). Patient selection and exclusions are summarized in **Figure 1** (flow diagram). HP status was determined by histopathological examination of gastric mucosal biopsies obtained during upper gastrointestinal endoscopy. Histopathological evaluation was performed using routine hematoxylin-eosin (H&E) staining, and the presence of HP was determined by experienced pathologists based on characteristic morphological features. No additional special staining methods or immunohistochemical analyses were performed. However, quantitative assessment of bacterial load or grading of colonization density was not performed in this study. In all included patients, gastric biopsies for HP testing were obtained contemporaneously during hospitalization for the index episode of acute pancreatitis. Patients were categorized into HP-positive and HP-negative groups based on the biopsy results. This retrospective design reflects real-world clinical practice and provides insight into hospitalized patients with acute pancreatitis. Upper gastrointestinal endoscopy was performed based on specific clinical indications rather than as a routine procedure in all patients with acute pancreatitis. These indications included evaluation of suspected upper gastrointestinal pathology (such as dyspepsia, anemia, or gastrointestinal bleeding), assessment prior to endoscopic retrograde cholangiopancreatography (ERCP) in selected biliary cases, and persistent or unexplained abdominal symptoms not fully attributable to pancreatitis.

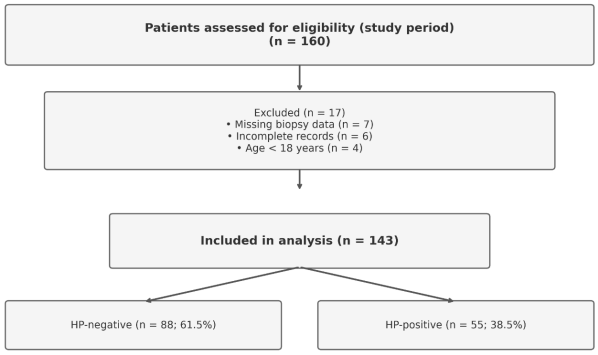

Figure 1. Flowchart of study population selection

Accordingly, the study population consisted of patients who underwent clinically indicated endoscopic evaluation during hospitalization. For subgroup analyses, patients were categorized according to pancreatitis etiology as biliary or non-biliary. The non-biliary group included alcohol-related, hyperlipidemia-associated, post-ERCP, and other less common etiologies.

Clinical and Laboratory Parameters

Demographic characteristics such as age and gender were recorded. Comorbidity burden was assessed using the Charlson Comorbidity Index (CCI). The clinical severity of pancreatitis was assessed using both the Ranson criteria and the BISAP score. Systemic inflammatory response syndrome (SIRS) was evaluated based on heart rate, respiratory rate, body temperature, and leukocyte count. The Computed Tomography Severity Index (CTSI) was used to assess morphologic severity based on contrast-enhanced abdominal CT scans. This scoring system evaluates the presence of pancreatic edema, necrosis, and peripancreatic fluid collections. Additionally, all patients were classified according to the revised Atlanta classification into morphologic subtypes (normal, edematous, necrotizing) and clinical severity categories (mild, moderate, severe). The final severity classification was determined retrospectively using clinical and radiological findings documented throughout the hospitalization period, including the development of local complications and organ failure when present. Clinical outcomes such as length of hospital stay, need for intensive care unit (ICU) admission, and pancreatitis-related complications were documented. Laboratory parameters included serum amylase, lipase, glucose, white blood cell count, hemoglobin, platelet count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), urea, creatinine, lactate dehydrogenase (LDH), total bilirubin, liver function tests, and triglyceride levels. Inflammatory status was assessed using serum CRP, erythrocyte sedimentation rate (ESR), white blood cell count, and the presence of SIRS.

Statistical Analysis

All data analyses were performed using IBM SPSS Statistics (version 28.0, IBM Corp., Armonk, NY, USA). Normality of continuous variables was evaluated using the Kolmogorov-Smirnov test. Variables with normal distribution are reported

as mean±standard deviation, whereas those not normally distributed are described using median values along with interquartile ranges (IQR: 25th to 75th percentile). Categorical variables were expressed as counts and percentages, and compared using the chi-square test or Fisher's exact test, as appropriate. Categorical data were summarized as frequencies and percentages. For comparisons between two groups (HP positive and HP negative), the independent samples t-test was employed for continuous variables with normal distribution, while the Mann-Whitney U test was used for those not following a normal distribution. Categorical variables were compared using either the Chi-square test or Fisher's exact test, based on the expected cell counts. Specifically, the association between HP status and acute pancreatitis severity was assessed using Chi-square or Fisher's exact tests for categorical severity classifications (revised Atlanta criteria), and Mann-Whitney U tests for continuous severity scores (CTSI, BISAP, Ranson). Subgroup analyses according to pancreatitis etiology (biliary vs. non-biliary) were performed to explore potential confounding effects. In addition, exploratory multivariate logistic regression analysis was considered to adjust for potential confounders such as age, gender, comorbidity burden, and etiology. However, due to the limited number of moderate and severe cases, inclusion of multiple variables in the regression model was not statistically feasible. Therefore, the analysis was restricted to univariate and subgroup comparisons, and this limitation was acknowledged when interpreting the findings. A p-value of <0.05 was considered statistically significant. As this was a retrospective study based on an available dataset, an a priori power analysis was not performed. However, the sample size was determined by the number of eligible patients within the study period. The potential limitation related to statistical power has been acknowledged in the discussion section.

Missing data were handled using available-case analysis, meaning that patients were not excluded from the study due to missing laboratory or imaging values. Analyses were performed using the maximum number of available observations for each variable. The overall proportion of missing data was low (<5% for all variables), and no variable exceeded 10% missingness. Sensitivity analysis comparing complete-case versus available-case results showed no material differences in statistical significance. Therefore, multiple imputation was not deemed necessary. Percentages were calculated using available denominators, and totals may not always equal 100% due to rounding.

RESULTS

A total of 143 patients diagnosed with acute pancreatitis were included in the analysis. Among these, 88 (61.5%) were HP negative and 55 (38.5%) were HP positive. In the present cohort, the most common etiology was biliary origin, accounting for 69.2% (n=99) of cases. Alcohol-related pancreatitis was the second most frequent cause, observed in 17.5% (n=25) of the patients. Hyperlipidemia was identified in 9.8% (n=14) of cases. Additionally, pancreatitis following endoscopic retrograde cholangiopancreatography (ERCP) was reported in 0.7% (n=1), and other rare etiologies constituted 2.8% (n=4).

The demographic and clinical characteristics of the study population are presented in **Table 1**. There were no statistically significant differences between HP-positive and HP-negative groups in terms of age (p=0.904), gender distribution (p=0.420), length of hospital stay (p=0.120), CTSI (p=0.773), Ranson score (p=0.333), BISAP score (p=0.120), or ICU admission rate (p=0.414). The CCI tended to be lower in the HP-positive group but did not reach statistical significance (p=0.069). The frequency of pleural effusion and fever also did not differ significantly between groups (p=0.806 and p=0.060, respectively).

There were no statistically significant differences between HP groups in terms of CRP (p=0.132), ESR (p=0.175), white blood cell count (p=0.463), hemoglobin (p=0.330), platelet count (p=0.510), glucose (p=0.367), urea (p=0.947), creatinine (p=0.355), amylase (p=0.818), LDH (p=0.788), AST (p=0.847), ALT (p=0.947), total bilirubin (p=0.853), or triglyceride levels (p=0.381). These parameters were used as markers of systemic inflammation.

The distribution of Atlanta classification subtypes in the study population is presented in **Figure 2**. In the morphologic categorization, 18.2% of HP-negative patients were classified as normal, 71.6% as edematous, and 10.2% as necrotizing. Among HP-positive patients, 10.9% were classified as normal, 83.6% as edematous, and 5.5% as necrotizing. Regarding clinical severity, HP-negative patients were classified as normal (18.2%), mild (43.2%), moderate (38.6%), and severe (0%), while HP-positive patients were classified as normal (10.9%), mild (52.7%), moderate (34.5%), and severe (1.8%). No statistically significant association was observed between HP status and Atlanta morphologic classification (p=0.256). Similarly, no significant association was found between HP status and the Atlanta Clinical Severity Index (p=0.311). As summarized in **Table 2**, the distribution of clinical severity according to the revised Atlanta classification (mild, moderately severe, severe) was comparable between HP-positive and HP-negative groups. Similarly, median CTSI, BISAP, and Ranson scores did not differ significantly between the two groups (**Table 3**).

Subgroup analyses according to pancreatitis etiology (biliary vs. non-biliary) were performed to explore potential confounding effects. The results are presented in **Table 4**. In the biliary pancreatitis subgroup, HP-positive patients demonstrated significantly higher clinical severity scores (Ranson and BISAP) compared to HP-negative patients. However, no significant difference was observed in radiological severity (CTSI). In contrast, no statistically significant differences were observed between HP-positive and HP-negative patients in the non-biliary subgroup (all p>0.05). These findings should be interpreted cautiously due to subgroup sample size.

DISCUSSION

The current study investigated whether HP infection has any clinical relevance in the context of acute pancreatitis, specifically in relation to disease severity and radiologic classification. Although HP has been implicated in several extra-gastric inflammatory conditions, clinical studies evaluating its association with acute pancreatitis have yielded inconsistent results.[14,15] The theoretical basis for HP's involvement in pancreatic disease lies in its capacity to trigger systemic inflammation, alter gut microbiota composition, and modulate immune responses. Animal models have suggested that HP infection may influence pancreatic injury through cytokine-mediated cross-talk or via bacterial translocation

Table 1. Demographic, clinical, and laboratory features of acute pancreatitis patients stratified by HP status

Parameters	Study population (n=143)	HP negative group (n=88)	HP positive group (n=55)	p-value
Age (years)	56.59±15.95	56.72±17.02	56.38±14.22	0.904
Gender (F) n (%)	59 (41.3%)	34 (38.6%)	25 (45.5%)	0.420
Length of hospital stay (days)	7 (4-11)	7 (4-13)	6 (3-10)	0.120
CTSI	2 (2-3)	2 (1-3)	2 (2-3)	0.773
CCI	2 (1-4)	2.5 (1-4)	2 (0-4)	0.069
Ranson score	1 (0-2)	1 (0-2)	1 (0-2)	0.333
BISAP score	1 (0-2)	1 (0-2)	0 (0-1)	0.120
Pleural effusion n (%)	17 (11.9%)	10 (11.4%)	7 (12.7%)	0.806
Fever n (%)	74 (51.7%)	51 (58.0%)	23 (41.8%)	0.060
ICU admission rate n (%)	17 (11.9%)	12 (13.6%)	5 (9.1%)	0.414
ESR (mm/h)	23 (11.8-40)	25.5 (13-39.8)	20 (8.8-40.5)	0.175
CRP (mg/L)	125 (40-252.3)	140 (50-243)	84 (26-249)	0.132
White blood cell count (10^3/μL)	12169.65±5032.12	12414.77±4355.33	11777.45±5981.00	0.463
Hemoglobin (gr/dl)	12.88±4.24	12.61±4.64	13.32±3.50	0.330
Platelet count (10^3/μL)	244811.19±86639.77	248602.27±97688.76	238745.45±65599.58	0.510
Glucose (mg/dl)	146.20±68.94	150.33±70.23	139.60±66.93	0.367
Urea (mg/dL)	30.43±12.38	30.49±11.07	30.35±14.34	0.947
Serum creatinine (mg/dl)	0.84 (0.65-0.98)	0.82 (0.65-0.96)	0.89 (0.61-1.01)	0.355
Amylase	678 (313-1684)	738 (371.8-1545.5)	593 (238-2211)	0.818
LDH	306.56±152.84	309.30±162.15	302.18±137.96	0.788
AST (U/L)	43 (18-110)	36 (22-98.5)	47 (16-153)	0.847
ALT (U/L)	38 (17-116)	36 (17.3-89.8)	38 (17-183)	0.947
Total bilirubin (mg/dl)	0.82 (0.39-1.53)	0.81 (0.38-1.47)	0.83 (0.39-1.81)	0.853
Triglycerides (mg/dl)	117 (85-166)	121 (82.3-177)	113 (87-156)	0.381

Data are shown as mean±SD, median (IQR), or n (%). Percentages are based on available-case denominators. Totals may not equal 100% due to rounding. No statistically significant differences were observed between HP-positive and HP-negative groups. HP: *Helicobacter pylori*, F: Female, CTSI: Computed Tomography Severity Index, CCI: Charlson Comorbidity Index, BISAP: Bedside Index for Severity in Acute Pancreatitis, ICU: Intensive care unit, SIRS: systemic inflammatory response syndrome, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, LDH: Lactate dehydrogenase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, SD: Standard deviation, IQR: Interquartile range

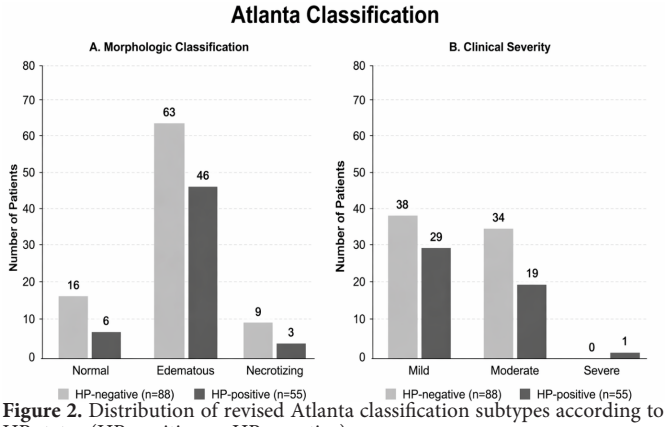

Figure 2. Distribution of revised Atlanta classification subtypes according to HP status (HP-positive vs. HP-negative)

HP: *Helicobacter pylori*

Table 2. Distribution of acute pancreatitis severity according to revised Atlanta classification by HP status

Revised Atlanta severity	HP-positive (n=55)	HP-negative (n=88)	p-value
Mild	29 (52.7%)	38 (43.2%)	
Moderately severe	19 (34.5%)	34 (38.6%)	
Severe	1 (1.8%)	0 (0%)	
Normal*	6 (10.9%)	16 (18.2%)	
Total	55 (100%)	88 (100%)	0.311

*The "normal" category was used as a descriptive designation for patients without radiologically detectable pancreatic abnormalities (CTSI=0). It does not represent an additional clinical severity category within the revised Atlanta classification. Data are presented as n (%). p-value calculated by chi-square test (Fisher's exact when applicable). No statistically significant differences were observed between HP-positive and HP-negative groups. HP: *Helicobacter pylori*

Table 3. Severity scores in HP-positive vs HP-negative patients

Severity score	HP-negative [median (IQR)]	HP-positive [median (IQR)]	p-value
CTSI	2 (1-3)	2 (2-3)	0.773
BISAP	1 (0-2)	0 (0-1)	0.120
Ranson	1 (0-2)	1 (0-2)	0.333

Data are presented as median (interquartile range). p-values calculated by Mann-Whitney U test. HP: *Helicobacter pylori*, IQR: Interquartile range, CTSI: Computed Tomography Severity Index, BISAP: Bedside Index for Severity in Acute Pancreatitis

from the upper gastrointestinal tract to the pancreatic microenvironment.[4,8-12,16] In addition, HP is known to upregulate pro-inflammatory cytokines such as TNF-α, IL-6, and IL-8, which have also been implicated in the progression of severe acute pancreatitis.[17-19] However, the clinical evidence supporting such interactions remains weak. A case-control study by Khan et al.[14] examined the potential association between HP infection and alcoholic acute pancreatitis by comparing 50 patients with first-episode alcoholic pancreatitis to 50 alcohol-matched controls without pancreatitis. The seroprevalence of HP infection did not significantly differ between the two groups, suggesting no causal link with the onset of pancreatitis. Our results indicate that HP infection was not associated with overall clinical or radiologic severity of acute pancreatitis. This suggests that the presence of HP may represent an incidental finding rather than a definitive contributing factor in disease progression.

Table 4. Subgroup analysis of clinical and radiological severity according to pancreatitis etiology and HP status

Parameter	Biliary HP-negative (n=61)	Biliary HP-positive (n=38)	p-value	Non-biliary HP-negative (n=27)	Non-biliary HP-positive (n=17)	p-value
Ranson score	1 (0-2)	2 (1-3)	0.004	1 (0-2)	1 (0-2)	0.812
BISAP score	1 (0-1)	2 (1-2)	<0.001	1 (0-2)	1 (0-1)	0.734
CTSI	2 (1-3)	2 (2-3)	0.218	2 (1-3)	2 (1-3)	0.911

Data are presented as median [interquartile range]. P-values correspond to comparisons between HP-positive and HP-negative groups within each etiology subgroup and were calculated using the Mann-Whitney U test. HP: *Helicobacter pylori*, BISAP: Bedside Index for Severity in Acute Pancreatitis, CTSI: Computed Tomography Severity Index

One of the key strengths of this study lies in its well-defined cohort, composed of patients with a confirmed diagnosis of acute pancreatitis and systematically assessed HP status based on histopathological examination of gastric biopsies. Unlike studies relying solely on serology or antigen tests, our diagnostic method reflects active infection, thereby improving the validity of group stratification. Additionally, the use of established clinical and radiologic severity indices (Ranson, BISAP, CTSI, and Atlanta classification) allowed for comprehensive assessment of disease burden across multiple dimensions. The inclusion of detailed laboratory and clinical data, combined with objective outcomes such as ICU admission and hospital length of stay, further strengthens the internal consistency and clinical relevance of our findings. Moreover, our study is among the few to investigate not only the presence of HP infection but also its potential correlation with inflammatory indices and multi-dimensional severity markers in acute pancreatitis. Importantly, the use of histopathological examination of gastric biopsies ensured accurate identification of active HP infection, reducing the risk of misclassification inherent in serology-based studies. Interestingly, exploratory subgroup analysis revealed higher clinical severity scores among HP-positive patients in the biliary pancreatitis group. However, this finding was not observed in non-biliary cases and was not supported by radiological severity indices. Given the relatively small subgroup sizes and multiple comparisons, the possibility of a type I error (false-positive finding) cannot be excluded. Therefore, these findings should be considered hypothesis-generating and require confirmation in larger prospective studies.

The retrospective design, selected study population, and absence of quantitative HP assessment should be considered when interpreting these findings, as discussed in the Limitations section.

Although our study did not demonstrate a significant overall association, HP infection may theoretically influence pancreatic inflammation through alterations in gut microbiota, immune dysregulation, epithelial barrier disruption, and activation of pro-inflammatory signaling pathways.[5,6,8,16] Increased expression of inflammatory mediators, including IL-6 and TNF-α, has also been reported in association with HP infection;[17-19] however, the clinical relevance of these mechanisms to acute pancreatitis severity remains uncertain.

Limitations

Several limitations should be acknowledged. First, the retrospective design and relatively small sample size may limit statistical power and the ability to control for potential confounding factors. Second, HP testing was restricted to patients who underwent clinically indicated upper gastrointestinal endoscopy and gastric biopsy, introducing potential selection bias and limiting the generalizability of the findings. Although baseline characteristics were compared between included and excluded patients, residual selection bias cannot be excluded. Therefore, these findings may not be directly generalizable to the broader population of patients with acute pancreatitis who do not undergo upper gastrointestinal endoscopy.

Multivariate analysis was not feasible due to the small number of severe cases. Another limitation of our study is that potential confounders such as pancreatitis etiology (e.g., gallstones, alcohol use) could not be fully adjusted for in the analysis, which may have influenced the observed associations. Third, the study population was drawn from a single tertiary care center, which may limit the generalizability of findings to broader or more diverse populations. Missing data were minimal and addressed using available-case analysis, with sensitivity checks confirming consistency of results. Furthermore, due to the observational design, causality cannot be inferred. While our findings suggest no clear association between HP positivity and acute pancreatitis severity, prospective longitudinal studies are required to determine whether HP plays any modulatory or predisposing role in pancreatic inflammation, particularly in idiopathic or recurrent cases.

CONCLUSION

As a result, HP infection was not significantly associated with the overall clinical or radiological severity of acute pancreatitis. However, subgroup findings suggest that this relationship may vary depending on pancreatitis etiology, particularly in biliary cases. These findings should be interpreted cautiously and require confirmation in larger prospective studies. Although its biological plausibility in pancreatic inflammation has been suggested, our findings do not provide sufficient evidence to support a clinically meaningful association. From a clinical perspective, the present findings do not currently provide sufficient evidence to support routine HP screening or eradication specifically for patients with acute pancreatitis. Future prospective multicenter studies are warranted to further explore potential immunologic or microbiome-mediated links between HP and pancreatic pathology.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Ankara Training and Research Hospital Ethics Committee (Date: 09.10.2024, Decision No: 258/2024).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and

there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: YHP, BÇ; Design: YHP, BÇ; Control: YHP, BÇ; Resources: YHP, BÇ; Materials: YHP, BÇ; Data Collection and/or Processing: YHP, BÇ; Analysis and/or Interpretation: YHP, BÇ; Literature Review: YHP, BÇ; Writing the Article: YHP, BÇ; Critical Review: YHP, BÇ.

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Relationship between wound fluid antibiotic concentration and clinical healing time in diabetic foot infections: a meropenem-focused analysis

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ABSTRACT

Aims: The penetration of antibiotics used to treat diabetic foot infection (DFI) into the target tissue is critical for clinical success. This study aimed to evaluate the penetration rates of carbapenem antibiotics into wound fluid, the factors affecting this penetration, and the effects of this penetration on clinical healing time in patients with DFI.

Methods: Twenty patients aged ≥18 years with DFI and open, draining wounds were prospectively included in the study. Thirteen patients received meropenem, four received ertapenem, and three received imipenem. After steady state had been achieved, wound fluid and serum samples were analyzed for antibiotic concentrations using LC-MS/MS.

Results: In accordance with quantitative measurement standards, the analyses focused on the meropenem group (n=13). A linear relationship was observed between serum and wound fluid meropenem concentrations. Wound fluid meropenem concentrations were significantly higher in patients with lower Wagner stages and in those receiving hyperbaric oxygen therapy (HBOT). Patients with comorbid chronic diseases had significantly higher wound fluid meropenem concentrations than those without comorbidities (p=0.034). A correlation was observed between wound fluid meropenem concentrations and clinical healing parameters.

Conclusion: Meropenem penetration into wound fluid during the treatment of DFI is influenced by factors such as comorbidities, wound stage, and HBOT. Monitoring antibiotic concentrations in wound fluid may help optimize treatment, reduce costs, and inform decisions regarding the timing of surgery.

Keywords: Diabetic foot infection, meropenem, wound fluid concentration, pharmacokinetics, Wagner grade

INTRODUCTION

Diabetic foot infection (DFI) is a severe complication of diabetes mellitus that carries a substantial economic burden, impairs quality of life, and represents a leading cause of lower-extremity amputations.[1] Globally, it is estimated that approximately 25% of individuals with diabetes will develop a foot ulcer at least once in their lifetime, with more than half of these lesions subsequently becoming infected.[2] The management of DFI necessitates a multidisciplinary approach that encompasses surgical debridement, appropriate wound care, and systemic antimicrobial therapy.[3]

Clinical success in the treatment of DFIs depends not only on the in vitro susceptibility of the pathogen, but fundamentally on achieving therapeutic antibiotic concentrations at the target site of infection, specifically within wound tissue and fluid. In patients with diabetes, concomitant peripheral artery disease and microvascular dysfunction can substantially impair the target-tissue penetration of systemically administered antibiotics.[4] Consequently, subtherapeutic drug concentrations may occur at the wound site despite adequate serum levels, thereby predisposing to therapeutic failure and the emergence of antimicrobial resistance.[5]

Due to their broad-spectrum activity against common polymicrobial pathogens (gram-positive, gram-negative, and anaerobes), carbapenems represent a cornerstone of empirical therapy in moderate-to-severe DFI.[6] Meropenem is a carbapenem derivative characterized by favorable tissue penetration owing to its low protein binding and large volume of distribution. However, prospective studies evaluating real-time meropenem concentrations in diabetic wound fluid and their correlation with clinical healing times remain limited in the literature.[7,8]

METHODS

Ethics

The study was carried out with the permission of the Gülhane Military Medical Academy Command Clinical Researches Ethics Committee (Date: 24.12.2015, Decision No: 2015-KAEK-59). We obtained an informed consent form from all

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patients for procedure. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This prospective study was conducted among patients hospitalized with a diagnosis of DFI in the department of infectious diseases and clinical microbiology and associated surgical units of a tertiary training and research hospital.

Study Population and Patient Eligibility

The study was conducted between July 18, 2015, and May 31, 2016. During the initial period, patients were evaluated as part of routine clinical care. Following ethics committee approval, prospective patient enrollment and study-specific sample collection were initiated. A total of 20 patients aged 18 years or older with diabetic foot infections and open, draining wounds were included in the study. The inclusion criteria were the presence of an actively exudative wound and a clinical indication for systemic carbapenem therapy (meropenem, ertapenem, or imipenem). Patients with suspected osteomyelitis or those with wounds covered by necrotic tissue that precluded fluid sampling were excluded from the analysis. The Wagner classification system was utilized to assess the ulcers, categorizing them based on wound depth and the presence of infection or necrosis, ranging from grade 0 (intact skin) to grade 5 (whole foot gangrene).

Antibiotic Administration and Sampling Procedure

Intravenous carbapenem therapy was initiated in all patients according to established clinical indications. To ensure that steady-state concentrations were achieved in both serum and tissue, biological sampling was performed at least 72 hours after the initiation of antimicrobial therapy. Thirty minutes after the completion of the initial antibiotic infusion, paired biological samples were collected simultaneously: a serum sample obtained via peripheral venipuncture and a wound fluid sample harvested directly from the wound bed using a sterile syringe or sponge. The collected samples were preserved at -80°C until bioanalysis.

Sample Preparation and Bioanalytical Assay Protocol

Quantification of antibiotic concentrations was performed using an AB SCIEX 3200 QTRAP LC-MS/MS system (AB Sciex, Framingham, MA, USA) coupled to a Shimadzu Nexera HPLC system equipped with a DGU-20A degasser, LC-20AD solvent delivery units, and a SIL-20A autosampler (Shimadzu Corporation, Kyoto, Japan). Although all three carbapenem agents (ertapenem, imipenem and meropenem) were initially evaluated, analytical assay standardization and reliable quantification could only be fully validated and optimized for meropenem. Consequently, the primary pharmacokinetic and statistical analyses were restricted to the 13 patients receiving meropenem who yielded quantifiable drug concentrations.

Preparation of Analytical Standards and Calibration Curves

Two distinct mobile phases were prepared for the liquid chromatography analyses. The first mobile phase was prepared by completely dissolving 1.0 g of ammonium acetate (CH3COONH4) in approximately 500 ml of distilled water using a magnetic stirrer, followed by the addition of 0.1% formic acid, and adjusting the final volume to 1000 ml with distilled water. The second mobile phase consisted of methanol containing 0.1% formic acid. For calibration procedures, a meropenem stock solution (1 mg/ml) was prepared in distilled water, and colchicine solution, used as an internal standard, was prepared in a methanol-water (2:8, v/v) mixture and stored in aliquots at +4°C until analysis.

Clinical Specimen Collection and Pre-analytical Processing

Once steady state concentrations were attained under carbapenem therapy, specimen collection was initiated 30 minutes following the cessation of the intravenous infusion in patients with DFI. Sterile Whatman® filter paper discs were applied to collect wound fluid, with an absorption period of approximately 30-40 minutes to achieve complete saturation. Following collection, the impregnated filter papers were transferred into sterile glass tubes and concurrent serum samples were placed into Eppendorf tubes. All specimens were preserved at -80°C until quantitative determination. Prior to analysis, the LC-MS/MS system was validated using known concentrations of meropenem and colchicine standards.

Quantification of Meropenem Concentrations by LC-MS/MS

During the study, to deproteinize serum samples, 200 µL of acetonitrile was added to 100 µL of serum, and the mixture was vortexed for 1 minute. The samples were centrifuged in a refrigerated centrifuge at +4°C and 5,000 rpm for 5 minutes. After centrifugation, the supernatant was transferred to insert vials for analysis. Wound fluid filter papers were cut to a width of 5 µm in a sterile environment, collected in glass tubes, and 1 ml of acetonitrile was added followed by vortexing for 1 minute. The samples were centrifuged in a refrigerated centrifuge at +4°C and 5,000 rpm for 5 minutes. The supernatant was collected for analysis after centrifugation.

Statistical Analysis

In descriptive statistics, frequencies and percentages were used for categorical data, and the mean, standard deviation, median, minimum, maximum, and range were used for continuous data. The normality of distribution for continuous variables was assessed using the Kolmogorov-Smirnov test. For normally distributed variables, an independent samples Student's t-test was conducted, whereas the Mann-Whitney U test was employed for non-normally distributed data. The correlation between two continuous variables was evaluated using Spearman's rank correlation coefficient. Statistical analyses were performed using IBM SPSS version 22.0 (IBM Corporation, Armonk, NY, USA), and a p-value <0.05 was considered statistically significant.

RESULTS

Among the 13 patients diagnosed with DFI and treated with meropenem, the mean age was 59.6±6.7 years and the mean duration of diabetes was 11.5±6.5 years. Ten patients (76.9%) were male and 3 (23.1%) were female. According to the Wagner classification, 7 patients (53.8%) had grade 3 ulcers and 6 (46.2%) had grade 4 lesions. The mean concentration of meropenem was 14.765±14.123 ng/ml in serum and 4.279±4.893 ng/ml in wound fluid. Other laboratory values for the patients are presented in **Table 1**.

When factors affecting wound fluid meropenem concentrations were analyzed, we evaluated tissue concentrations according to Wagner stages; although drug penetration was higher in patients with lower Wagner stages (stage 3 vs. stage 4),

Table 1. Demographic, clinical, and laboratory findings of the patients

	Mean±SD	Median	Min-max
Age (years)	59.6±6.7	60	49-75
Duration of diabetes (years)	11.5±6.5	10	1-25
HbA1c (%)	8.3±2.4	7.3	5.6-13.9
ESR (mm/h)	90±30	92	47-135
CRP (mg/L)	159±177	103	4-600
Serum meropenem concentration (ng/ml)	14.765±14.123	7700	3780-48900
Wound fluid meropenem concentration (ng/ml)	4279±4893	553	19100-18547

*This table summarizes the demographic characteristics and descriptive statistics of laboratory parameters for patients with diabetic foot infections included in the study. Continuous variables are presented as mean, SD, median, and min-max values according to data distribution. SD: Standard deviation, Min-max: Minimum-maximum, HbA1c: Glycated hemoglobin, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

the difference was not statistically significant (p=0.316). Similarly, higher levels of meropenem were detected in the wound fluid of the group receiving hyperbaric oxygen therapy (HBOT) compared with those who did not receive it, but the difference was not statistically significant (p=0.622). Similarly, elevated meropenem levels were noted in female patients and individuals with peripheral vascular disease; however, neither difference was statistically significant (p=0.469). In patients with underlying chronic comorbidities (particularly pronounced in those with renal dysfunction), wound fluid meropenem levels were significantly higher (p=0.034) (Table 2).

Table 2. Comparison of meropenem concentration levels in the wound fluid of patients

	Mean±SD	p*
Gender		
Male	2166±1330	0.469
Female	4913±5440	
Presence of peripheral vascular disease		
No	2393±1277	0.692
Yes	4845±5479	
Wagner stage		
Stage 3	5593±6344	0.316
Stage 4	2746±1983	
Presence of chronic disease other than DM		
No	1423±791	0.034
Yes	5548±5458	
Hyperbaric oxygen therapy status		
Receiving	5262±6058	0.622
Not receiving	2706±1605	

*This table presents a comparative analysis of the impact of various clinical and demographic characteristics on wound fluid meropenem levels. Continuous variables are presented as mean± SD. Intergroup comparisons were performed using the Mann-Whitney U test. A two-tailed p-value <0.05 was considered statistically significant. SD: Standard deviation, DM: Diabetes mellitus

In the meropenem cohort where analytical (quantitative) determination was achievable, a significant positive correlation was identified between serum levels and wound fluid concentrations (Figure).

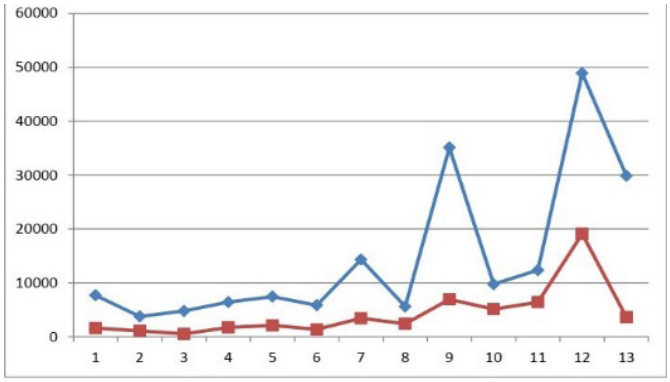

Figure. Comparative concentration profiles of meropenem in serum and wound fluid across patients

This graph illustrates the concurrent changes in serum (blue line) and wound fluid (red line) concentrations of meropenem in treated patients. Examination of the curves reveals a generally parallel relationship between systemic antibiotic levels and concentrations in the target tissue

DISCUSSION

In the management of diabetic foot infections, systemic antibiotic penetration into target tissues is frequently unpredictable and markedly variable due to pathophysiological barriers such as chronic vascular insufficiency, edema, and tissue necrosis.[4] The present study prospectively evaluated the relationship between clinical parameters and wound fluid concentrations of meropenem, a cornerstone agent in both empirical and definitive treatment of DFIs owing to its broad-spectrum efficacy. These data demonstrate a correlation between serum meropenem levels and wound fluid concentrations, indicating that tissue penetration is significantly influenced by underlying comorbidities, alongside observable differences based on Wagner grade and HBOT use.[5,7] In a recent pharmacokinetic study evaluating patients with DFIs, Finazzi et al.[8] reported that meropenem tissue penetration was substantially more variable than that observed in non-diabetic individuals. The positive correlation observed between serum and wound fluid concentrations suggests that the pharmacokinetic profile of meropenem is preserved to a certain extent despite tissue ischemia. Nevertheless, this degree of tissue penetration does not inherently equate to therapeutic efficacy; the severity of local inflammation and the extent of wound bed vascularization remain critical determinants of clinical outcome.[2]

Importantly, tissue penetration of meropenem was considerably higher in patients with less advanced Wagner grades, although this observed difference did not reach statistical significance. Wagner staging serves as an indicator of ulcer depth, tissue necrosis, and bone involvement, with advancing grades characterized by progressive microvascular compromise and worsening tissue hypoxia. As emphasized in the 2023 International Working Group on the Diabetic Foot (IWGDF) guidelines by Senneville et al.,[3] standard dosing regimens may be insufficient to attain target tissue concentrations exceeding the minimum inhibitory concentration (MIC) in patients with advanced DFIs. These observations indicate that antibiotics penetrate wound fluid more effectively during earlier stages when vascular architecture remains relatively preserved, thereby underscoring the critical need for dose optimization and timely surgical intervention in advanced disease.[1,6]

The observation of elevated wound fluid antibiotic concentrations among patients receiving hyperbaric oxygen therapy provides valuable preliminary data to the ongoing

debate surrounding adjuvant modalities in the literature. By promoting angiogenesis and regulating microvascular permeability, hyperbaric oxygen therapy counteracts local hypoxia and restores capillary perfusion in ischemic wound tissues. The elevated meropenem concentrations observed in the HBOT group suggest that this adjuvant modality not only improves tissue oxygenation but may also enhance the delivery of pharmacological agents to the target site. In support of this observation, Armstrong et al.[1] highlighted that multidisciplinary care and the synergy of adjuvant HBOT with antimicrobial therapy optimize local tissue bioavailability, thereby translating into improved outcomes in diabetic foot infections.

The marked influence of underlying chronic comorbidities, particularly altered renal function, on meropenem concentrations represents an expected pharmacokinetic phenomenon given the predominantly renal elimination of the drug. The statistically significantly higher concentrations observed in patients with comorbidities (p=0.034) may be attributed to a prolonged elimination half-life of the drug and, consequently, extended retention within the tissue compartment.[4] In line with this pharmacokinetic rationale, Roberts and Lipman demonstrated that impaired drug clearance in critically ill and comorbid patients substantially prolongs exposure and promotes tissue accumulation.[7] However, while elevated tissue retention may enhance local antibacterial efficacy, it concurrently escalates the risk of systemic toxicity-particularly neurotoxicity-thereby warranting judicious dose titration and close therapeutic monitoring.[9]

Limitations

Several limitations of the present study should be acknowledged. First, although 20 patients were initially enrolled, technical constraints in the bioanalytical quantification of the imipenem and ertapenem arms restricted the final pharmacokinetic evaluation to 13 meropenem-treated patients, thereby constraining overall sample size and the statistical power of subgroup comparisons. Secondly, wound categorization was based solely on the Wagner classification system. While widely used, this system does not fully account for the presence or severity of peripheral ischemia and neuropathy, which are critical variables that can significantly influence local tissue drug concentrations. Utilizing a classification system that incorporates ischemia, such as the University of Texas classification, might have resulted in more homogeneous study groups and should be considered in future research.

CONCLUSION

Meropenem represents an effective therapeutic agent that achieves favorable penetration into wound fluid during the management of DFIs. Nevertheless, clinical and pharmacokinetic success remains intrinsically linked to ulcer severity (Wagner stage), hyperbaric oxygen therapy, and the underlying burden of systemic comorbidities. Larger prospective trials are warranted to translate wound fluid pharmacokinetic dynamics into personalized dosing protocols, thereby moving clinical practice closer to precision antimicrobial therapy in DFIs.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Gülhane Military Medical Academy Command Clinical Researches Ethics Committee (Date: 24.12.2015, Decision No: 2015-KAEK-59).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: YÇ, OD; Design: YÇ, OD; Control: YÇ, OD; Data Collection and/or Processing: YÇ, OD; Analysis and/ or Interpretation: YÇ, OD; Literature Review: YÇ; Provision of Cases/Equipment: YÇ, OD; Article Writing: YÇ, OD; Critical Review: YÇ, OD.

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Original Article

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Cardiopulmonary complications and critical care in scorpion envenomation: a bibliometric analysis

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ABSTRACT

Aims: This study aimed to characterize publication and citation patterns in the literature on cardiopulmonary complications and critical care in scorpion envenomation and to map its thematic and intellectual structure.

Methods: The Web of Science Core Collection was searched on September 24, 2026. Records were screened against predefined eligibility criteria. Descriptive bibliometric indicators were calculated, and author-keyword co-occurrence (minimum three occurrences) and cited-reference co-citation (cited by at least 20 included records) networks were mapped using VOSviewer version 1.6.21.

Results: Of 462 retrieved records, 239 published between 1982 and 2026 were included; the 2026 count was partial. The records had received 5,346 citations (median, 10; h-Index, 41). Toxicon was the leading source (n=37), and India was the most frequently represented affiliation country (n=44). The author-keyword map, based on 162 records with author keywords, contained 28 terms in eight clusters. The co-citation map included 38 cited references in three clusters: foundational cardiovascular toxicity, myocardial injury and severity, and treatment and syntheses.

Conclusion: The literature is organized around acute cardiac and pulmonary injury, pediatric envenomation, and treatment-related themes. Combined keyword and co-citation mapping provides clinicians and researchers with a structured entry point to mechanistic, severity, assessment, and treatment literature and can guide focused evidence synthesis, without estimating complication incidence or comparative treatment effectiveness.

Keywords: Shock, cardiogenic, pulmonary edema, scorpion stings, critical care, bibliometrics

INTRODUCTION

Scorpion envenomation is an important public health problem, particularly in tropical and subtropical regions. Chippaux and Goyffon estimated approximately 1.2 million stings and more than 3,250 deaths annually, while noting that surveillance and burden estimates vary across regions.[1] Most stings cause local symptoms; a smaller subset progresses to systemic toxicity. In severe cases, autonomic disturbance and catecholamine excess can accompany myocardial injury, ventricular dysfunction, pulmonary edema, cardiogenic shock, and respiratory failure.[2-7] These complications can evolve rapidly, are especially consequential in children, and may require coordinated toxicology, emergency, pediatric, cardiology, and intensive care management.

The clinical literature is difficult to interpret as a single evidence base. A systematic review of scorpion-associated myocarditis assembled 703 patients from 30 case reports and 34 case series, illustrating the substantial contribution of small observational reports. These selected myocarditis cases cannot establish complication rates among all patients with scorpion stings.[8] Controlled treatment studies address different envenomation syndromes and clinical settings, which complicates comparison across publications.[9-11] This heterogeneity provides a rationale for examining how the literature is organized before undertaking a focused clinical evidence synthesis.

Recent clinical studies have examined bedside cardiac assessment, candidate biomarkers, hemodynamic monitoring, and prediction of transfer to the intensive care unit (ICU) in scorpion envenomation.[12-16] These studies illustrate the range of clinical questions currently being addressed in scorpion envenomation. Earlier bibliometric analyses have addressed broader scorpionism epidemiology and venom and antivenom research rather than the cardiopulmonary and critical care focus considered here.[17,18] A scoping review would characterize the breadth and nature of available clinical evidence, whereas bibliometric analysis maps indexed metadata and citation relationships to describe thematic and intellectual structure; the latter therefore better fits the present aim of characterizing field structure rather than synthesizing study-level findings.[19-21]

Accordingly, this study analyzed Web of Science Core Collection records on cardiopulmonary complications and critical care management in scorpion envenomation. The objectives were to characterize publication output and citation

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activity, describe source and geographic representation, and map the field's thematic and intellectual structure using author-keyword co-occurrence and cited-reference co-citation analyses.

METHODS

Ethics

The study analyzed bibliographic records and did not involve human participants, animals, or identifiable patient-level data. Ethics committee approval and informed consent were not applicable. The study was conducted in accordance with the relevant ethical principles and publication ethics standards.

Study Design and Data Source

This descriptive bibliometric study used records retrieved from the Web of Science (WoS) Core Collection. The search was run on September 24, 2026, in the topic (TS) field. A WoS Topic search covers titles, abstracts, author keywords, and keywords plus. Because keywords plus terms are generated from cited-reference titles, they may retrieve records with only tangential relevance to the clinical question; eligibility screening was used to exclude such records. The search was conducted in the Web of Science Core Collection, with all indexes available through the institutional subscription enabled. No publication-year, language, or document-type limits were applied at retrieval. The search covered the full available WoS record range; the included publications span 1982 (the earliest eligible record retrieved) through September 24, 2026 (the search date), with 2026 therefore representing a partial year. The complete search strategy was:

TS=[("scorpion sting*" OR "scorpion envenom*" OR scorpionism) AND (cardiac OR cardiovascular OR cardiopulmonary OR myocardial OR myocarditis OR cardiomyopathy OR "myocardial dysfunction" OR "cardiac dysfunction" OR "heart failure" OR "left ventricular dysfunction" OR "ventricular dysfunction" OR "pulmonary edema" OR "pulmonary oedema" OR "cardiogenic shock" OR "circulatory shock" OR "respiratory failure" OR "acute respiratory distress syndrome" OR ARDS OR "mechanical ventilation" OR "noninvasive ventilation" OR "non-invasive ventilation" OR intubation OR "intensive care" OR "critical care" OR ICU OR vasopressor* OR inotrope* OR prazosin OR dobutamine OR ECMO OR "extracorporeal membrane oxygenation")]

The search returned 462 records. All 462 WoS accession numbers were unique, so no duplicate records were removed. Full Record and Cited References data were exported for the final included set. The data export was retrieved on September 24, 2026, coinciding with the search date. Citation counts are those present in this export snapshot and may change as WoS records are updated.

Eligibility and Screening

The target literature comprised human clinical publications on scorpion envenomation that substantively addressed cardiopulmonary manifestations, critical care management, or directly relevant diagnostic or therapeutic topics. Original clinical studies, case reports and series, and substantive topic-specific reviews were eligible. Letters were retained when they reported independent patient data or provided substantial topic-specific analysis. Animal, in vitro, and basic venom studies; taxonomy-focused reports; records unrelated to scorpion envenomation; and publications without substantive relevance to the target clinical topics were excluded. For the mutually exclusive **Figure 1** categories, "no substantive cardiopulmonary/critical care focus" denoted clinical scorpion records whose primary clinical subject was outside the target manifestations or management; "insufficient relevance" denoted records that mentioned a target topic only tangentially, without analyzable clinical content; and "local or epidemiological focus only" denoted geographic, surveillance, or burden reports without eligible cardiopulmonary or critical care findings. "Ineligible format or no eligible clinical data" covered publication types or records lacking eligible human clinical data.

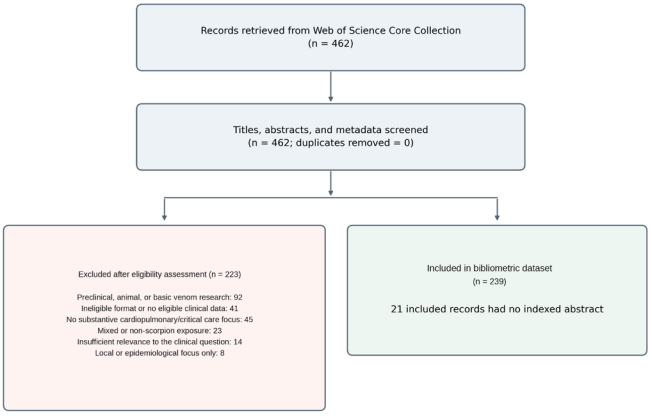

Figure 1. Record selection from the Web of Science Core Collection. Exclusion reasons are mutually exclusive and represent the primary eligibility reason for each record. Of the 239 included records, 21 had no abstract in the WoS export

The author screened titles, abstracts, and available WoS metadata for all retrieved records against predefined eligibility criteria. Records with uncertain eligibility were flagged for discussion with an independent research colleague; both rechecked these records against the eligibility criteria and resolved uncertainties by consensus. Full texts were consulted when available and needed to clarify eligibility. Full-text availability alone was not an exclusion criterion: records were included when relevance was clear from the title, abstract, or bibliographic metadata. No formal methodological quality or risk-of-bias appraisal of the included clinical publications was undertaken.

Data Items and Bibliometric Analysis

The extracted WoS fields included publication year, document type, source title, author names, affiliation addresses, author keywords, keywords plus, cited references, and times cited. Publication counts were summarized by year, source, document type, language, and affiliation country. Countries were counted once per record for each country represented. "Turkey" and "Turkiye" were harmonized as Turkiye; United States address forms ending in "USA" were grouped as United States, and capitalization variants were standardized. Records without affiliation data were excluded from country tabulations. Publication year was taken from the WoS PY field as indexed in the September 24, 2026 export; records tagged early access were not reassigned to a later final-issue year. Citation counts were treated as a database snapshot rather than as a time-independent measure. The h-Index was calculated for the 239-record set from the WoS times-cited values.

The author-keyword co-occurrence analysis was conducted using VOSviewer (version 1.6.21; Centre for Science and Technology Studies, Leiden University, Leiden, the Netherlands), with full counting and a minimum occurrence threshold of three. A thesaurus file harmonized selected spelling and synonym variants, including "scorpion envenoming" and "scorpionism" with "scorpion envenomation," "pulmonary oedema" with "pulmonary edema," "scorpion stings" with "scorpion sting," and "scorpion venoms" with "scorpion venom." The singular/plural variants of each term were harmonized, whereas "scorpion sting" and "scorpion envenomation" were retained as separate author-keyword concepts to preserve the distinction between the exposure event and the clinical consequences of venom inoculation. "Tityus" and "Tityus serrulatus" were retained as distinct concepts. The overlay visualization displays average publication year on a 2000-2025 scale. Cited-reference co-citation was analyzed in VOSviewer using full counting and a minimum threshold of 20 citations per cited reference (that is, cited by at least 20 of the 239 included records). No inferential tests were used. Author keywords were used for thematic mapping because they represent terminology explicitly assigned by the authors; Keywords Plus were not incorporated into the co-occurrence network to avoid combining author-assigned terms with algorithmically generated indexing terms. The thresholds were selected pragmatically to retain recurrent items while maintaining interpretable network sizes and were not intended as statistical significance criteria.

RESULTS

Selection and Publication Profile

Of 462 records screened, 239 were included in the bibliometric dataset and 223 were excluded after eligibility assessment (Figure 1). Preclinical, animal, or basic venom research was the largest exclusion category (92/223; 41.3%). Publications ranged from 1982 to 2026. Annual output was uneven, with the highest number of included records in 2015 (n=16), followed by 2025 (n=14) and 2014 (n=13). Eleven records were published in each of 2013 and 2018. Seven records were dated 2026 in the export; this year was incomplete at the time of retrieval (Figure 2).

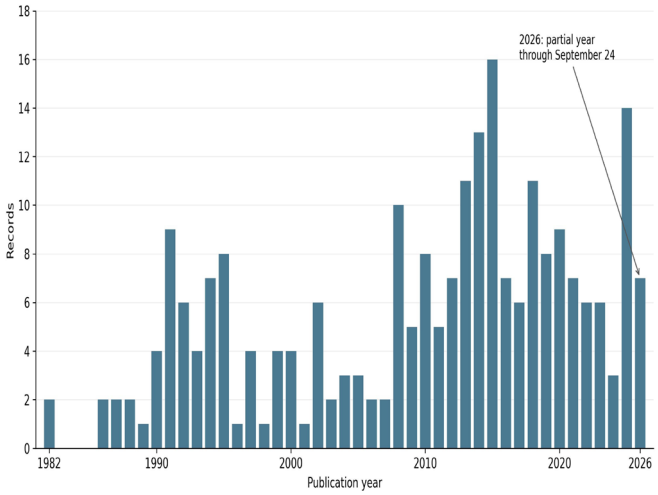

Figure 2. Annual publication output in the included dataset. The 2026 value is partial because the search was conducted on September 24, 2026

The dataset contained 196 records classified as articles, including two records also tagged as early access and one record also tagged as a book chapter; 27 reviews, including one record also tagged as early access; 9 letters; 6 notes; and 1 editorial material record. English was the indexed language for 224 records, with French (n=7), Turkish (n=4), Spanish (n=2), and Portuguese (n=2) accounting for the remainder. Abstracts were available for 218 records (Table 1).

Table 1. Bibliometric characteristics of the included records

Characteristic	Value
Records included	239
Publication years	1982-2026*
WoS citations in export snapshot	5.346
Mean citations per record	22.4
Median citations per record	10
Uncited records	24
Set-level h-Index	41
Source titles	113
Records with affiliation data	214 (89.5%)
Records with abstract	218 (91.2%)
Article records**	196 (82.0%)
Reviews	27 (11.3%)
Letters	9 (3.8%)
Notes	6 (2.5%)
Editorial material	1 (0.4%)
Records with author keywords	162 (67.8%)

*2026 is partial through September 24, 2026. Publication year follows the WoS PY field as indexed at retrieval; an early access record was not reassigned when a final issue year became available. **The article group includes two records also tagged early access and one also tagged book chapter; the review group includes one record also tagged early access

Sources and Geographic Distribution

The 239 records were distributed across 113 source titles. Toxicon published the largest number (n=37), followed by Clinical Toxicology and Wilderness & Environmental Medicine (n=9 each), Human & Experimental Toxicology and Journal of Clinical and Diagnostic Research (n=7 each), and Annals of Tropical Paediatrics and the American Journal of Tropical Medicine and Hygiene (n=6 each; Table 2). WoS affiliation data were present for 214 records (89.5%). Under record-level full counting, India was most frequently represented (n=44), followed by Turkiye and Tunisia (n=30 each), Brazil (n=21), Israel (n=17), and the United States (n=14). A record could contribute to more than one country count; country totals are reported in Table 3.

Table 2. Most productive source titles

Source title	Records
Toxicon	37
Clinical Toxicology	9
Wilderness & Environmental Medicine	9
Human & Experimental Toxicology	7
Journal of Clinical and Diagnostic Research	7
Annals of Tropical Paediatrics	6
American Journal of Tropical Medicine and Hygiene	6
Chest	5
Intensive Care Medicine	5
Journal of Tropical Pediatrics	4

Table 3. Most frequently represented affiliation countries

Country	Records	% of records with affiliation data
India	44	20.6
Turkiye	30	14.0
Tunisia	30	14.0
Brazil	21	9.8
Israel	17	7.9
United States	14	6.5
Egypt	12	5.6
Morocco	10	4.7
Iran	7	3.3
Saudi Arabia	6	2.8
France	6	2.8

Country counts use record-level full counting. Records with affiliations in multiple countries contribute once to each represented country. Percentages use the 214 records with affiliation data as the denominator

Citation Profile

The included records had received 5,346 citations in the WoS export snapshot (mean, 22,4; median, 10). Twenty-four records had no citations; the h-Index of the included set was 41. The most cited record was Ismail's 1995 description of the scorpion envenoming syndrome (245 citations), followed by the 2014 New England Journal of Medicine review by Isbister and Bawaskar (211) and Chippaux's 2012 review of management options (174). The ten most cited records are listed in Table 4.

38 references in three co-citation clusters: foundational cardiovascular toxicity (18 references), myocardial injury and severity (7 references), and treatment and syntheses (13 references), with 671 links and a total link strength of 3,812 (Figure 5; Table 6). These clusters spanned 1970-2000 (median, 1990,5), 1998-2007 (median, 2003), and 1999-2014 (median, 2010), respectively. No reference published after 2014 met the 20-citation threshold. Chippaux and Goyffon's[1] 2008 paper had the highest total link strength (399) and was cited by 69 included records, followed by Gueron's 1970 paper (307; cited by 51), Bahloul et al.'s[3] 2004 paper (301; cited by 35), and Abroug et al.'s[4] 1995 paper (304; cited by 37).

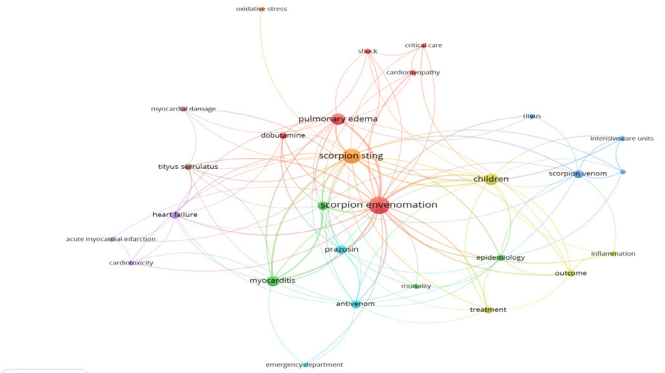

Figure 3. VOSviewer author-keyword co-occurrence network based on the 162 records with author keywords within the 239-record dataset. Node size represents keyword occurrence, node color represents cluster assignment, and links represent co-occurrence strength. The map contains 28 terms in eight clusters, 117 links, and a total link strength of 262

Table 4. Ten most cited records in the included dataset

First author	Year	Title	Source	Citations
Ismail	1995	The scorpion envenoming syndrome	Toxicon	245
Isbister	2014	Scorpion envenomation	New England Journal of Medicine	211
Chippaux	2012	Emerging options for the management of scorpion stings	Drug Design Development and Therapy	174
Abroug	1999	Serotherapy in scorpion envenomation: a randomised controlled trial	Lancet	132
Freire-Maia	1994	Approaches to the treatment of scorpion envenoming	Toxicon	130
Boyer	2009	Antivenom for critically ill children with neurotoxicity from scorpion stings	New England Journal Of Medicine	126
Gueron	1992	The cardiovascular-system after scorpion envenomation-a review	Journal Of Toxicology-Clinical Toxicology	126
Santos	2016	Clinical and epidemiological aspects of scorpionism in the world: a systematic review	Wilderness & Environmental Medicine	103
Ghalim	2000	Scorpion envenomation and serotherapy in morocco	American Journal of Tropical Medicine and Hygiene	97
Sofer	1988	Respiratory-failure in children following envenomation by the scorpion Leiurus-quinquestriatus-hemodynamic and neurological aspects	Toxicon	95

Citation counts reflect the WoS export retrieved on September 24, 2026 (5,346 citations across the included set)

Keyword and Co-citation Networks

After thesaurus-based harmonization, the author-keyword co-occurrence map, based on the 162 records with author keywords, included 28 terms in eight clusters, with 117 links and a total link strength of 262 (Figure 3 and 4; Table 5). "Scorpion envenomation" had the highest occurrence count (68) and total link strength (90), followed by "scorpion sting" (47 and 75). "Children" and "pulmonary edema" each occurred 26 times, with total link strengths of 38 and 36, respectively. "Myocarditis" occurred 20 times (total link strength, 35), while "echocardiography" and "prazosin" each occurred 14 times (27 and 26, respectively). In the overlay visualization, pulmonary edema had an earlier mean publication year (2009,3) than myocarditis (2016,3) and echocardiography (2016,9). The cited-reference co-citation network included

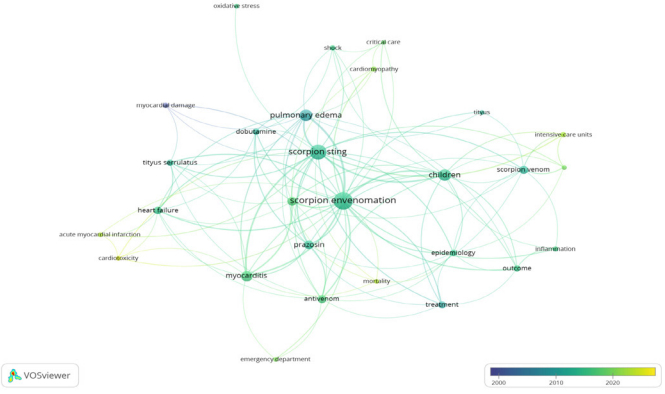

Figure 4. VOSviewer overlay visualization of the author-keyword co-occurrence network

Node color represents average publication year on the displayed 2000-2025 scale; node sizes and links match Figure 3

Table 5. Author-keyword clusters in the VOSviewer co-occurrence map

Cluster	Interpretive label	Author keyword	Occurrences	Links	Total link strength	Mean publication year
1	Cardiopulmonary and critical care	Scorpion envenomation	68	24	90	2014,3
		Pulmonary edema	26	14	36	2009,3
		Dobutamine	7	7	13	2012,1
		Cardiomyopathy	4	4	6	2020,3
		Shock	4	6	7	2015,3
		Critical care	3	5	6	2018,0
2	Cardiac assessment and epidemiology	Myocarditis	20	11	35	2016,3
		Echocardiography	14	13	27	2016,9
		Epidemiology	7	10	15	2014,1
		Mortality	3	5	5	2022,0
3	Species, venom, and health-system terms	Scorpion venom	11	10	15	2012,5
		Intensive care units	4	4	10	2021,5
		Public health	3	5	9	2019,0
		Tityus	3	3	4	2012,3
4	Pediatric outcomes and treatment	Children	26	15	38	2014,1
		Treatment	8	7	12	2010,4
		Outcome	6	7	13	2015,2
		Inflammation	4	4	7	2015,8
5	Cardiac complications	Heart failure	9	10	18	2014,6
		Acute myocardial infarction	3	4	5	2021,7
		Cardiotoxicity	3	5	7	2024,0
6	Acute treatment and care setting	Prazosin	14	10	26	2013,3
		Antivenom	11	12	20	2016,5
		Emergency department	3	3	4	2019,3
7	No interpretive label assigned	Scorpion sting	47	23	75	2013,6
		Oxidative stress	3	1	1	2015,7
8	No interpretive label assigned	Tityus serrulatus	6	8	15	2013,0
		Myocardial damage	4	4	5	2001,5

Based on the 162 records with author keywords within the fixed 239-record dataset; full counting; minimum occurrence threshold: 3; thesaurus harmonization as described in methods. This table provides the cluster membership and term-level metrics underlying Figures 3 and 4. Cluster numbers are VOSviewer assignments; labels are interpretive summaries used in the discussion. Clusters 7 and 8 each contain only two terms and were not assigned separate interpretive labels. Occurrences are the number of records containing the keyword. Links and total link strength are counted from each term's perspective; across all terms they sum to twice the network totals (117 links; total link strength 262). Mean publication year is the average WoS publication year of records containing the term and corresponds to the node colors in Figure 4

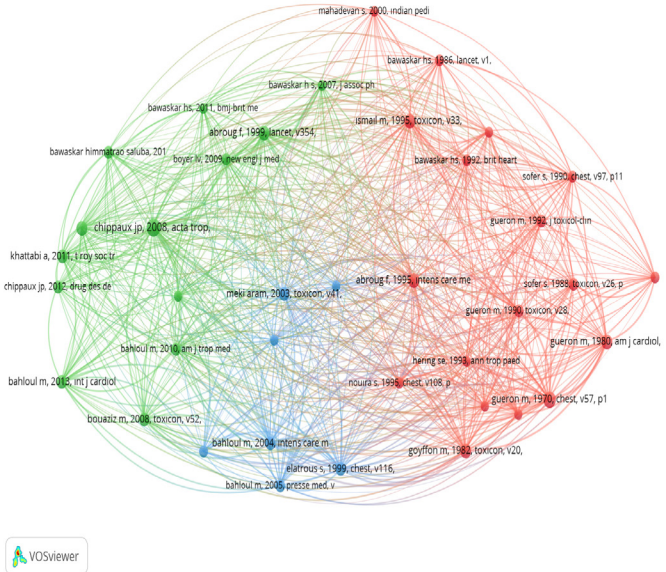

Figure 5. Cited-reference co-citation network generated in VOSviewer from the 239-record WoS export. Node size represents the number of included records citing each reference, node color represents cluster assignment, and links represent co-citation strength. The map contains 38 cited references in three clusters, 671 links, and a total link strength of 3,812

DISCUSSION

The present bibliometric analysis reveals a clinically coherent body of literature centered on acute cardiac and pulmonary injury, pediatric envenomation, and treatment-related themes. Its intellectual structure is further defined by three interconnected co-citation clusters representing foundational cardiovascular toxicity, myocardial injury and severity, and treatment and syntheses (Figure 5; Table 6). Notably, no cited reference published after 2014 reached the selected co-citation threshold, indicating that the most strongly shared reference base remains anchored in earlier literature. By integrating keyword co-occurrence with co-citation analysis, this study extends broader bibliometric work on scorpionism epidemiology and venom science by focusing specifically on cardiopulmonary complications and critical care.[17,18] Annual publication output fluctuated over time rather than showing uninterrupted growth, and the partial 2026 count should therefore be interpreted cautiously.

The co-citation structure reflects successive but overlapping layers of the field. The foundational cardiovascular toxicity cluster includes early descriptions of cardiovascular effects and

Table 6. Cited references in the VOSviewer co-citation map

VOSviewer cited-reference label	Cluster	Year	Occurrences (citing records)	Links	Total link strength
Gueron M, Chest, 57:156	1: Foundational cardiovascular toxicity	1970	51	37	307
Gueron M, Am J Cardiol, 45:979	1: Foundational cardiovascular toxicity	1980	41	35	230
Goyffon M, Toxicon, 20:337	1: Foundational cardiovascular toxicity	1982	41	35	279
Bawaskar HS, Lancet, 1:510	1: Foundational cardiovascular toxicity	1986	23	34	134
Gueron M, Toxicon, 25:121	1: Foundational cardiovascular toxicity	1987	25	31	123
Sofer S, Toxicon, 26:931	1: Foundational cardiovascular toxicity	1988	27	36	204
Gueron M, Toxicon, 28:1005	1: Foundational cardiovascular toxicity	1990	29	36	253
Rahav G, Chest, 97:1478	1: Foundational cardiovascular toxicity	1990	21	36	165
Sofer S, Chest, 97:118	1: Foundational cardiovascular toxicity	1990	23	36	181
Abroug F, Chest, 100:1057	1: Foundational cardiovascular toxicity	1991	20	34	182
Bawaskar HS, Brit Heart J, 68:478	1: Foundational cardiovascular toxicity	1992	25	35	145
Gueron M, J Toxicol-Clin Toxic, 30:245	1: Foundational cardiovascular toxicity	1992	29	36	159
Hering SE, Ann Trop Paediatr, 13:173	1: Foundational cardiovascular toxicity	1993	20	37	169
Sofer S, J Pediatr-Us, 124:973	1: Foundational cardiovascular toxicity	1994	20	34	154
Abroug F, Intens Care Med, 21:629	1: Foundational cardiovascular toxicity	1995	37	37	304
Ismail M, Toxicon, 33:825	1: Foundational cardiovascular toxicity	1995	39	37	238
Nouira S, Chest, 108:682	1: Foundational cardiovascular toxicity	1995	22	36	200
Mahadevan S, Indian Pediatr, 37:504	1: Foundational cardiovascular toxicity	2000	21	27	100
Abroug F, Lancet, 354:906	2: Treatment and syntheses	1999	39	37	266
Bouaziz M, Clin Toxicol, 44:293	2: Treatment and syntheses	2006	21	36	159
Bawaskar H S, J Assoc Physicians India, 55:14	2: Treatment and syntheses	2007	20	36	156
Bouaziz M, Toxicon, 52:918	2: Treatment and syntheses	2008	31	35	209
Chippaux JP, Acta Trop, 107:71	2: Treatment and syntheses	2008	69	37	399
Boyer LV, New Engl J Med, 360:2090	2: Treatment and syntheses	2009	24	37	193
Bahloul M, Am J Trop Med Hyg, 83:1084	2: Treatment and syntheses	2010	30	37	226
Bawaskar HS, Bmj-Brit Med J, 342	2: Treatment and syntheses	2011	20	36	152
Khattabi A, T Roy Soc Trop Med H, 105:364	2: Treatment and syntheses	2011	33	35	188
Bawaskar Himmatrao Saluba, J Assoc Physicians India, 60:46	2: Treatment and syntheses	2012	27	31	108
Chippaux JP, Drug Des Dev Ther, 6:165	2: Treatment and syntheses	2012	27	33	119
Bahloul M, Int J Cardiol, 162:86	2: Treatment and syntheses	2013	33	33	200
Isbister GK, Bawaskar HS, New Engl J Med, 371:457	2: Treatment and syntheses	2014	37	37	200
Karnad DR, Heart, 79:485	3: Myocardial injury and severity	1998	20	36	116
Elatrous S, Chest, 116:748	3: Myocardial injury and severity	1999	33	37	290
Cupo P, Toxicon, 40:823	3: Myocardial injury and severity	2002	20	37	183
Meki Aram, Toxicon, 41:129	3: Myocardial injury and severity	2003	36	36	270
Bahloul M, Intens Care Med, 30:461	3: Myocardial injury and severity	2004	35	37	301
Bahloul M, Presse Med, 34:115	3: Myocardial injury and severity	2005	27	36	207
Cupo P, Int J Cardiol, 116:98	3: Myocardial injury and severity	2007	25	34	155

Fixed 239-record dataset; full counting; minimum inclusion threshold: each cited reference had to be cited by at least 20 of the 239 included records. Cluster assignments and network values reproduce the retained VOSviewer map. Cluster labels are interpretive summaries. Cluster 1 (foundational cardiovascular toxicity) comprised 18 references published 1970-2000 (median year, 1990,5); cluster 3 (myocardial injury and severity) comprised 7 references published 1998-2007 (median, 2003); and cluster 2 (treatment and syntheses) comprised 13 references published 1999–2014 (median, 2010). "Occurrences (citing records)" is the number of records in the analyzed export citing that reference; "Links" is the number of co-citation links; total link strength is the sum of link weights. Reference labels are readable transcriptions of VOSviewer labels; network values were not recalculated or changed. VOSviewer: Visualization of similarities viewer

severe envenomation by Gueron, Sofer, Ismail, and Bawaskar. The myocardial injury and severity cluster brings together studies of myocardial dysfunction, hemodynamic assessment, and clinical severity, including work by Bahloul, Elatrous, Cupo, Karnad, and Meki. The treatment and syntheses cluster includes the Abroug and Boyer trials, Chippaux's management review, and the review by Isbister and Bawaskar.[2,6,9,10] These cluster labels are interpretive summaries of the underlying co-citation structure. Their publication periods span 1970-2000 (median year, 1990,5), 1998-2007 (median, 2003), and 1999-2014 (median, 2010), respectively, with substantial temporal overlap. The predominance of older references should not be interpreted as evidence that contemporary research has slowed, because more recent publications have had less time to accumulate citations. Co-citation patterns also depend on reference matching and the selected threshold.

Document-level citation counts provide a related but distinct perspective on scholarly influence. The citation profile was led by Ismail's 1995 syndrome description, followed by the

2014 New England Journal of Medicine review by Isbister and Bawaskar and Chippaux's 2012 management review. These publications represent syndrome description, clinical synthesis, and management-oriented literature, respectively. Citation counts indicate scholarly visibility rather than current guideline status or clinical effectiveness; for example, the Boyer trial focused on neurotoxicity in critically ill children rather than specifically on cardiopulmonary outcomes.[10]

The author-keyword network provides a complementary view of the field's thematic structure. Eight clusters were identified, with complete membership and term-level metrics provided in **Table 5**. The largest clusters grouped cardiopulmonary and critical care terms, cardiac assessment and epidemiology, species/venom and health-system terms, and pediatric outcomes and treatment. Smaller clusters represented cardiac complications, acute treatment and care setting, and two two-term groupings that were not assigned separate interpretive labels. Pulmonary edema, myocarditis, and echocardiography link major cardiopulmonary complications with their clinical assessment, whereas antivenom, prazosin, and dobutamine represent recurrent management topics. In the overlay visualization, myocarditis and echocardiography appeared later on average than pulmonary edema. This pattern reflects the timing of indexed author-keyword use and should not be interpreted as a change in disease incidence or clinical practice. Critical care-specific terminology was less prominent in the author-keyword network than cardiopulmonary manifestations: "critical care" and "intensive care units" occurred three and four times, respectively, whereas several management-related search terms, including mechanical ventilation, intubation, vasopressors, and ECMO, did not meet the three-occurrence threshold. Thus, critical care management was less frequently represented as an explicit author-keyword theme, although this should not be interpreted as an absence of critical care content in the underlying literature.

The mapped themes are consistent with the range of questions addressed in the contemporary clinical literature. A meta-analysis of controlled trials and the Brazilian clinical protocol show that treatment evidence and guidance are organized according to syndrome, species, and care setting.[11,22] Studies in the corpus also address point-of-care ultrasound, candidate cardiac biomarkers, noninvasive cardiac output monitoring, prediction of intensive care unit transfer, and extracorporeal support.[12-16] These examples illustrate the types of focused clinical questions represented in the literature rather than their prevalence or relative clinical importance. For clinicians, the bibliometric maps can serve as an entry point to the evidence by identifying mechanistic and severity studies, treatment trials, and clinical syntheses that can subsequently be appraised within the relevant species and care setting.

The geographic distribution of the literature also reflects established centers of research activity. India, Turkiye, Tunisia, and Brazil were among the most frequently represented affiliation countries, alongside Israel and the United States. These counts represent WoS-Indexed institutional addresses and should not be interpreted as measures of disease burden or the total research contribution of endemic countries. Costa et al.'s[17] Scopus-based bibliometric analysis of scorpionism likewise identified Brazil and Iran among leading contributors, although its broader epidemiological scope precludes direct rank comparison. Brazil contributed 21 records in the present dataset, and all six records using Tityus serrulatus as an author keyword included at least one Brazilian affiliation. This concentration is consistent with the major role of Tityus serrulatus in Brazilian scorpion accidents.[23]

The bibliometric findings also point to several areas where further clinical research could be valuable. The co-citation clusters provide a structured basis for focused evidence syntheses on cardiopulmonary mechanisms, treatment strategies, myocardial dysfunction, and clinical severity. Greater consistency in clinical definitions and more complete use of author keywords would improve comparability across specialties. The cited clinical literature also supports further prospective multicenter evaluation and external validation of diagnostic and prognostic tools.[8,11-14,22] Questions concerning treatment benefit, certainty of evidence, and unmet clinical need, however, require dedicated clinical synthesis rather than bibliometric analysis.

Limitations

This study has several limitations. Restricting retrieval to the Web of Science Core Collection may omit relevant literature indexed elsewhere. Author-keyword and co-citation maps depend on metadata completeness, thesaurus harmonization, cited-reference matching, and selected thresholds; author keywords were available for 162 of 239 records. The 2026 publication count is partial, and citation-based indicators reflect scholarly visibility rather than study quality or clinical effectiveness.

CONCLUSION

The WoS-indexed literature on cardiopulmonary complications and critical care in scorpion envenomation is organized around acute cardiac and pulmonary injury, pediatric envenomation, and treatment-related themes. Keyword and co-citation mapping delineated a field that links foundational cardiovascular toxicity with subsequent work on myocardial injury, severity assessment, and treatment. Together, these maps provide clinicians and researchers with a structured overview of the literature and can help identify relevant mechanistic, diagnostic, prognostic, and therapeutic evidence for focused synthesis. As a bibliometric analysis, however, these findings describe the structure and scholarly visibility of the literature rather than complication incidence or comparative treatment effectiveness.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study analyzed bibliographic records and did not involve human participants, animals, or identifiable patient-level data. Ethics committee approval and informed consent were not applicable.

Informed Consent

Since the study was conducted without the participation of any living being, no written consent form was obtained.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The author declares no conflicts of interest related to this study.

Financial Disclosure

The author received no financial support for the conduct or publication of this research.

Author Contributions

The author is solely responsible for the entirety of conception, execution, analysis, and writing of the manuscript.

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Review

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The gut microbiota-follicular axis in pilonidal sinus disease: lessons from hidradenitis suppurativa and surgical implications

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ABSTRACT

Pilonidal sinus disease (PSD) and hidradenitis suppurativa (HS) are both members of the follicular occlusion tetrad-a group of chronic inflammatory disorders sharing a common pathogenetic basis of follicular occlusion, subcutaneous tract formation, and recurrent abscess development. While PSD has traditionally been approached as a purely mechanical and anatomical problem, emerging evidence from the HS literature reveals a compelling gut microbiota-skin axis that may be equally operative in PSD. In HS, intestinal dysbiosis, increased intestinal permeability, and elevated systemic lipopolysaccharide levels have been documented through multiple study designs including Mendelian randomization analyses, providing causal evidence that gut microbial imbalance drives systemic immune dysregulation and amplifies local follicular inflammation. Both diseases harbor dysbiotic, anaerobic-predominant, biofilm-forming local microbiota-particularly *Prevotella* and *Finegoldia* species-capable of perpetuating chronic inflammation and resisting surgical eradication. This narrative review synthesizes current evidence on the gut microbiota-follicular axis in HS and PSD, examines the shared immunological and microbial mechanisms underlying both conditions, and proposes that the gut-skin axis insights established in HS are pathobiologically transferable to PSD. Importantly, PSD carries an understudied but emerging association with inflammatory bowel disease, mirroring the established HS-IBD comorbidity and further supporting a shared gut-driven inflammatory pathway. Microbiome-targeted adjunctive strategies-including perioperative probiotic supplementation, biofilm-disrupting local therapies, and dietary modulation-represent rational, evidence-informed approaches to reducing recurrence and postoperative complications in PSD surgery. We propose a structured research agenda for microbiome-integrated prospective PSD cohort studies and call for the first randomized trials of gut-targeted interventions in PSD surgical management. This is a narrative, non-systematic review; direct microbiome data in PSD remain limited, and the proposed framework requires prospective validation.

Keywords: Pilonidal sinus disease, hidradenitis suppurativa, gut microbiota, gut-skin axis, dysbiosis, wound healing

INTRODUCTION

Pilonidal sinus disease (PSD) is a chronic, recurrent inflammatory condition of the sacrococcygeal region affecting predominantly young males in the second and third decades of life, with an estimated annual incidence of 26 per 100,000 persons in high-income countries.[1,2] Despite a broad repertoire of surgical approaches-from midline excision to off-midline flap reconstructions and minimally invasive endoscopic techniques-recurrence rates following surgical treatment range from 10% to 30%, and a meaningful proportion of patients experience repeated episodes of disease.[3,4] The dominant explanatory framework for PSD remains mechanical: hair follicle distension, skin maceration in the intergluteal cleft, and forceful hair penetration into subcutaneous tissue drive sinus formation.[5] Yet this anatomical paradigm fails to explain why certain individuals experience chronic recalcitrant disease despite technically satisfactory surgery, or why systemic inflammatory markers are elevated in a subset of patients.

Hidradenitis suppurativa (HS)-a chronic, debilitating inflammatory disorder of the pilosebaceous unit-shares with PSD a common pathogenetic root: follicular occlusion.[6,7] Both conditions belong to the follicular occlusion tetrad (FOT), a nosological grouping that includes HS, PSD, acne conglobata, and dissecting cellulitis of the scalp, all of which demonstrate follicular hyperkeratosis, subcutaneous tract formation, anaerobic-dominant microbiota, and high surgical recurrence rates.[8,9] A 2023 systematic review and meta-analysis confirmed a significantly elevated prevalence of PSD among HS patients compared with unaffected controls, with some authors proposing that PSD may represent a uni-localized anatomical variant of HS.[10]

The past decade has seen remarkable advances in understanding the gut microbiota-skin axis in HS. Multiple studies have documented intestinal dysbiosis in HS patients-characterized by reduced microbial diversity, depletion of short-chain fatty acid (SCFA)-producing commensals, and elevated intestinal

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permeability-with Mendelian randomization analyses providing causal evidence linking specific gut microbial taxa to HS susceptibility.[11,12] Concurrently, the established comorbidity between HS and inflammatory bowel disease (IBD) points to shared immunological pathways operating at the gut-immune-skin interface.[13] Crucially, these mechanisms-systemic LPS translocation, SCFA depletion, and Th17/Treg imbalance-are precisely those postulated to impair wound healing, amplify follicular inflammation, and sustain chronic sinus disease.

If PSD and HS share not only their follicular pathogenesis but also their systemic immune and microbial dysregulation, then the gut microbiota-skin axis insights established in HS carry direct and transferable implications for PSD-both in understanding its pathophysiology and in designing rational adjunctive therapies. This narrative review aims to: (1) establish the shared pathobiological basis of PSD and HS within the follicular occlusion tetrad framework; (2) synthesize evidence for gut microbiota dysregulation in HS and its mechanistic relevance to follicular inflammation and wound healing; (3) characterize the local microbiome of PSD and its surgical implications; (4) evaluate the emerging PSD-IBD relationship as evidence of a shared gut-driven inflammatory axis; and (5) propose microbiome-targeted adjunctive strategies for PSD surgical management and a structured future research agenda.

PILONIDAL SINUS DISEASE AND HIDRADENITIS SUPPURATIVA: A SHARED PATHOBIOLOGICAL FRAMEWORK

The Follicular Occlusion Tetrad

The concept of the FOT, first consolidated in the 1970s, recognizes that PSD, HS, acne conglobata, and dissecting cellulitis of the scalp share a common initiating event: hyperkeratotic plugging of the follicular infundibulum.[8] In each condition, follicular occlusion leads to retention of sebaceous secretions, follicular distension, and eventual rupture into the dermis and subcutaneous tissue, triggering a foreign body-type granulomatous response and recruitment of neutrophils, macrophages, and lymphocytes.[6] The resulting chronic inflammatory cycle perpetuates tract formation, abscess recurrence, and fibrosis. A 2025 histologic and immunohistochemical study comparing PSD and HS tissue microenvironments found comparable expression of cytokeratin 5/6, KLK7, and filaggrin in both conditions, confirming their shared epithelial and inflammatory signatures at the tissue level.[14]

The clinical parallels are equally striking. Both PSD and HS present predominantly in young adults, are associated with obesity, metabolic syndrome, and smoking as modifiable risk factors, and are characterized by high post-surgical recurrence rates driven by factors beyond technical surgical adequacy.[3,15] A 2025 study in the Journal of the American Academy of Dermatology compared malignant transformation risk between HS and PSD, further cementing their classification as related follicular disorders on a shared biological spectrum.[16]

Microbial Overlap Between Pilonidal Sinus Disease (PSD) and HS

Both PSD and HS harbor dysbiotic, anaerobic-predominant local microbiota that differ substantially from adjacent healthy skin. In HS, skin microbiome studies have consistently identified *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Prevotella*, *Porphyromonas*, and anaerobic streptococci as dominant taxa in lesional tissue, with significant enrichment of biofilm-forming organisms.[17,18] In PSD, 16S rRNA sequencing has similarly revealed a predominance of *Prevotella bivia*, *Finegoldia magna*, *Peptostreptococcus*, and *Bacteroides* species within sinus tracts.[19,20] The comparative microbiological and clinicopathological features of HS and PSD are summarized in **Table**. The functional convergence is notable: in both diseases, local dysbiosis is characterized by organisms capable of TLR2/4-mediated immune activation, biofilm formation, and proteolytic extracellular matrix degradation-mechanisms that collectively sustain chronic inflammation and impair wound closure.[21,22]

Biofilm formation is a particularly important shared feature. In both conditions, polymicrobial biofilms embedded within sinus and fistula tracts exhibit markedly elevated antibiotic tolerance-estimated at 100-1,000-fold higher than planktonic forms-potentially explaining the failure of systemic antibiotic therapy to achieve disease resolution and the high recurrence rates observed after surgical drainage alone.[23] Recognition of this shared biofilm biology has prompted interest in biofilm-disrupting local therapies in both HS and PSD, as detailed in section 5.

Table. Comparative clinicopathological and microbiological features of HS and PSD within the follicular occlusion tetrad framework

Feature	Hidradenitis suppurativa	Pilonidal sinus disease	Shared?
Pathogenetic basis	Follicular occlusion & rupture	Follicular occlusion & hair penetration	✓ Yes
Classification	Follicular occlusion tetrad	Follicular occlusion tetrad	✓ Yes
Local microbiota	*Anaerobes, Staphylococcus, Prevotella*	*Prevotella bivia*, *Finegoldia magna*	✓ Yes
Biofilm formation	Documented, clinically relevant	Documented, clinically relevant	✓ Yes
Gut-skin axis evidence	Mendelian randomization, cohort data	Hypothesized, no direct data	Partial
Intestinal dysbiosis	↑ Permeability, ↓ diversity (proven)	Unexplored	Extrapolation
Systemic inflammation	↑ TNF-α, IL-1β, IL-17 (systemic)	Local dominant, systemic unclear	Partial
IBD comorbidity	Established (OR 2-4)	Reported, understudied	Partial
Surgical recurrence	High (30-50%)	High (10-30%)	✓ Yes
Probiotic evidence	Emerging case reports	None published	Gap

HS: Hidradenitis suppurativa, PSD: Pilonidal sinus disease, ✓ Yes: Feature confirmed in both conditions, TNF-α: Tumor necrosis factor-alpha, IL-1β: Interleukin-1 beta, IL-17: Interleukin-17, IBD: Inflammatory bowel disease, SCFA: Short-chain fatty acids, OR: Odds ratio, Partial: Confirmed in one, suggested in other, Extrapo-lation: Mechanistically inferred from HS data, Gap: Unaddressed in PSD literature

GUT MICROBIOTA IN HIDRADENITIS SUPPURATIVA: THE EVIDENCE BASE

Intestinal Dysbiosis in Hidradenitis Suppurativa (HS): Observational Data

Growing evidence demonstrates that HS patients exhibit measurable alterations in gut microbiota composition compared with healthy controls. A 2024 prospective cohort study by Lelonek and Szepietowski[12] assessed fecal microbiome composition in 80 participants (40 HS patients, 40 controls) using next-generation sequencing, identifying significant differences in the relative abundance of specific taxa-including enrichment of pro-inflammatory Proteobacteria and depletion of SCFA-producing Firmicutes-in HS patients compared to controls.[24] A subsequent 2025 study by the same group using comprehensive metagenomic analysis identified correlations between specific gut microbial functional pathways, LPS biosynthesis gene abundance, and HS disease severity as measured by Hurley staging.[25] These data suggest that gut dysbiosis in HS is not a non-specific epiphenomenon but reflects biologically relevant alterations in taxa and pathways with direct immunological consequences.

A systematic review of skin and gut microbiome alterations in HS (Moreno-Arrones et al.,[17] 2023) identified consistent patterns of reduced gut microbial diversity and decreased abundance of *Faecalibacterium prausnitzii*-a key butyrate producer and anti-inflammatory commensal-across multiple study designs. Reduced *Faecalibacterium* abundance has been independently associated with increased intestinal permeability, systemic LPS translocation, and elevated serum IL-6 and TNF-α levels in inflammatory conditions beyond HS, providing a mechanistic link between gut dysbiosis and systemic immune amplification relevant to all FOT members.[26]

Causal Evidence: Mendelian Randomization (MR)

Perhaps the most compelling evidence for a causal gut-HS relationship comes from a 2024 two-sample MR study by Liu et al.,[11] which used genome-wide association study (GWAS) data to assess causal relationships between specific gut microbial taxa and HS susceptibility. The MR framework-which uses genetic variants as instrumental variables to minimize confounding-identified causal associations between reduced abundance of *Bifidobacterium* and *Lactobacillus* genera and increased HS risk, as well as between elevated *Ruminococcus gnavus* a pro-inflammatory taxon associated with intestinal barrier disruption-and HS susceptibility.[11] These findings satisfy Hill's criteria for causality more robustly than observational data alone, and represent the strongest evidence to date that gut microbiome composition is not merely correlated with HS but causally involved in its pathogenesis.

Hidradenitis Suppurativa (HS)-Inflammatory Bowel Disease (IBD) Comorbidity: a Window into the Gut-Follicular Axis

The epidemiological association between HS and IBD is well-established and provides independent clinical evidence for shared gut-immune pathways operating across the FOT. Multiple population-based studies have documented odds ratios of 2.0 to 4.0 for IBD in HS patients compared with unaffected controls, with Crohn's disease showing a particularly strong association-likely reflecting the shared Th17-dominant immune environment, fistula formation biology, and genetic susceptibility loci (including NOD2 and FUT2).[13] The HS-IBD association is bidirectional: HS patients have elevated IBD risk, and IBD patients have elevated HS prevalence. Mechanistically, both conditions feature elevated intestinal permeability, dysbiosis-driven Th17 expansion, and tumor necrosis factor-alpha (TNF-α)-mediated mucosal inflammation-explaining why anti-TNF biologics (adalimumab) are effective in both.[13,27]

The emergence of case series and retrospective data suggesting a PSD-IBD comorbidity-while less well-characterized than the HS-IBD relationship-provides preliminary evidence that the same gut-immune axis may operate in PSD. Given the FOT classification shared by HS and PSD, and the mechanistic plausibility of a shared gut-inflammatory axis, systematic evaluation of IBD prevalence in PSD cohorts is warranted and represents a meaningful research gap.

THE GUT MICROBIOTA-FOLLICULAR AXIS: MECHANISMS TRANSFERABLE TO PSD

Short-chain Fatty Acid (SCFA) Depletion and Systemic Immune Dysregulation

The key mechanistic pathways linking gut dysbiosis to follicular skin disease are illustrated in **Figure**. SCFAs-principally butyrate, propionate, and acetate-are produced by colonic fermentation of dietary fiber by resident commensals including *Faecalibacterium prausnitzii*, *Roseburia*, and *Bifidobacterium* species. SCFAs exert broad immunomodulatory effects: butyrate inhibits histone deacetylase (HDAC) activity, suppresses NF-κB signaling, promotes regulatory T cell (Treg) differentiation, and reinforces intestinal tight junction integrity.[28] In states of gut dysbiosis-characterized by depletion of SCFA-producing taxa-these protective effects are lost, leading to systemic pro-inflammatory skewing. SCFA depletion has been directly associated with impaired keratinocyte proliferation, reduced fibroblast migration velocity, and diminished angiogenic signaling in wound healing models, providing a mechanistic link between gut dysbiosis and delayed cutaneous wound closure.[29] In the context of PSD surgery-which requires weeks of open wound healing in a highly contaminated anatomical site-SCFA-driven wound healing impairment could meaningfully contribute to poor outcomes.

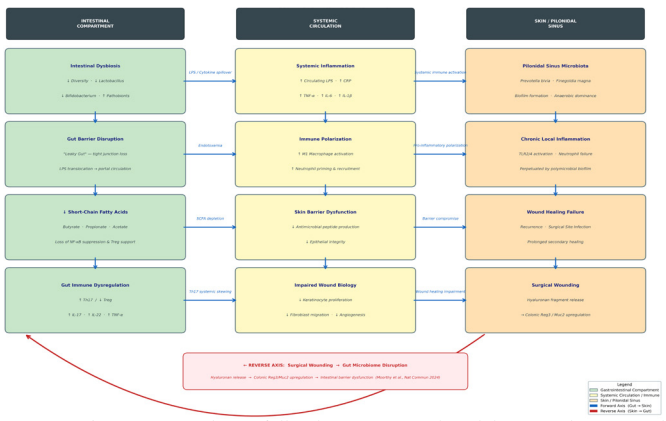

Figure. The gut microbiota-follicular axis in pilonidal sinus disease and hidradenitis suppurativa. The shared follicular occlusion tetrad framework places both conditions within a common pathobiological space

Gut dysbiosis drives systemic immune dysregulation through three parallel pathways: (1) SCFA depletion impairing Treg differentiation and wound healing; (2) intestinal barrier dysfunction and LPS translocation driving systemic TNF-α and IL-6 elevation; and (3) Th17/Treg imbalance amplifying local follicular inflammation. The reverse axis-by which surgical wounding releases hyaluronan fragments that upregulate colonic Reg3/Muc2 and disrupt intestinal microbiome homeostasis-provides a bidirectional link between skin surgery and gut microbial disruption. SCFA: Short-chain fatty acids, LPS: Lipopolysaccharide, SSI: Surgical site infection, IBD: inflammatory bowel disease, TNF-α: Tumor necrosis factor-alpha

Intestinal Permeability and Systemic Lipopolysaccharide (LPS) Translocation

Gut dysbiosis in HS is associated with increased intestinal epithelial permeability and translocation of bacterial LPS into the portal and systemic circulation-a state termed metabolic endotoxemia.[30] Circulating LPS activates systemic TLR4 signaling, triggering M1 macrophage polarization, neutrophil priming, and elevated production of TNF-α, IL-1β, and IL-6. In the context of PSD, this systemic inflammatory tone may amplify local follicular inflammatory cascades, impair the resolution phase of wound healing, and lower the threshold for recurrent abscess formation. Elevated serum LPS levels have been demonstrated in HS patients and correlate with disease severity,[30] suggesting that LPS endotoxemia represents a quantifiable and potentially modifiable biomarker of gut-driven systemic inflammation in FOT diseases.

Th17/Treg Imbalance and Follicular Immunity

Gut dysbiosis drives systemic Th17/Treg imbalance through multiple pathways: reduced butyrate production impairs Treg differentiation from naïve T cells, while dysbiosis-driven segmented filamentous bacteria (SFB) expansion promotes Th17 polarization.[31] The resulting excess of IL-17A, IL-17F, and IL-22 in the systemic circulation has been demonstrated in both HS and PSD patients compared with controls. IL-17 signaling at the skin level promotes neutrophil recruitment, keratinocyte activation, and amplification of the inflammatory cascade within follicular units.[32] In PSD specifically, the anaerobic microbiota of sinus tracts-particularly *Prevotella* species-directly activate TLR2/4 signaling on resident macrophages, which in a Th17-primed systemic environment may result in disproportionate inflammatory amplification and impaired resolution. This mechanistic convergence suggests that gut-driven Th17 excess is not merely a bystander phenomenon in PSD but a pathophysiologically relevant contributor to chronicity.

MICROBIOME-TARGETED THERAPEUTIC STRATEGIES IN PILONIDAL SINUS DISEASE (PSD) SURGERY

Perioperative Probiotic Supplementation

The strongest transferable evidence for microbiome intervention in surgical settings comes from randomized trials in colorectal surgery, where perioperative probiotic supplementation-primarily with *Lactobacillus rhamnosus* GG, Bifidobacterium longum, and multi-strain formulations-has consistently demonstrated reductions in surgical site infection (SSI) rates, shortened antibiotic treatment duration, and accelerated wound healing in meta-analyses.[33,34] The mechanistic basis is well-characterized: probiotics restore SCFA production, reinforce intestinal tight junction integrity, competitively exclude enteric pathogens, and modulate systemic immune polarization toward a Treg-dominant anti-inflammatory phenotype.[35] In HS, case reports and small pilot studies have documented symptom improvement and reduced flare frequency with oral probiotic supplementation, consistent with the gut-HS axis model.[36] No published trial has yet evaluated perioperative probiotics in PSD surgery, representing the most clinically proximate and methodologically tractable knowledge gap in the field.

Biofilm-Disrupting Local Therapies

Given the documented biofilm dominance in both PSD and HS sinus tracts, systemic antibiotics targeting planktonic bacteria provide inadequate local coverage of the biologically relevant pathogen population. In HS, topical clindamycin and systemic rifampicin combinations-which have anti-biofilm properties in addition to direct antimicrobial activity-are recommended in evidence-based guidelines, with mechanistic rationale grounded in biofilm disruption.[15] For PSD, a prospective randomized trial by Arslan et al.[37] demonstrated that triclosan-coated sutures-which provide sustained antimicrobial activity at the wound interface-significantly reduced SSI rates compared with conventional sutures. Antiseptic wound irrigation with dilute hypochlorite or povidone-iodine solutions, and more recently negative pressure wound therapy (NPWT), represent further approaches to reducing local microbial bioburden in the early postoperative period.[38] Bacteriophage-based therapies targeting biofilm-embedded *Prevotella* and Staphylococcal species represent an emerging frontier applicable to both HS and PSD, and a comprehensive recent review by Singh et al.[39] provides further guidance on the parallel surgical management of these two conditions.

Dietary and Lifestyle Modulation

Dietary modification targeting gut microbiota composition represents a low-risk, accessible adjunctive strategy supported by the HS literature. A Mediterranean-pattern diet-rich in fermentable dietary fiber, polyphenols, and omega-3 fatty acids-has been associated with increased fecal SCFA concentrations, reduced intestinal permeability, and lower systemic inflammatory markers in HS patients.[24] Obesity-a shared risk factor for both HS and PSD-is independently associated with gut dysbiosis and reduced microbial diversity, and weight loss has been shown to improve HS outcomes through mechanisms that include microbiome normalization.[15] For PSD, structured preoperative dietary intervention as part of a prehabilitation pathway, targeting gut microbiome optimization prior to surgical wounding, represents a testable and mechanistically rational strategy.

FUTURE RESEARCH AGENDA

The framework proposed in this review generates several high-priority research questions for the PSD field. First, fecal microbiome profiling should be incorporated into prospective PSD surgical cohort studies, comparing alpha- and beta-diversity, SCFA-producing taxa abundance, and intestinal permeability biomarkers (zonulin, fecal calprotectin) between primary and recurrent disease, and correlating these with postoperative outcomes. Second, the reverse skin-to-gut axis-demonstrated experimentally by Moorthy et al.,[40] who showed that dermal injury releases hyaluronan fragments that upregulate colonic Reg3/Muc2 and disrupt intestinal microbiome homeostasis-should be prospectively evaluated in PSD surgical cohorts through pre- and postoperative paired fecal sampling. Third, the PSD-IBD comorbidity should be systematically evaluated in large administrative database studies, paralleling the epidemiological methodology used to establish the HS-IBD relationship. Fourth, a multicenter randomized controlled trial evaluating perioperative probiotic supplementation in PSD surgery-with primary endpoints of wound healing duration and 12-month

recurrence, and secondary endpoints of SSI rate and fecal SCFA concentrations-is both feasible and urgently needed. Fifth, comparative microbiome profiling studies between HS and PSD using standardized tissue sampling and sequencing protocols would test the hypothesis of shared local dysbiotic signatures and identify common therapeutic targets. Sixth, Mendelian randomization analyses analogous to those conducted in HS should be performed using available PSD GWAS data to evaluate causal gut-PSD microbial associations.

Methodological standardization across future PSD microbiome studies is essential. Specimen collection protocols should specify anatomical sampling sites (sinus tract epithelium versus adjacent skin), storage conditions (RNAlater or immediate freezing at -80°C), DNA extraction methods, and sequencing depth targets. The establishment of multicenter PSD registries with embedded biobanking infrastructure would enable adequately powered microbiome-outcome association studies that single-center retrospective designs cannot provide.

CONCLUSION

Pilonidal sinus disease and hidradenitis suppurativa occupy a shared pathobiological space within the follicular occlusion tetrad, united by common mechanisms of follicular occlusion, dysbiotic local microbiota, biofilm-mediated chronicity, and high surgical recurrence. The robust evidence base linking gut microbiota dysregulation to HS through intestinal permeability, SCFA depletion, Th17 immune skewing, and causal Mendelian randomization data provides a well-evidenced framework that is mechanistically transferable to PSD. The emerging HS-IBD and PSD-IBD comorbidities further support the existence of a shared gut-driven inflammatory axis operative across the FOT. By reframing PSD within this gut-follicular axis framework-rather than as a purely mechanical anatomical problem-this review opens new avenues for understanding treatment failure and recurrence, and identifies microbiome-targeted adjunctive strategies as rational candidates for clinical investigation in PSD surgery.

The surgical community managing PSD has an opportunity to learn from the dermatological experience with HS and to accelerate microbiome research in its own field. Prospective cohort studies with integrated microbiome profiling, rigorous epidemiological evaluation of the PSD-IBD comorbidity, and the first randomized trials of perioperative probiotic supplementation in PSD surgery represent achievable near-term priorities. Ultimately, a microbiome-informed surgical approach to PSD-combining anatomical correction with systemic immune optimization-may represent the next frontier in reducing the disease's unacceptably high recurrence burden. As a narrative, non-systematic review, the present work is limited by the absence of direct microbiome data in PSD and the extrapolatory nature of the proposed gut-follicular axis framework; prospective validation in dedicated PSD cohorts is required before clinical translation.

ETHICAL DECLARATIONS

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This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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