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NIR-II biomedical optics: evolution and prospects from technological advances towards clinical translation

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Abstract: The second near-infrared window (NIR-II, 900-1880 nm) overcomes critical limitations of visible (360-760 nm) and NIR-I (760-900 nm) imaging—including restricted penetration depth, low signal-to-background ratio, and tissue autofluorescence—establishing its pivotal role for *in vivo* deep-tissue bioimaging. With exponential growth in NIR-II photodiagnosis and phototherapy research over the past decade, bibliometric analysis is essential to map the evolving landscape and guide strategic priorities. We systematically analyzed 2, 491 NIR-II-related publications (2009-2023) from the Web of Science Core Collection, employing scientometric tools for distinct analytical purposes: (a) VOSviewer, SCImago Graphica, and Gephi for co-authorship and co-occurrence network mapping; (b) the R bibliometrix package for tracking field evolution and identifying high-impact publications/journals. The search retrieved 2491 studies from 359 journals originating from 54 countries. The country with the most published articles is China. Chinese institutions drive >60% of publications, with Stanford University (USA) and Nanyang Technological University (Singapore) ranked as the top two institutions by research quality. International cooperation is becoming increasingly frequent. Fan Quli, Tang Benzhong and Dai Hongjie are the top 3 productive authors in this field. Keyword evolution identifies "photodynamic therapy" and "immunotherapy" as pivotal future directions. We summarize the most cited literatures and NIR-II imaging clinical trials. This study delineates the NIR-II research trajectory, highlighting China´s leadership, intensifying global collaboration, and interdisciplinary convergence. Future efforts should prioritize the novel NIR-II probe development for NIR-II imaging and clinical translation of photodynamic/immunotherapy combinational platforms.

Key words: second near-infrared window (NIR-II), biomedical optics, clinical translation, research trend

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近红外二区生物医学光学:从技术进展向临床转化的演进与展望

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摘要:近红外二区(NIR-II,900~1 880 nm)克服了可见光(360~760 nm)和近红外一区(760~900 nm)成像的关键局限性,包括受限的穿透深度、低信噪比和高组织自发荧光,确立了其在体内深部组织生物成像中的关键作用。随着近红外二区光诊断和光疗研究在过去十年中呈指数级增长,文献计量分析对于绘制不断变化的格局和指导战略重点至关重要。我们系统地分析了来自Web of Science核心合集的2491篇与NIR-II相关的出版物(2009~2023),采用科学计量工具进行不同的分析目的:(a)VOSviewer、SCImago Graphica和Gephi用于合著和共现网络映射;(b)R bibliometrix包,用于跟踪领域演变和识别高影响力出版物/期刊。该搜索从来自54个国家的359种期刊中检索到2 491项研究。发表文章最多的国家是中国。中国机构推动了超过60%的出版物,斯坦福大学(美国)和南洋理工大学(新加坡)在研究质量方面排名前两位。国际合作日益频繁。范曲立、唐本忠、戴洪杰是该领域三位最具生产力的作家。关键词进化将“光动力疗法”和“免疫疗法”确定为未来的关键方向。我们总结了被引用最多的文献和NIR-II成像相关临床研究。本研究描绘了NIR-II的研究轨迹,突出了中国的领导地位、加强全球合作和跨学科融合。未来的工作应优先考虑新型NIR-II探针的开发,用于NIR-II成像和光动力/免疫治疗组合平台的临床转化。

关 键 词:近红外二区;生物医学光学;临床转化;研究趋势

中图分类号:O43 **文献标识码**:A

Introdution

NIR-II window is widely used in the field of biomedical imaging and therapy. The use of NIR-II window reduces the influence of tissue scattering and minimizes autofluorescence compared with the traditional in vivo biological imaging using visible light and NIR-I window[1, 2]. It has unique advantages in imaging depth and spatial resolution [1, 3], and is generally considered a “biological window”. Dai Hongjie′s research team first reported a method to generate biocompatible fluorescent single-walled carbon nanotubes in 2009 [4], which expanded the window of in vivo fluorescence imaging. With the continuous development of the field, NIR-II window expanded from the original 1 000-1 700 nm to 900-1 880 nm [5]. More and more near-infrared fluorophores are available, such as rare-earth-doped nanoparticles[6, 7], quantum dots[8, 9], organic conjugated polymer nanoparticles[10, 11] and AIEgen [12, 13]. To date, NIR-II biological imaging technology has been widely used to help biomedical researchers for accurate diagnosis and treatment.

Bibliometric analysis is a statistical evaluation of published papers and academic research [14]. After extracting the words and phrases from literatures, different sorts of software are used for statistical analysis and visual processing to evaluate the link between different countries, institutions, authors and journals and reveal the hotspots and development trends in specific research fields [15, 16]. As a rising research method, bibliometric analysis provides us with a macro perspective and allows us to dig into the details in a certain field [17, 18].

Since 2009, hundreds of reviews related to NIR-II have been published, but there is no bibliometric analysis on this field. Here, we extracted data from the Web of Science Core Collection and made a historical review of the development of the NIR-II research in 2009-2023. Different sorts of bibliometrics software were used to analyze countries / regions, institutions, authors and keywords. A bibliometric comparison of four related therapeutic applications was also performed. Finally, we listed top 20 most influential documents in this field, top 20 most cited reference in the field and NIR-II imaging clinical trials. We hope to provide an overview of this field, create opportunities for cooperation among countries, institutions and authors, assess the status of journals in this field, and find hot topics, top papers and research trends.

1 Analysis Methods

1.1 Search strategy

We performed a literature search in the Web of Science Core Collection database on February 28, 2024. The retrieval strategies were TS=("near infrared") AND (TS=("900-1 880 nm")OR TS=("0. 9-1. 88 μm")OR TS

=("1 000-1 700 nm") OR TS=("1-1.7 μm") OR TS=("900-1 700 nm") OR TS=("0.9-1.7 μm") OR TS=("1 000-1 400 nm") OR TS=("1.0-1.4 μm") OR TS=("900-1 880 nm") OR TS =("0.9-1.88 μm") OR TS=("1 000-1 700 nm") OR TS=("1-1.7 μm") OR TS=("900-1 700 nm") OR TS=("0.9-1.7 μm") OR TS=("1 000-1 400 nm") OR TS =("1-1.4 μm")) OR (TS=("near-infrared") AND TS=("second window")) OR TS=(“second near-infrared”) OR TS= (NIR-II) OR TS=(“the second NIR window"). We wanted to include as many NIR-II articles as possible by adopting relatively complex strategies, so several wavelength ranges used since the development of NIR-II were selected. The publication year was limited to 2009-2023, and only the articles and reviews were included. Finally, 2,491 documents were obtained and analyzed. Then we used keywords to further classify them. Detailed inclusion criteria are shown in Figure 1.

1.2 Data analysis

Vosviwer 1.6.18, Gephi 0.9.2, SCImago Graphica Beta 1.0.17, and the R bibliometrix package v3.2.1 were used for bibliometric analysis. Venn diagram was performed by the R VennDiagram package v1.7.3. Calculation and graphing of publications and citations, scat-

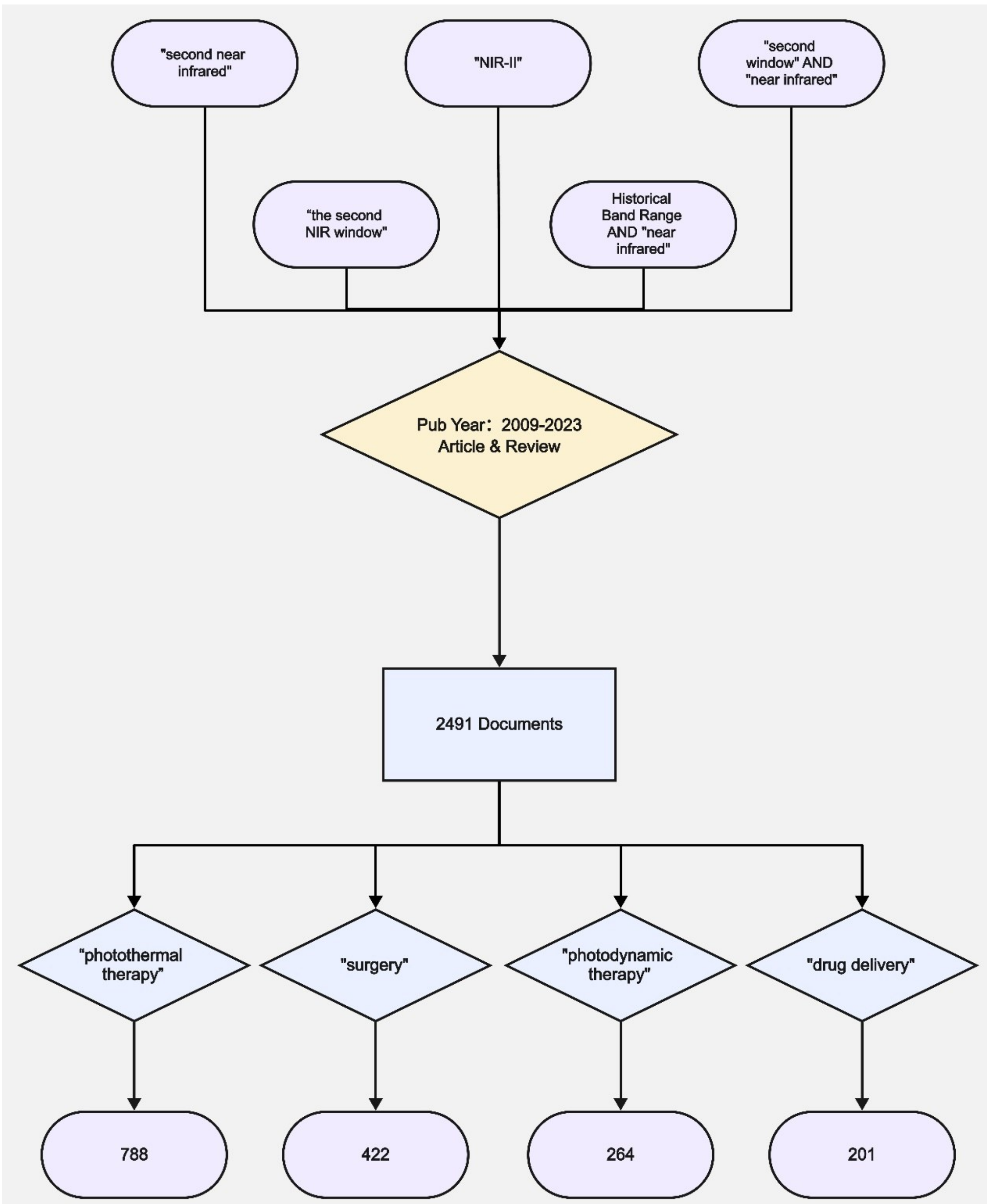

Fig. 1 Detailed document screening and classification process
图1 详细的文献筛选和分类过程

ter plot of impact factor and citations were performed by Graphpad Prism 6.01. The IFs were retrieved from the Journal Citation Reports 2023 (JCR 2023). The impact factor and the annual average citations of the four therapeutic applications related articles were proved to follow the normal distribution by IBM SPSS 19.0, and the test method was t-test.

2 Results

2.1 Growth of publication and citation

Selecting the optimal optical window is critical for successful in vivo fluorescence imaging. The high absorption of visible light (360-760 nm) by endogenous chromophores (e.g., hemoglobin) and the strong absorption of infrared light by water and lipids initially directed scientific focus toward the first near-infrared window (NIR-I, 760-900 nm) [13]. Compared to visible light, NIR-I experiences significantly reduced tissue absorption, along with diminished autofluorescence and scattering [14]. However, the penetration depth and spatial resolution achievable within the NIR-I window remained limited. A pivotal advancement occurred in 2009 when Kevin Welsher, working with Dai Hongjie's team, demonstrated in vivo imaging in the second near-infrared window (NIR-II, 1000-1700 nm) using carbon nanotube probes in mice. This work revealed the significant potential of the NIR-II window [13], later attributed to its further reduced scattering and favorable absorption profile. Additionally, NIR-II offers superior tissue penetration compared to NIR-I, which is advantageous for deep-tissue phototherapy applications.

Over the past decade, substantial research efforts have been dedicated to the NIR-II field. To quantitatively analyze its development, we retrieved relevant publications from the Web of Science Core Collection database. A total of 2,491 documents met our inclusion criteria. These publications received 97,862 citations, averaging 39.3 citations per item. Both annual publication counts and citation numbers exhibited consistent year-on-year growth (Figure 2a). Publications surged from 3 in 2009 to 618 in 2023, while citations increased from 2 to 26,885 during the same period.

By classifying the number of publications and citations according to countries, we can easily observe that the number of publications and citations in China was rapidly increasing throughout the years (Figure 2b, c). Since 2012, China's share of both publications and citations in this field has shown a clear upward trajectory, despite minor annual fluctuations (Figure 2d). This trend underscores China's steadily increasing contribution to the NIR-II field.

Given the characteristically low initial publication volume in NIR-II research, followed by a mid-phase surge and recent stabilization trends, we modeled annual publication growth using a logistic curve (Figure 2e). Notably, by determining the intersection point of tangents fitted to the lag phase and logarithmic growth phase, we identified 2017—approximately eight years after the field's inception—as the inflection point marking accelerated publication growth. Based on this temporal partitioning, subsequent analyses segregate the domain into two distinct stages: the foundational period (≤2016) and the developmental period (≥2017).

2.2 Most productive countries / regions and cooperation networks

National publication outputs reflect the contributions and growth trajectories of countries in this field, while global collaboration networks reveal their cooperative relationships. Our analysis identified 54 countries/regions contributing to NIR-II research. Table 1 ranks the top 15 countries/regions by publication volume, supplemented by key impact metrics: total citations, average citations per publication, and Total Link Strength (indicating co-publication frequency with other nations). China dominates the field with 2,123 publications, 81,674 citations, and a Total Link Strength of 449. The United States ranks second in publications (304) and citations (27,463), while also exhibiting the second-highest Total Link Strength (255). Notably, Singapore (93.0) and the United States (90.3) demonstrate the highest average citations, suggesting their research consistently attracts scholarly interest. Though China leads in productivity and total citation volume, its average citation rate (38.5) ranks fifth among the top 15 countries, which means that the potential of Chinese researchers is still not fully released, and more in-depth cooperation with researchers from other countries are strongly needed.

To intuitively visualize international collaboration patterns, we generated country cooperation networks using Scimago Graphica. Further analyzing collaborative evolution, we designated 2017—a pivotal year marking accelerated publication growth—as the temporal boundary. This delineation enabled comparative visualization of publication outputs and international cooperation intensity across two distinct phases: the foundational era (2009-2016) and the developmental era (2017-2023). Connection strength between nations is encoded through line attributes: thicker, more opaque lines indicate stronger collaborative linkages.

During the foundational period (pre-2017), the field comprised only 94 publications. Given the pioneering nature of early-stage research, articles from this era generally achieved high average citation rates across multiple countries. While international collaborations were already emerging, these were predominantly concentrated between China and developed economies (Figure 3a). All-time analysis reveals China as the central hub of the global collaboration network, establishing linkages with 35 countries (Figure 3(c)). The most intensive cooperation occurred between China and the United States, followed by China-Singapore partnerships. Comparative network visualization demonstrates significant evolution: whereas only China-U.S. collaboration exhibited substantial visibility before 2017, the developmental period shows not only expanded publication volumes (denoted by larger nodes) but also intensified connections. Crucially, China-U.S. cooperation remains exceptionally robust, while China-Singapore collaborations have become

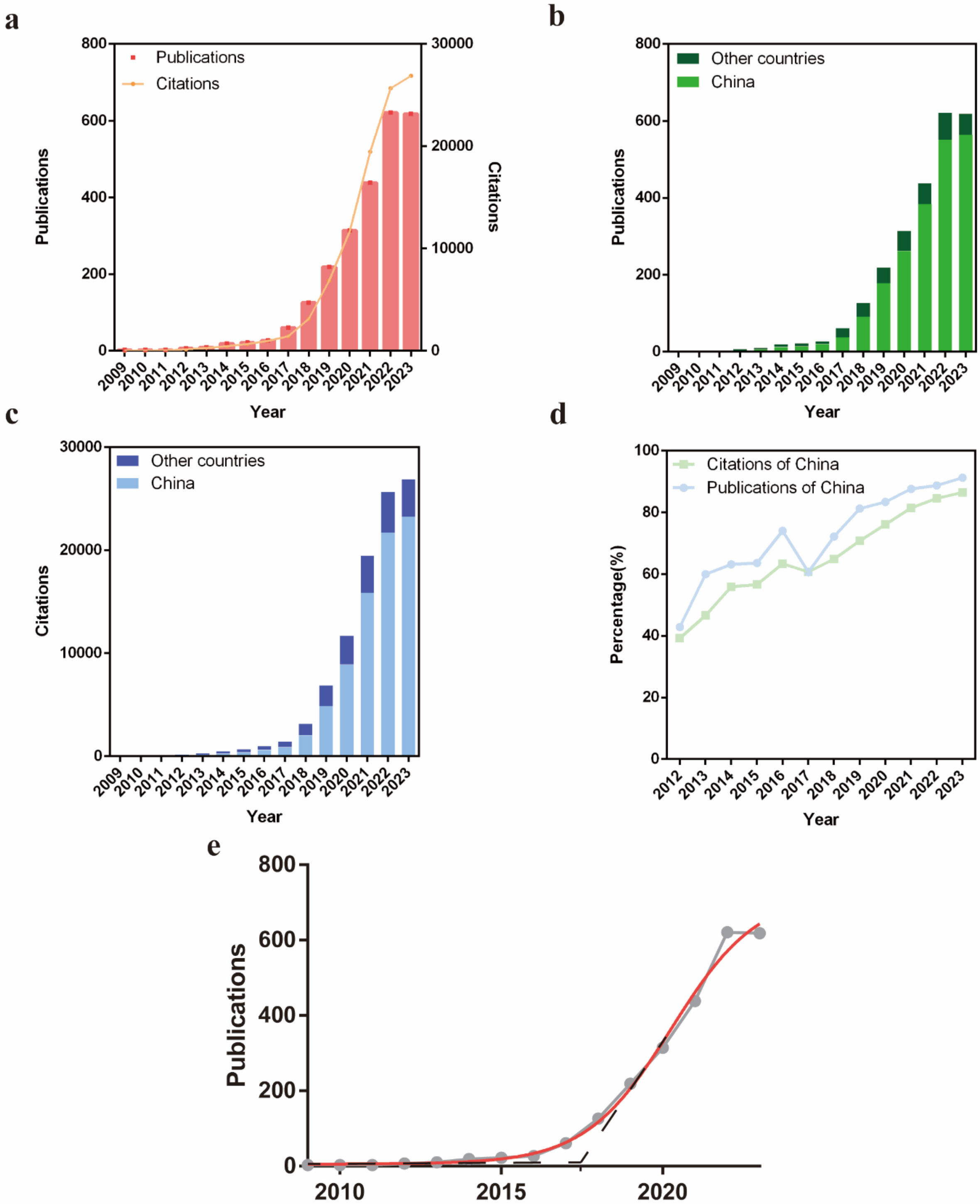

Fig. 2 (a) Annual publications and citations of NIR-II documents; (b) annual publications of NIR-II documents from China and other countries; (c) annual citations of NIR-II documents from China and other countries; (d) proportion change of annual publications and citations of NIR-II documents from China. (e) annual publication of NIR-II documents (grey) and its logistics curve fitting (red, $R^2>0.99$). Tangent of lag period and logarithmic growth period (black dashed line)

图2(a)NIR-II研究的年度发文量和引文量;(b)中国和其他国家NIR-II研究的年度发文量;(c)中国和其他国家NIR-II文献的年度引文量;(d)中国NIR-II文献年度发文和引文占比的变化;(e) NIR-II的年度发文量(灰色)及其logistic曲线拟合(红色,$R^2>0.99$);停滞期和对数增长期的切线(黑色虚线)

visibly established. Emerging intercontinental linkages now connect European nations, Australia (Oceania), and Brazil (South America) with global partners. Notably, South Africa's inclusion marks the extension of NIR-II research to Africa – confirming active scientific engagement across all inhabited continents. To further delineate the collaborative landscape during the most active phase of NIR-II research, the partnership network for the

Table 1 Top 15 productive and influential countries from 2009 to 2023
表1 2009年至2023年发文量影响力排名前15位的国家

Rank	Countries/Regions	Documents	Citations	Average citations	Total link strength
1	Peoples R China	2123	81674	38.471	449
2	USA	304	27463	90.3388	255
3	Singapore	124	11534	93.0161	114
4	Japan	61	1450	23.7705	32
5	South Korea	44	1475	33.5227	44
6	England	36	1106	30.7222	37
7	France	35	654	18.6857	40
8	Germany	35	1041	29.7429	50
9	Taiwan, China	35	700	20	24
10	Australia	32	1664	52	45
11	India	24	488	20.3333	20
12	Canada	20	831	41.55	17
13	Spain	17	537	31.5882	27
14	Switzerland	16	321	20.0625	16
15	Poland	14	96	6.8571	10

developmental period (2017 - 2023) is provided in Figure 3b. The network topology is highly consistent with the overall network (Figure 3c), reinforcing that the international collaboration framework in this field has been predominantly shaped and solidified by developments within the last seven years.

This demonstrates rapid global development of NIR-II research over the past decade. We posit that growing international interest will further diversify participation and intensify collaborative networks in this field.

2.3 Most productive institutions and cooperation networks

Research institutions within countries exhibit significant heterogeneity in NIR-II publication output and scholarly impact. Institutional collaborations often demonstrate more direct linkages than international partnerships. 1299 institutions have contributed to the field of NIR-II, of which the Chinese Academy of Sciences was the institution with the largest number of publications (425) (Table 2). When ranked according to the average citations, Stanford University was far ahead of other institutions with 171.7172. Much of this had to do with Hongjie Dai, whose team published three of the top 5 cited articles, including the first work to enable animal imaging in the NIR-II, published in 2009 in Nature Nanotechnology [4], and a fluorescent NIR-II molecule that can be rapidly excreted through urine, reported in 2016 in Nature Materials [19] and a review of NIR bioimaging fluorophores published in Nature Biomedical Engineering in 2017 [20]. The second place was Nanyang University of technology (123.6825). Notably, these two institutions represent the only non-Chinese institutions within the top 20 by publication volume, further evidencing China's dominance in this research domain.

To delineate institutional collaboration patterns, we constructed a co-authorship network using Gephi, encompassing institutions with >20 publications (Figure 4a). In this network visualization, node size corresponds to publication volume, color saturation reflects average citation impact, while connection thickness and hue intensity jointly represent collaboration strength. As the institution with the largest number of publications, the Chinese Academy of Sciences participated in six of the top 10 cooperation. In addition to cooperating closely with his two subordinate Universities - University of Chinese Academy of Sciences (121) and University of Science and Technology of China (67), Chinese Academy of Sciences also cooperated frequently with Stanford University (23), Beihang University (20) and Xiamen University (19). Nanjing University of Posts and Telecommunications had particularly close cooperation with Northwestern Polytechnical University (32). Wuhan University had a lot of cooperation with Tibet University (28). There was also a lot of cooperation between the two institutions in Shanghai, Fudan University and Shanghai Jiao Tong University (26). The Chinese University of Hong Kong and Shenzhen University also had a deep cooperation (23).

In 1964, Dr. Garfield, founder of the Institute for Scientific Information (ISI), introduced the impact factor (IF) as an independent metric for assessing journal quality [15]. Nevertheless, IF's validity faces ongoing debate given its reflection of historical averages rather than individual article impact [16]. Since article influence is ultimately measured by citation counts—the core component underlying IF—we generated IF-citation scatter plots to evaluate institutional publication quality. These visualizations encompassed all cited research articles (≥1 citation) in our dataset, with institution-specific color coding [17]. Figure 4b presents a comparative analysis of publication influence across nine leading institutions, including the top two Chinese institutions (Chinese Academy of Sciences and Fudan University), the top two non-Chinese institutions (Stanford University and Nanyang

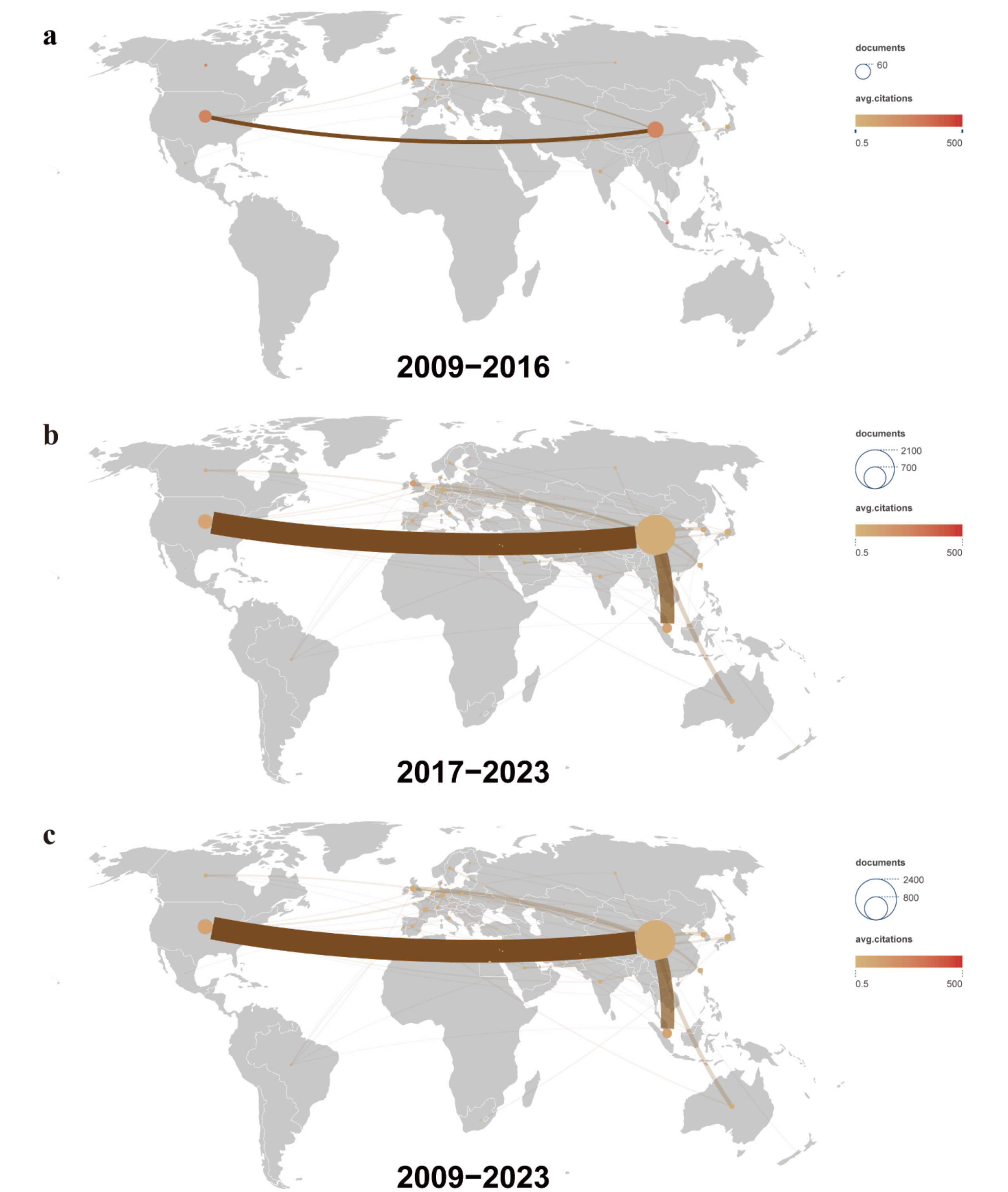

Fig. 3 (a) Global cooperation in NIR-II research among countries / regions before 2017; (b) Global cooperation in NIR-II research among countries / regions in 2017-2023; (c) Global cooperation in NIR-II research among countries / regions in 2009-2023
图3(a)2017年前国家/地区在NIR-II研究方面的全球合作;(b)2017-2023年国家/地区在NIR-II研究方面的全球合作;(c)2009-2023年国家/地区在NIR-II研究方面的全球合作

Technological University), as well as five additional Chinese institutions ranked among the top 10 by publications (Nanjing University of Posts and Telecommunications, Zhejiang University, Wuhan University, Shenzhen University, and Shanghai Jiao Tong University). Among articles with more than 500 citations, eight were from Stanford University, five from the Chinese Academy of Sciences (three of which resulted from collaboration with

Table 2 Top 20 productive and influential institutions from 2009 to 2023
表2 2009年至2023年发文量影响力排名前20位的机构

Rank	Insititutions	Documents	Citations	Average citations	Total link strength
1	Chinese Acad Sci	425	21825	51.3529	816
2	Fudan Univ	151	9291	61.5298	159
3	Univ Chinese Acad Sci	142	6679	47.0352	325
4	Nanjing Univ Posts & Telecommun	131	4146	31.6489	172
5	Zhejiang Univ	116	4852	41.8276	172
6	Wuhan Univ	111	5956	53.6577	149
7	Shenzhen Univ	110	4517	41.0636	167
8	Univ Sci & Technol China	102	4204	41.2157	164
9	Stanford Univ	99	17000	171.7172	177
10	Shanghai Jiao Tong Univ	96	3647	37.9896	151
11	Fuzhou Univ	81	2543	31.3951	86
12	Soochow Univ	80	5423	67.7875	101
13	Jilin Univ	75	2934	39.12	135
14	Southern Univ Sci & Technol	73	2499	34.2329	135
15	South China Univ Technol	71	2906	40.9296	89
16	Nanyang Technol Univ	63	7792	123.6825	68
17	Xiamen Univ	62	2066	33.3226	104
18	Chinese Univ Hong Kong	59	1633	27.678	63
19	Nanjing Univ	59	1949	33.0339	138
20	Southern Med Univ	58	1200	20.6897	124

Stanford University), one from Fudan University, and one from Nanyang Technological University. Notably, the two non-Chinese institutions showed a sparse distribution of publications in the low-citation region, whereas the Chinese institutions exhibited a denser concentration in this area.

2.4 Most productive authors and cooperation networks

Between 2009 and 2023, 6,476 authors contributed to NIR-II research. Table 3 ranks the top 20 most prolific authors, revealing Fan Quli (Nanjing University of Posts and Telecommunications) as the field leader with 104 publications. Tang Benzhong—renowned for his work on aggregation-induced emission (AIE)—ranks second (68 publications), followed by Huang Wei (67 publications), who maintains close collaboration with Fan. When assessed by average citation count, Dai Hongjie leads decisively (321.8 citations/publication), followed by Wang Qiangbin (126.4) and Sun Yao (117.9). As the pioneering contributor to NIR-II technology, Dai's publications exhibit the earliest mean publication year among the top 15 authors. His exceptional scholarly impact is further evidenced by nearly 12,000 total citations—significantly surpassing other high-output researchers.

To delineate author collaboration patterns, we constructed a co-authorship network using Gephi (Figure 5a). Each node represents an individual author, scaled by publication volume, with connection thickness encoding collaboration intensity. Applying Gephi's modularity algorithm [15], we identified eight major research communities distinguished by color, where authors within the same community exhibit closer collaborative ties. Authors with ≥ 30 publications are explicitly labeled. While distinct community boundaries are evident, cross-community collaborations remain frequent. Within each community, the highest-output author typically serves as principal leader, often fulfilling corresponding authorship roles. The largest community (green) centers around Cheng Zhen, followed by the second largest anchored by Fan Quli, Huang Wei, and Sun Pengfei. Tang Benzhong, Qian Jun, and Wang Dong collectively lead the third-ranked community. Chen Xiaoyuan, Zhu Shoujun, and Dai Hongjie form the core of the fourth largest community through intensive collaboration. Song Jibin, Wang Qiangbin, Zhang Fan, and Chen Yu each direct independent research groups, confirming these collaborative teams as the field's primary knowledge producers.

To observe the change of the amount of papers published by authors over time, we employed R's bibliometrix package to visualize author output dynamics. Figure 5b illustrates the annual productivity of the top 10 authors (2009-2023), where circle size corresponds to yearly publication count and blue saturation indicates annual citation impact. Author names and connecting lines adopt the community color scheme from Figure 5a. Notably, Zhang Fan (Fudan University) and Cheng Zhen (Stanford University) initiated research prior to 2015. While most authors entered the field around 2017, they nonetheless generated substantial contributions.

Given the pronounced output surge during 2016-2017, Figure 5c specifically analyzes the 20 most prolif-

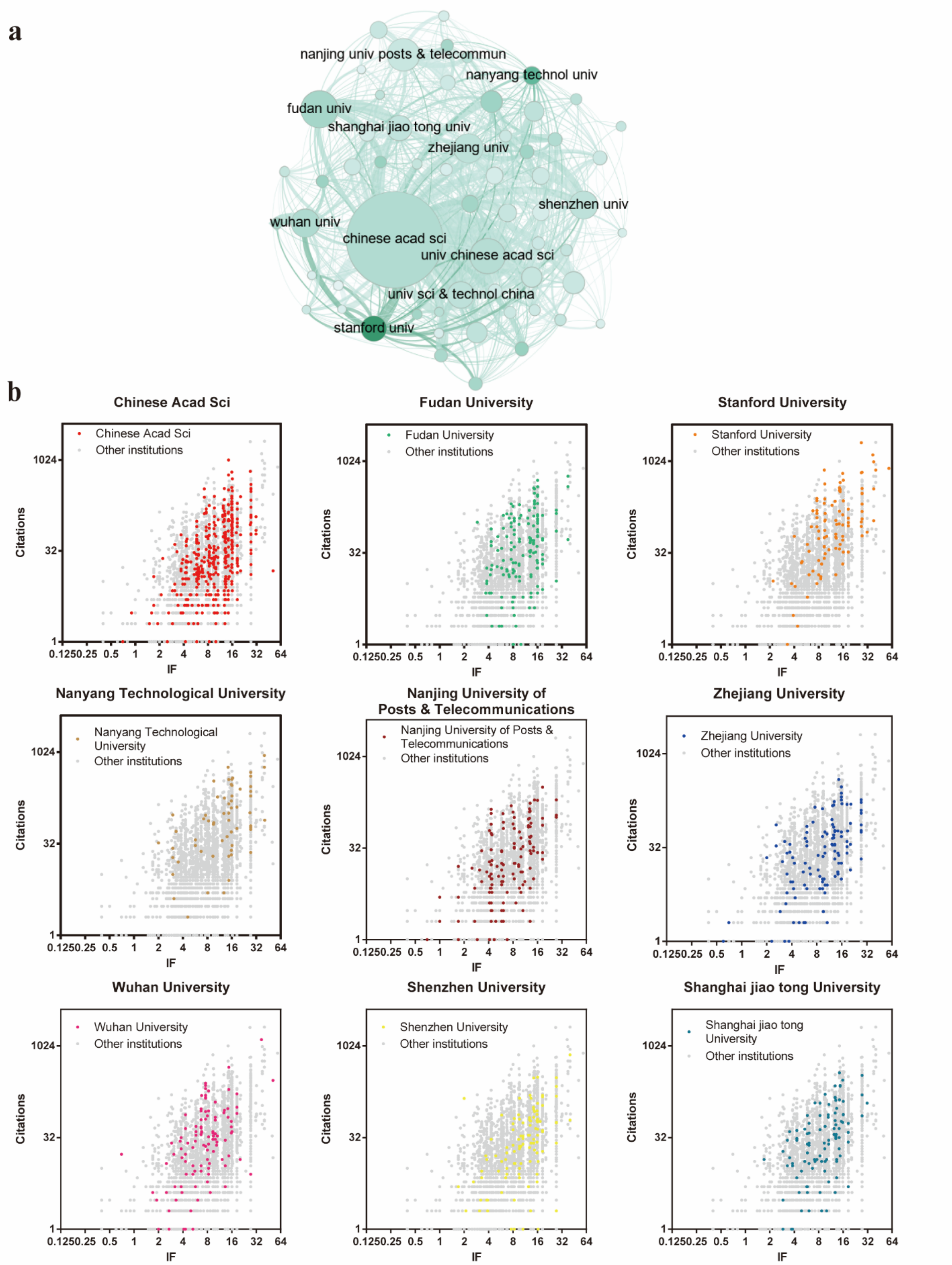

Fig. 4(a) Institutional cooperation network in the NIR-II field (publications ≥ 20); (b) IF-citations scatter diagram of NIR-II documents published by institutions (citations ≥ 1)
图4(a)NIR-II领域的机构合作网络(发文量≥20篇);(b)机构发表的NIR-II文献的影响因子——引用量散点图(引用次数≥1)

ic authors from 2017–2023 to identify contemporary leaders. These authors represent six distinct research communities and maintained uninterrupted publication through 2023. Community affiliations include: Fan Quli, Huang Wei, and Sun Pengfei (Nanjing University of Posts and Telecommunications); Zhang Fan (Fudan University);

Table 3 Top 20 most contributing authors in NIR-II from 2009 to 2023
表3 2009年至2023年NIR-II中贡献最大的20位作者

Rank	Author	Documents	Citations	Average citations	Total link strength
1	Fan, Quli	104	3952	38	501
2	Tang, Benzhong	68	3538	52. 0294	297
3	Huang, Wei	67	3398	50. 7164	331
4	Cheng, Zhen	64	5717	89. 3281	340
5	Zhang, Fan	62	6453	104. 0806	260
6	Song, Jibin	54	2007	37. 1667	270
7	Zhu, Shoujun	44	4198	95. 4091	269
8	Chen, Xiaoyuan	43	4860	113. 0233	176
9	Chen, Yu	41	3285	80. 122	87
10	Sun, Pengfei	40	1178	29. 45	195
11	Wang, Qiangbin	40	5056	126. 4	177
12	Qian, Jun	39	2243	57. 5128	194
13	Dai, Hongjie	37	11907	321. 8108	220
14	Li, Chunyan	37	3636	98. 2703	142
15	Hong, Xuechuan	36	3929	109. 1389	242
16	Sun, Yao	34	4007	117. 8529	141
17	Yang, Huanghao	34	1720	50. 5882	190
18	Zhang, Ruiping	33	1041	31. 5455	126
19	Li, Yang	32	1101	34. 4062	120
20	Wang, Dong	32	1274	39. 8125	120

Sun Yao (Central China Normal University) collaborating with Cheng Zhen; Song Jibin (Fuzhou University); Tang Benzhong (The Hong Kong University of Science and Technology) partnering with Qian Jun (Zhejiang University); and Chen Xiaoyuan (National University of Singapore) co-leading with Zhu Shoujun (Jilin University). These six communities constitute the field's primary driving forces for the foreseeable future, representing strategic collaboration opportunities for interested researchers.

2. 5 Keyword analysis and hotspot exploration

Keywords represent the core topics of the articles and give a general idea of research hotspots. Analyzing keywords can also help us understand the direction of concern in the field and, to some extent, reveal the intrinsic links in the distribution of knowledge within a subject area [21]. Therefore, in order to understand the research trend of NIR-II, we made a word cloud of keywords (Figure 6a). High-frequency terms include "fluorophores", "in vivo", "nanocrystals", and "fluorescence". Quantum dots—semiconductor nanocrystals functioning as prevalent fluorophores [5]—offer advantages like broad excitation/narrow emission spectra, long Stokes shifts, and tunable surface chemistry, though biosafety concerns persist. Additional signature materials emerge: "carbon nanotubes", "gold nanoparticles", and "indocyanine green". Therapeutic applications are evidenced through terms like "photothermal therapy", "photodynamic therapy", "drug delivery", and "surgery". The non-invasive, controllable, and target-specific nature of NIR-II phototherapies has stimulated significant research interest [16].

To delineate the temporal evolution of high-frequency keywords, we employed R's bibliometrix package to map trending topics from 2009 to 2023 (Figure 6b). This figure lists the keywords that appear frequently in different time periods and reveals distinct research phases. In the early days, semiconductor nanocrystals attracted the interest of researchers and lasted for a long time. Moreover, researchers also pay attention to the wavelength range, which is the decisive factor distinguishing NIR-II from NIR-I. After 2016, trend topics began to emerge with words related to materials science, indicating that in the early stages of development in this field, researchers began to improve the materials they used. In recent years, more trend topics in vocabulary related to biology and medicine have been observed. This signals the field's transition from fundamental exploration toward clinical translation, epitomized by the rise of "photodynamic therapy" and "immunotherapy" as frontier research foci in the past biennium.

To delineate keyword positioning across developmental phases, we generated thematic maps for 2009-2016 and 2017-2023 using R bibliometrix package (Figure 6c). Thematic map is composed of four quadrants divided by density and centrality [15]. The themes in the quadrant Ⅰ are core themes with high maturity, which are driving the development of the field. Well-developed but isolated themes are in the quadrant Ⅱ. Themes in the quadrant Ⅲ have low density and centrality, and they are either about to emerge or disappear. The themes in the quadrant Ⅳ have low maturity but high centrality,

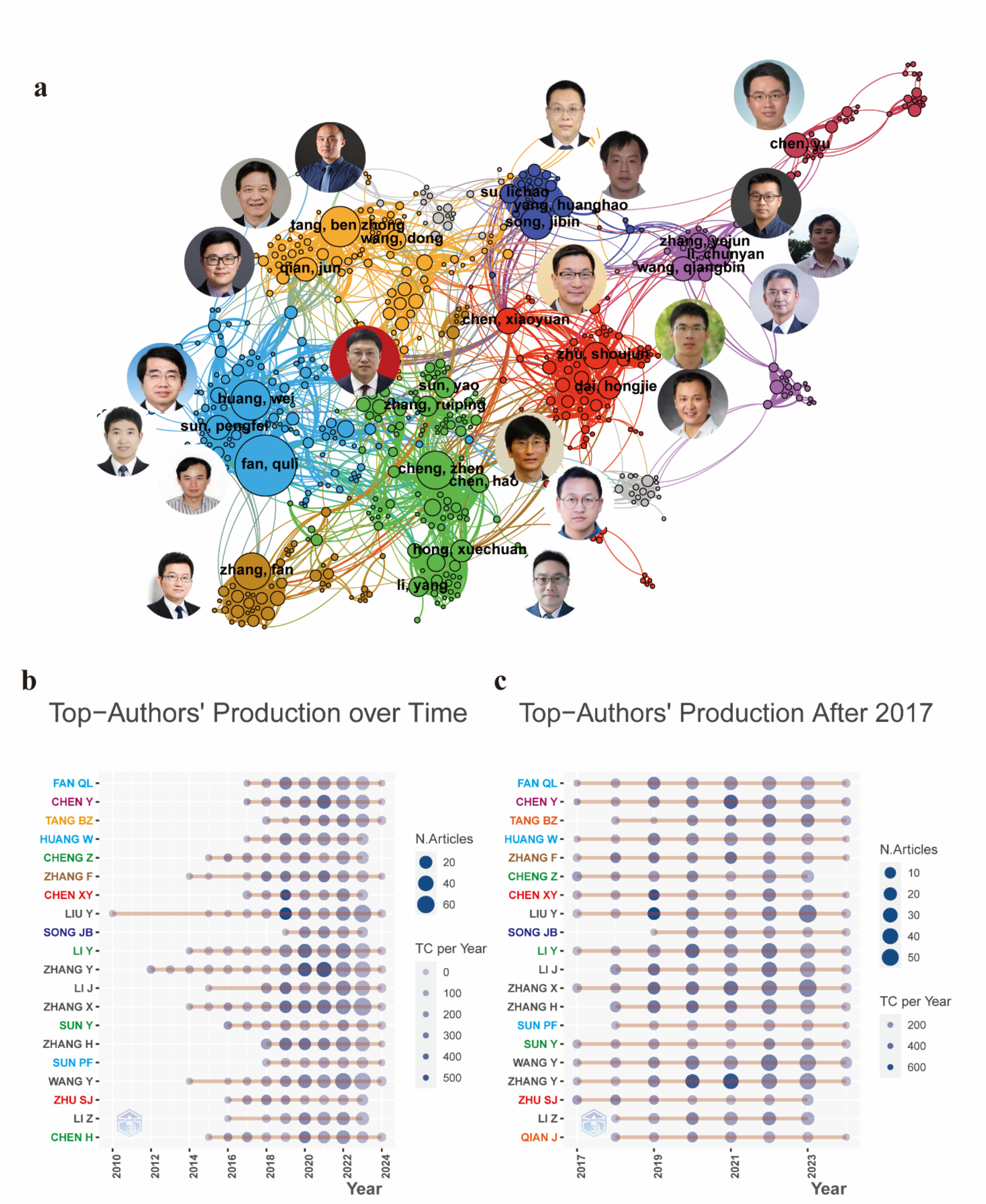

Fig. 5(a) Author cooperation network in NIR-II field and the largest eight clusters (publications ≥ 5); (b) annual publications and citations of top 20 authors from 2009 to 2023; (c) Annual publications and citations of top 20 authors from 2017 to 2023.

图5(a)NIR-II领域的作者合作网络和最大的八个集群(出版物≥5篇);(b)2009年至2023年发文量前20位作者的年度发文量和引文量;(c)2017年至2023年发文量前20位作者的年度发文量和引文量

which is likely to become a research hotspot in the future [15]. During the foundational period (2009-2016), "Carbon nanotubes" and "cells" is the foundation. This is related to the early research and application of carbon nanotubes in the field. At that time, gold nanoparticles and cancer cells became emerging keywords. At the stage of rapid development of the field (2017-2023), we can see that the most themes of had become basic themes supporting this field. There are three keywords in the first quadrant, indicating that they have been very popular recently. The emergence of "facile synthesis" means that researchers are pursuing the simple preparation of materials. The concepts of "water" and "chemistry" indicate the pursuit of researchers in biological tissues (where the proportion of water is the highest, and the development of water-soluble materials is also a necessary requirement for in vivo applications) and materials. This demonstrates the field's maturation toward application-driven research.

2.6 Analysis of NIR-II guided therapeutic applications

It is well known that NIR-II is closely related to Biomedicine. Many related pieces of research have proved the advantages of NIR-II in precise medical therapies [22-24]. Medical practitioners looked forward to the application of NIR-II in the field of treatment. We focused on four dominant applications—ranked top in keyword frequency—through systematic literature screening: photothermal therapy (PTT), photodynamic therapy (PDT), drug delivery, and surgery. First of all, we wanted to know the intersection degree between these applications, so we made the Venn diagram with the R Venndiagram package (Figure 7a). Consistent with that reflected in Figure 6, "photothermal therapy" appeared frequently in these documents (788), followed by "surgery" (422). There are relatively few documents on "photodynamic therapy" (264) and "drug delivery" (201). There were many combinations between "photothermal therapy" and "surgery", "photothermal therapy" and "photodynamic therapy". From the annual literature growth (Figure 7b), it can be seen that the number of articles related to "photothermal therapy" has been increasing. The articles related to the other three keywords have been growing until 2022, with a slight decrease until 2023.

Comparative analysis of annual mean citations (Figure 7c) and journal impact factors (Figure 7d) reveals differential scholarly impact and attention across the four therapeutic applications. As shown in the figure, the average IF of documents related to these four applications were all above 10, indicating that articles using NIR-II for therapeutic applications were favored by many high impact journals. Notably, the annual average citations of documents in the field of "photodynamic therapy" were higher than those in "drug delivery". This suggests sustained academic interest in PDT despite comparable IF distributions between these applications.

2.7 Most global cited and local cited documents

The influence of an article can be measured by how many times it has been cited by later researchers. Here we listed top 20 most cited documents, including 6 reviews and 14 articles (Figure 8a). The most cited document (1867 citations) is a review entitled "Photothermal therapy and photoacoustic imaging via nanotheranostics in fighting cancer" [25]. This review is from Chen Xiaoyuan's team at Singapore National University, mainly focusing on PTT and PAI, published on "*Chemical Society Reviews*" in 2019. This article summarizes the development of inorganic and organic photothermal transduction agents (PTA) and strategies to improve PTT results, introduces the advantages of PTT and other therapies in cancer treatment, and also provides examples of the new applications of PAI in cancer-related research. The second cited document (1,817 citations) was also a review entitled "Near-infrared fluorophores for biomedical imaging" by Hong Guosong from Dai Hongjie's team, and published on "*Nature Biomedical Engineering*" in 2017 [20]. It focused on biocompatible near-infrared fluorophores, which was increasingly developed and span the whole near-infrared window, including inorganic nanoparticles, organic macromolecules and small molecules with adjustable emission wavelength.

Local citation analysis examines the frequency with which two documents are cited together within a defined dataset—here, our collection of NIR-II literature. Figure 8b lists the top 20 most co-cited references, with the 2016 study by Antaris et al. (Dai Hongjie's team) ranking highest—indicating that this article has aroused the most interest of peers [19]. It was published by Dai Hongjie's team in 2016. They reported a rapidly excreted NIR-II fluorophore based on a synthetic 970-Da organic molecule. Targeted molecular imaging of tumors in vivo by coupling anti-EGFR antibody could be used to complete accurate image-guided tumor resection due to its high tumor to background signal ratio. The review by Hong Guosong in 2017, which has the second number of citations, also rank second here [20].

2.8 Clinical research of NIR-II

The development of NIR-II imaging has evolved over more than 15 years, progressing through stages of initial exploration, material optimization, and animal experimentation. This foundational work is now transitioning toward clinical applications, with a growing number of studies advancing to human trials. As summarized in Table 4, 12 articles document clinical NIR-II imaging research—all originating from China, consistent with the country's prominent role in the field as outlined in Section 3.1. The earliest clinical study was led by Tian Jie in 2019 [26], who has since contributed eight articles on NIR-II clinical research and is widely recognized as a leading pioneer in its clinical translation. In terms of contrast agents, the majority of studies utilize clinically approved dyes such as ICG and IRDye800CW, emphasizing safety and translational practicality. Several investigations also employ antibody-modified NIR-II probes to improve tissue-specific targeting [24,27]. Furthermore, these efforts demonstrate the versatility of NIR-II imaging across diverse surgical specialties, including hepatology, neurosurgery, thoracic surgery, orthopedics, and

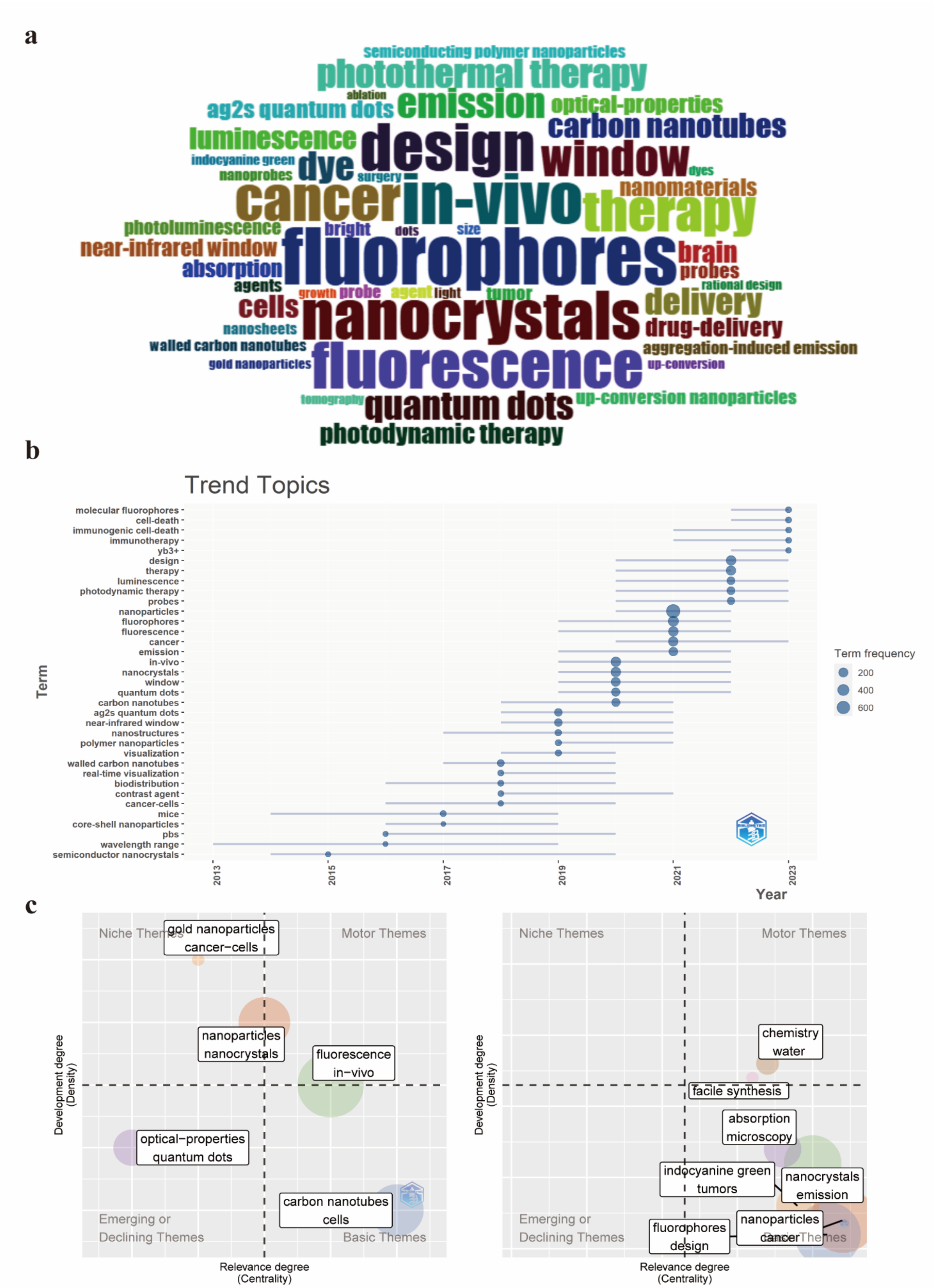

Fig. 6 (a) Word clouds of keywords in NIR-II field (frequencies ≥ 50); (b) trend topics in NIR-II; (c) changes of thematic map in two time periods (2009-2016, 2017-2023)

图6(a)NIR-II领域关键词词云(出现频次≥50);(b)NIR-II领域的趋势主题变化;(c)两个时期(2009-2016年、2017-2023年)主题地图的变化

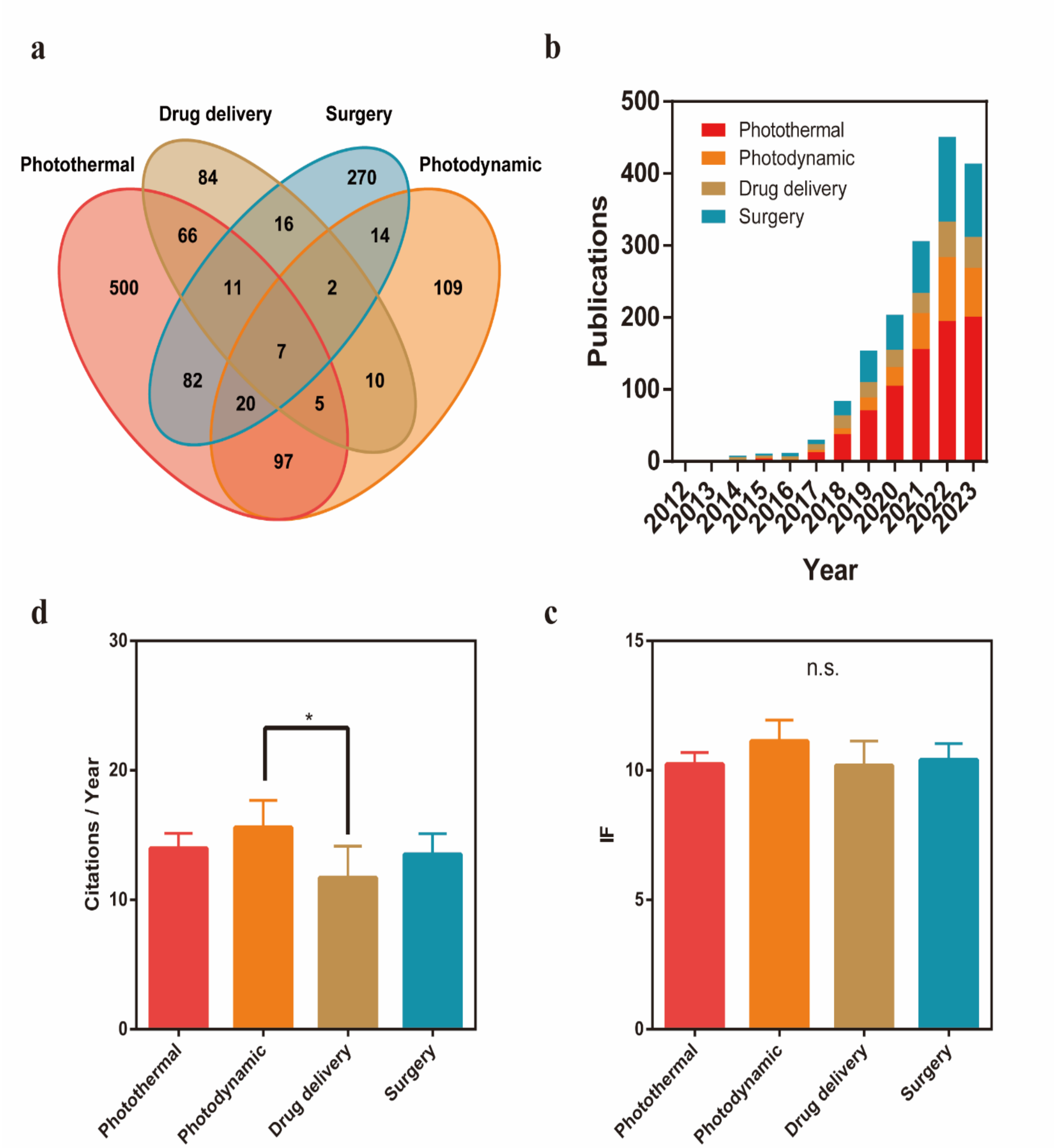

Fig. 7 (a) Venn diagram of four applications in NIR-II; (b) Annual publications of four applications in NIR-II documents; (c) Comparison of annual average citations of four applications ($* p < 0.05$); (d) Comparison of impact factors of four applications
图7(a)NIR-II中四种应用相关文章的Venn图;(b)四种应用的年度发文量;(c)四种应用的文章年平均引用量比较($*p<0.05$);(d)四种应用的文章影响因子比较

ophthalmology.

These studies collectively indicate that NIR-II imaging shows promise in improving intraoperative visualization and precision, while also suggesting potential clinical benefits such as higher tumor resection rates, better survival outcomes, and reduced surgical risks. As the technology continues to develop, future efforts should focus on gradually optimizing imaging protocols, carefully expanding the use of novel NIR-II probes, and strengthening validation through multi-center clinical studies. Importantly, deeper collaboration between research groups and clinical teams—incorporating expertise from optics, bioengineering, oncology, and surgery—will be essential to address practical challenges and systematically advance NIR-II imaging toward broader clinical adoption.

Table 4 NIR-II Imaging in Clinical Studies before 2025
表4 2025年之前近红外二区成像在临床研究中的应用

Publish Year	First Affiliation/ Support hospital	NIR-II Material	Number of Cases	Imaging Target	Clinical Values/Advantages	Ref.
2019	Chinese Acad Sci/ Southwest Med Univ, Dept Hepatobiliary Surg Pathol & Nucl Med, Affiliated Hosp	ICG	23	Liver/ Liver cancer	NIR-II imaging demonstrates superior tumor detection sensitivity, resolution, and real-time guidance capabilities compared to NIR-I, significantly improving precision in liver cancer surgery and highlighting its clinical potential for intraoperative use.	[26]
2021	Chinese Acad Sci/ Capital Med Univ, Beijing Tiantan Hosp, Dept Neurosurg	ICG	23	Brain/ Neuroglioma	NIR-II imaging combined with deep CNN (Convolutional Neural Networks) enables real-time, high-accuracy intraoperative tumor diagnosis and precise resection guidance, significantly improving glioma surgery outcomes while preserving neurological function.	[27]
2022	Beihang Univ/Southwest Med Univ, Dept Gen Surg Hepatobiliary Surg, Affiliated Hosp	IgG-IRDye800CW	1	Liver/HCC	NIR-II imaging with IgG-IRDye800CW provides real-time, high-contrast guidance for precise HCC resection in cirrhotic livers, effectively distinguishing tumors from surrounding tissue to improve surgical accuracy and preserve function.	[24]
2022	Wuhan Univ/Wuhan Univ, Dept Orthoped Trauma & Microsurg, Zhongnan Hosp	ICG	39	Vessels	NIR-II fluorescence enables superior intraoperative visualization of microvasculature, providing real-time, high-resolution guidance for microsurgery and outperforming traditional imaging.	[28]
2022	Beihang Univ/ Peking Univ, Dept Thorac Surg, Peoples Hosp	Anti-EGFR-IRDye800CW	10	Lung/Lung Cancer/ Lymph nodes	NIR-II imaging with EGFR-targeted probes enables rapid, high-contrast identification of lung cancer margins and metastatic lymph nodes in excised tissue, providing a precise tool for intraoperative decision-making.	[29]
2022	Chinese Acad Sci/ Capital Med Univ China, Dept Neurosurg, Beijing Tiantan Hosp	ICG	7	Brain/ Neuroglioma	NIR-IIa/IIb imaging enables maximal, precise resection of high-grade gliomas with superior real-time vessel visualization and high spatial resolution, significantly reducing blood loss.	[30]
2022	Chinese Acad Sci/ Capital Med Univ, Beijing Tiantan Hosp, Dept Neurosurg	ICG	40	Brain/ Neuroglioma	NIR-II fluorescence-guided surgery maximizes GBM resection with improved precision and safety, significantly prolonging patient survival while preserving neurological function.	[31]
2023	Peking Univ/Peking Univ, Dept Thorac Surg, Peoples Hosp	ICG	102	Lung/Lung Cancer	NIR-II outperforms NIR-I in lung cancer ICG imaging, offering superior clarity and deeper tissue penetration.	[32]
2023	Capital Med Univ/Capital Med Univ, Beijing Tiantan Hosp, China Natl Clin Res Ctr Neurol Dis, Dept Neurosurg, Beijing Neurosurg Inst,	BV-4B	3	Surgical suture	The study identifies BV-4B, a clinically used and biocompatible dye, as a promising NIR-II material for coating devices like catheters and sutures, allowing real-time tracking of device integrity and degradation without radiation.	[33]
2024	Chinese Peoples Liberat Army Gen Hosp/Chinese Peoples Liberat Army Gen Hosp, Med Ctr 2	ICG	12	Vessels	NIR-II fluorescence angiography with ICG provides safe, non-invasive, real-time high-resolution imaging of superficial vasculature, supporting surgical planning for hemodialysis access. It demonstrates excellent consistency with ultrasound, avoids radiation, reduces renal burden, and—when enhanced with AI and hemodynamic simulation—improves outcomes by identifying key veins for preservation.	[34]

续表

Publish Year	First Affiliation/ Support hospital	NIR-II Material	Number of Cases	Imaging Target	Clinical Values/Advantages	Ref.
2024	Beihang Univ/ Southwest Med Univ, Dept Gen Surg Hepatobiliary Surg, Affiliated Hosp	ICG	53	Liver/Liver Cancer	NIR-II fluorescence molecular imaging (FMI) significantly improves hepatocellular carcinoma (HCC) detection rates and enables more radical resections, leading to markedly superior relapse-free survival (RFS) compared to conventional surgery	[35]
2024	Beihang Univ/ Chinese Peoples Liberat Army Gen Hosp, Med Ctr 3, Sr Dept Ophthalmol	ICG	22	Orbit/Tumor of orbit	NIR-II fluorescence imaging using ICG enables precise resection of orbital tumors by providing real-time intraoperative guidance, distinguishing tumors from non-tumorous lesions with high sensitivity and specificity, and facilitating surgical decision-making for complete tumor removal.	[36]
2024	Chinese Peoples Liberat Army Gen Hosp/ Chinese Peoples Liberat Army Gen Hosp, Med Ctr 3, Sr Dept Ophthalmol	ICG	39	Orbit/Tumor of orbit	NIR-II fluorescence imaging enables precise intraoperative identification of orbital tumors by quantifying ex vivo fluorescence signals. The study identifies orbital fat as the optimal control tissue due to its consistently low and stable fluorescence, which enhances the accuracy of tumor-background differentiation and supports reliable surgical decision-making in head and neck oncology	[37]

3 Conclusion

In conclusion, this study presents the first comprehensive bibliometric analysis of the NIR-II research field. Our investigation delineated the domain's evolution from 2009 to 2023, revealing accelerated growth post-2016. Key trends were identified through multidimensional analysis of national contributions, institutional networks, author productivity, keyword dynamics, therapeutic applications, and landmark publications. Crucially, Chinese institutions have consolidated leadership in the field, while international collaborations expanded significantly. This cooperative landscape features intensive institutional partnerships, with Stanford University and Nanyang Technological University emerging as pivotal nodes of high-impact research. Institutional networks exhibit dense cross-community linkages, with six major research collectives driving innovation. We conducted a visual analysis of keywords to identify potential future research hotspots, including "photodynamic therapy" and "immunotherapy. " Additionally, we compared four NIR-II therapeutic applications, identifying photothermal therapy as the most established modality while noting photodynamic therapy's superior citation impact, and listed highly cited references. Finally, we summarized the articles on NIR-II clinical studies conducted before 2025. NIR-II imaging has progressed from preclinical research to initial clinical trials—predominantly led by Chinese researchers using clinically approved probes—demonstrating strong potential for advantaging in multiple surgical specialties. This study aims to assist prospective NIR-II researchers in swiftly comprehending the global research landscape in this field. Furthermore, it offers valuable insights for researchers regarding potential collaborators, target journals for paper submission, and emerging research frontiers.

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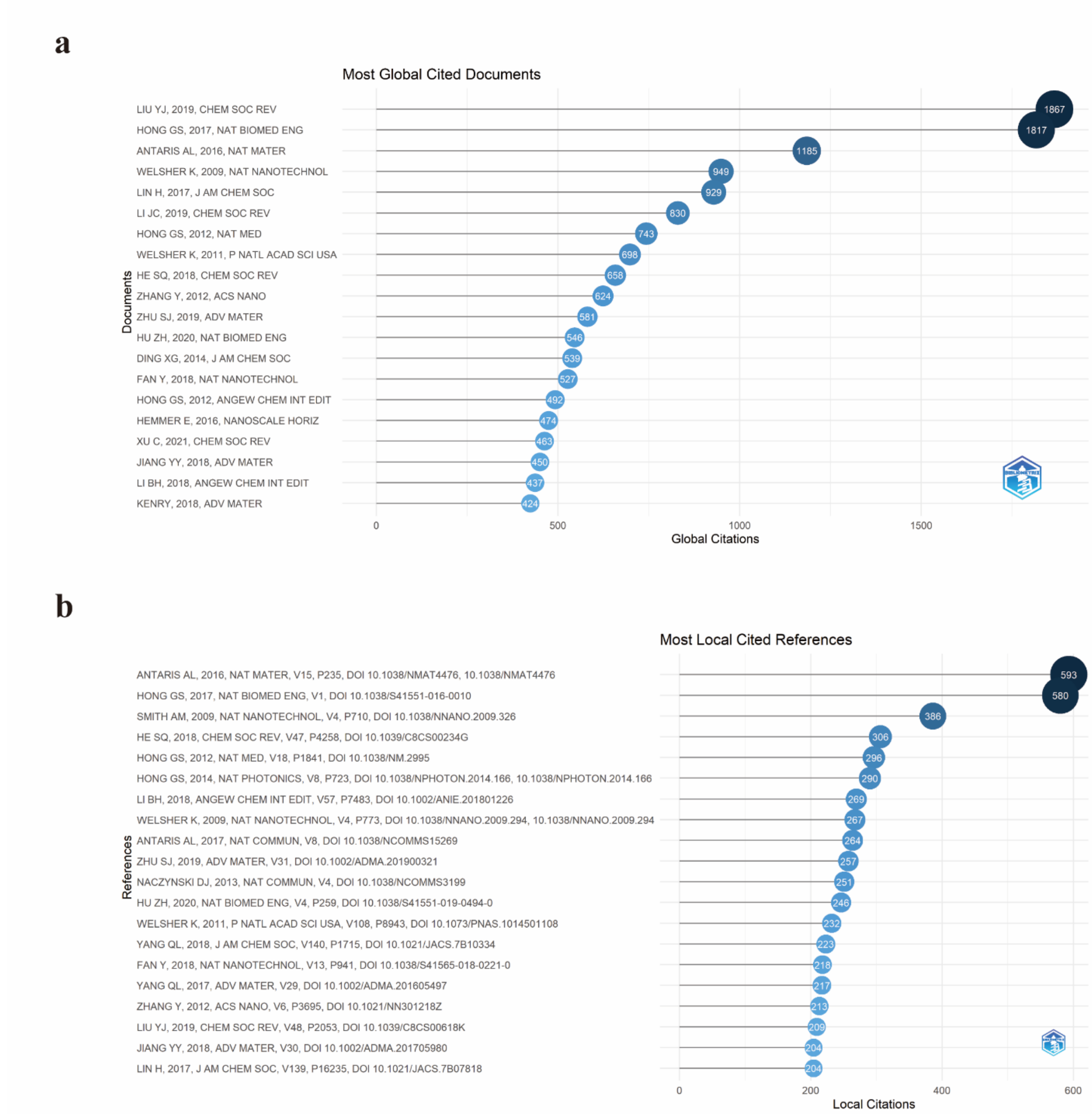

Fig. 8 (a) Top 20 most global cited documents in NIR-II field; (b) top 20 most local cited references in NIR-II field
图8(a)NIR-II领域全球引用最多的20篇文献;(b)NIR-II领域内部引用最多的20篇文献

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