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Comparative investigation of neoadjuvant immunotherapy versus adjuvant immunotherapy in perioperative patients with cancer: a global-scale, cross-sectional, and large-sample informatics study

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Background: Neoadjuvant and adjuvant immunotherapies for cancer have evolved through a series of remarkable and critical research advances; however, addressing their similarities and differences is imperative in clinical practice. Therefore, this study aimed to examine their similarities and differences from the perspective of informatics analysis.

Methods: This cross-sectional study retrospectively analyzed extensive relevant studies published between 2014 and 2023 using stringent search criteria, excluding nonpeer-reviewed and non-English documents. The main outcome variables are publication volume, citation volume, connection strength, occurrence frequency, relevance percentage, and development percentage. Furthermore, an integrated comparative analysis was conducted using unsupervised hierarchical clustering, spatiotemporal analysis, regression statistics, and Walktrap algorithm analysis.

Results: This analysis included 1373 relevant studies. Advancements in neoadjuvant and adjuvant immunotherapies have been promising over the last decade, with an annual growth rate of 25.18 vs. 6.52% and global collaboration (International Co-authorships) of 19.93 vs. 19.84%. Respectively, five dominant research clusters were identified through unsupervised hierarchical clustering based on machine learning, among which Cluster 4 (Balance of neoadjuvant immunotherapy efficacy and safety) and Cluster 2 (Adjuvant immunotherapy clinical trials) [Average Publication Year (APY): 2021.70 ± 0.70 vs. 2017.54 ± 4.59] are emerging research populations. Burst and regression curve analyses uncovered domain pivotal research signatures, including microsatellite instability ($R^2 = 0.7500$, $P = 0.0025$) and biomarkers ($R^2 = 0.6505$, $P = 0.0086$) in neoadjuvant scenarios, and the tumor microenvironment ($R^2 = 0.5571$, $P = 0.0209$) in adjuvant scenarios. The Walktrap algorithm further revealed that 'neoadjuvant immunotherapy, nonsmall cell lung cancer (NSCLC), immune checkpoint inhibitors, melanoma' and 'adjuvant immunotherapy, melanoma, hepatocellular carcinoma, dendritic cells' (Relevance Percentage: 100 vs. 100%, Development Percentage: 37.5 vs. 17.1%) are extremely relevant to this field but remain underdeveloped, highlighting the need for further investigation.

Conclusion: This study identified pivotal research signatures and provided substantial predictions for neoadjuvant and adjuvant cancer immunotherapies. In addition, comprehensive quantitative comparisons revealed a notable shift in focus within this field, with neoadjuvant immunotherapy taking precedence over adjuvant immunotherapy after 2020; such a qualitative finding facilitate proper decision-making for subsequent research and mitigate the wastage of healthcare resources.

Keywords: adjuvant immunotherapy, biomarker, immune checkpoint inhibitor, informatics analysis, neoadjuvant immunotherapy, safety

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Introduction

Immunotherapy for perioperative cancer patients includes neoadjuvant and adjuvant immunotherapies, depending on the timing and treatment objectives. Both approaches play crucial roles in cancer treatment. Neoadjuvant immunotherapy refers to the immunotherapy applied before the cancer surgery by activating the body's immune system to attack and eliminate cancer cells, which reduces the tumor bulk, thereby enabling a favorable condition for surgical intervention in patients with advanced cancer[1–3]. Adjuvant immunotherapy is an immunotherapeutic modality applied after cancer surgery. Compared with traditional surgery and chemotherapy, persistent immunotherapy reduces the risk of recurrence and metastasis for postoperative cancer patients by maintaining the body's immune system's response to, recognition of, and killing of cancer for an extended period of time[4–7].

In clinical practice, both of these approaches have demonstrated a series of remarkable and critical research advances that have revolutionized and continued to transform cancer treatment patterns[8–13]. Nevertheless, many controversial experimental findings and unmet clinical needs in current immunotherapy practice still exist[14–17]. Exploring the similarities and differences between neoadjuvant and adjuvant immunotherapies, and the type of approach or combination regimens that will offer optimal benefit to patients with cancer is imperative and needs to be addressed to refine treatment strategies and improve patient outcomes in clinical practice.

Therefore, this cross-sectional study mainly aimed to comprehensively investigate and comparatively analyze the similarities and differences between neoadjuvant and adjuvant immunotherapies from the perspective of machine learning-based informatics analysis. Although the role of adjuvant immunotherapy in perioperative cancer patients should not be underestimated, considering the intervention stage and effect characteristics of these two therapies, we propose the scientific hypothesis that neoadjuvant immunotherapy warrants additional attention to leverage the body's anticancer immunity in a more integrated manner at an earlier intervention stage to achieve more robust control of cancer development and dissemination. Specifically, this study aimed to present and comparatively analyze the fundamental metrological information, intrinsic connections, evolutionary processes, and mutual interactions of crucial research elements for neoadjuvant and adjuvant immunotherapies to identify pivotal research signatures and provide substantial predictions for subsequent preclinical and clinical research in the domain.

Materials and methods

The inclusion and exclusion criteria, information source, search strategy, data collection, outcome measurement, quality assessment, and statistical analysis of this retrospectively cross-sectional study were performed according to the PRISMA guidelines and compliant with the strengthening the reporting of cohort, cross-sectional, and case–control studies in surgery (STROCSS) criteria[18–20].

HIGHLIGHTS

- This cross-sectional study provided the first comparative analysis of the global scientific landscape of neoadjuvant and adjuvant immunotherapies.
- Through unsupervised hierarchical clustering and time-series analyses, we identified several crucial emerging research populations for neoadjuvant and adjuvant immunotherapies.
- With the random-walk-strategy-based Walktrap algorithm, we predicted several crucial but unexplored directions in this field that warrant further investigation.
- Comprehensive quantitative comparisons revealed that neoadjuvant immunotherapy gained considerable attention after 2020, demonstrating a notable shift away from on adjuvant immunotherapy; such a qualitative finding will facilitate proper decision-making for subsequent research and prevent substantial wastage of healthcare resources.

Eligibility criteria

For neoadjuvant immunotherapy, studies focusing on tumor and neoadjuvant immunotherapy were included (Supplemental Digital Content 1, http://links.lww.com/JS9/C412). Similarly, studies focusing on tumor and adjuvant immunotherapy were included for adjuvant immunotherapy (Supplemental Digital Content 1, http://links.lww.com/JS9/C412). The exclusion criteria for both scenarios were non-English and nonpeer-reviewed documents, specifically Meeting Abstract, Editorial, Letter, Correction, and News Item. The neoadjuvant ($n = 607$) and adjuvant ($n = 766$) immunotherapies were divided into two independent groups for subsequent data synthesis and comparative analyses.

Information source

Of the several professional retrieval databases, such as Web of Science (WOS), PubMed, Embase, and Scopus, that are currently available for literature review, WOS is the most utilized for informatics analysis because of its comprehensive and all-encompassing high-quality data. Therefore, the WOS core database (WOSCC, Website: https://webofscience.clarivate.cn/wos/woscc/advanced-search) was used as the data source in our study (date of data retrieval and download: 14 October 2023).

Search strategy

The data discovery criteria comprised two main components: tumor-related and neoadjuvant immunotherapy-related or adjuvant immunotherapy-related terms. Extremely restrictive discovery terms and conditions were used to comprehensively and accurately include data on neoadjuvant and adjuvant immunotherapy in the field of oncology (Supplemental Digital Content 1, http://links.lww.com/JS9/C412). The advanced search of the WOS was used as a filter in this study. The field identifier TS was used for study subject limitation. Boolean operators were used to perform logical operations and conditional judgments. The vague matching character '*' ensured a comprehensive search of all relevant documents.

Selection process

Peer-reviewed and English documents related to neoadjuvant or adjuvant immunotherapy were screened for inclusion in this group. Study selection was exclusively performed by an individual, ensuring that standardized procedures and methods were followed during the selection process and that all necessary parameters were recorded. Subsequently, the other two reviewers independently proofread the selection process. No automated tools were used during this process.

Data collection process

Standardizing and duplicating the data collection process would considerably reduce the bias in the final results. One responsible individual was in charge of raw data collection, ensuring that standardized operating procedures and methods were followed during the data collection process and that all necessary parameters were recorded. Subsequently, the other two reviewers independently proofread the collected data, including checking the data format, extent, and coherence. No automated tools were used during this process. This analysis included 1373 relevant studies.

Data item

Relevant metrology informatics variables were mined, quantified, and further differentially analyzed using substantial neoadjuvant and adjuvant immunotherapy data. The outcome variables were publication volume, citation volume, connection strength, occurrence frequency, relevance percentage, and development percentage. All outcome variables were collected for each study. The other variables enrolled in this study were the h-index, m-index, and g-index. No missing or unclear information was present.

Reduction of study bias risk

To avoid interfering factors and confounding bias, a high-quality database was employed, and nonpeer-reviewed and non-English documents were excluded. Extremely restrictive discovery terms and conditions were used to ensure the accuracy and completeness of the data (Supplemental Digital Content 1, http://links.lww.com/JS9/C412). Homogenization was performed during data collection and processing in the two groups to ensure comparability. A triplicate independent proofreading strategy was implemented for the study selection and data collection processes to avoid artificial factor bias.

Effect measure

For connection strength, the total link strength was used as an effect indicator in the synthesis or presentation of the results. For occurrence frequency, slope, goodness of fit, and statistical significance were used as effect indicators in the synthesis or presentation of the results. For publication volume, total publication, annual publication, average publication year (APY), and mean difference between publication years were used as effect indicators in the synthesis or presentation of the results. For citation volume, total, annual, global, and local citations were used as effect indicators in the synthesis or presentation of the results.

Synthesis method

Studies in the same subgroup were used for data synthesis, with no missing summary statistics. The basic characteristics of the data pool and the corresponding top 10 citation classics are presented in a tabular format. Total publications or citations were visualized using a world map, radar chart, and ray diagram. Annual publications or citations were visualized using bubble charts, heatmaps, and river charts. Interactions between countries and affiliations were visualized using chord and Sankey diagrams. The synthesized results of occurrence frequency were visualized using spatiotemporal network diagrams. The annual occurrence frequency of a single individual was visualized using a regression curve. The same semantic results were subjected to synthesis, slope, regression, and statistical analyses.

Reporting bias and certainty assessment

During study selection, data collection, and data synthesis, a three-person independent verification method was applied, and the percentage of result consistency was used as an evaluation indicator of bias risk. The authenticity of the data sources (whether certified by authoritative organizations), the amount of evidence, and their peer-review status were used to evaluate the certainty of the outcome evidence.

Unsupervised learning clustering

Hierarchical clustering is a dominant method in unsupervised learning in which data samples are progressively grouped into multiple hierarchical cluster structures by measuring the similarity or distance between them. The advantages of hierarchical clustering include the ability to discover cluster structures of different levels and sizes, the nonrequirement to define a predetermined number of clusters, and improved performance in modeling the structure of the data space. Without subjective artificial intervention, hierarchical clustering produces multiple appropriate clusters that objectively present the intrinsic constructs and relationships of research signatures, thereby providing valuable information for subsequent data analysis. By hierarchically clustering all the research signatures in a given domain and then analyzing the weight share of the contained research signatures and the meanings that the whole group collectively reflects, the individual clusters will have specific definitions, which in turn facilitates subsequent temporal and spatial analysis[21,22].

Walktrap algorithm and research potentiality discovery

The random walk-strategy-based Walktrap algorithm is a clustering algorithm that constructs the similarity between nodes by modeling the random wandering paths between them and finally identifies the community structure. The clustering performance in complex networks is good and provides an effective tool for solving community discovery problems. By running the Walktrap algorithm, all research signatures were divided into four quadrants. Research signatures in Quadrant IV in particular have the highest research potential since they are notably significant to the field; however, they require additional funding[21,23].

Software applications and statistical analysis

Data processing and graphical plotting were performed using R packages such as ‘ggplot2’ and ‘bibliometrix’. VOSviewer

1.6.18(0) and GraphPad Prism 9.0 were used for the visual presentation of research signatures and linear regression modeling and graphing, respectively[24–26]. Continuous variables are presented as mean ± SD with 95% CI. A *P*-value <0.05 indicated statistical significance.

Results

Visualization overview of metrological information in the field of neoadjuvant immunotherapy and adjuvant immunotherapy in oncology

Neoadjuvant and adjuvant immunotherapies have shown promising advancements (Annual Growth Rate: 25.18 vs. 6.52%) and global collaboration (International Co-authorships: 19.93 vs. 19.84%) over the last decade (Table 1). The annual publication and citation volumes for neoadjuvant immunotherapy between 2000 and 2017 have increased from <10 to 200. The annual publication and citation volumes exceeded these values and showed an exponential growth trend after 2017 (Fig. 1A). The predictive function of annual publications and annual citations in the last 4 years was $y = 53.9x–108811$ ($R^2 = 0.98065$, $P < 0.0001$) and $y = 987.6x–2E+06$ ($R^2 = 0.95755$, $P < 0.0001$), respectively. The annual publication and citation volumes for adjuvant immunotherapy between 2000 and 2016 were <30 and 900. The annual publications and citations exceeded these values and showed an exponential growth trend after 2016 (Fig. 1B). The predictive function of annual publications and citations for the last 4 years was $y = 15.3x–30843$ ($R^2 = 0.96353$, $P < 0.0001$) and $y = 606.1x–1E+06$ ($R^2 = 0.99645$, $P < 0.0001$), respectively. The top 10 cited classics in neoadjuvant immunotherapy demonstrated an annual increasing trend in citations, whereas those in adjuvant immunotherapy showed a decreasing trend. For neoadjuvant immunotherapy, the title of the locally most cited citation classic was Neoadjuvant PD-1 Blockade in Resectable Lung Cancer ($n = 202$), and Adjuvant Immunotherapy with Autologous Cytokine-induced Killer Cells for Hepatocellular Carcinoma ($n = 48$) was the most cited for adjuvant immunotherapy (Fig. 1C–F, Supplemental Digital Content 2, http://links.lww.com/JS9/C413, Supplemental Digital Content 3, http://links.lww.com/JS9/C414).

Table 1

Basic characteristics of the data pool.

Description	Neoadjuvant immunotherapy	Adjuvant immunotherapy
Timespan	2000–2023	2000–2023
Journals	227	365
Documents	607	766
Article	405	562
Review	202	204
References	15 581	29 941
Authors	4573	5167
Keywords plus	1036	2000
Author's keywords	923	1553
Annual growth rate	25.18%	6.52%
Document average age	2.19	7.83
Average citations per document	20.35	28.83
Authors of single-authored documents	6	25
Single-authored documents	6	26
Co-authors per document	10.2	7.94
International co-authorships	19.93%	19.84%

Metrological comparative investigation of the prolific scholars or journal leaders in neoadjuvant and adjuvant immunotherapies

Blank CU was the most comprehensive scholar in neoadjuvant immunotherapy, ranking in the top three for all metrological indicators, peaking with the maximum number of annual publications ($n = 5$) and citations ($n = 379$) in 2021 (Fig. 2A, B, E, F, Supplemental Digital Content 4, http://links.lww.com/JS9/C416). With the most number of annual publications ($n = 1$) and citations ($n = 72$) in 2017, Morton DL was the most comprehensive scholar in adjuvant immunotherapy, ranked among the top three for all metrological indicators (Fig. 2C, D, G, H, Supplemental Digital Content 4, http://links.lww.com/JS9/C416). Because of the highest ratio of citations to publications, the Annals of Oncology (1077/2, 538.5) and Nature (598/1, 598) were defined as the journal leaders in neoadjuvant and adjuvant immunotherapies, respectively (Fig. 2I and J). The Annals of Oncology, the journal leader in neoadjuvant immunotherapy, showed an increasing trend in the percentage of annual citations (Fig. 2K), whereas Nature, the journal leader in adjuvant immunotherapy, showed a decreasing trend in the percentage of annual citations (Fig. 2L).

Spatial and temporal distribution and interactions of the prolific countries and affiliations in neoadjuvant and adjuvant immunotherapies

The two leading countries with the most publications were China and the USA (1047 vs. 822), and the USA and China (968 vs. 549) in neoadjuvant and adjuvant immunotherapies, respectively (Fig. 3A, D, C, F). In addition, regarding citations in neoadjuvant and adjuvant immunotherapies, the USA (6116 vs. 7337) ranked first, followed by China (1980 vs. 2709) (Fig. 3B, C, E, F). For both neoadjuvant and adjuvant immunotherapies, the number of citations per year in China showed an upward trend similar to that in the USA (Fig. 3G, H). The USA had the most collaborations with other countries (Italy, 22; UK, 16; Netherlands, 14; France, 12; Japan, 9; Germany, 8; Australia, 8; and Spain, 4) in neoadjuvant immunotherapy (Fig. 3I), and the same was true (Germany: 19; Italy: 16; China: 15; France: 13; Canada: 13; UK: 9; Japan: 6; Australia: 6; Netherlands: 4) in adjuvant immunotherapy (Fig. 3J). The Sun Yat-sen University from China (114 vs. 41) and the MD Anderson Cancer Center from the USA (85 vs. 28) ranked first and second in terms of publications on both neoadjuvant and adjuvant immunotherapies (Fig. 3K, L).

Comparative investigation of spatial and temporal networks of research signatures in neoadjuvant and adjuvant immunotherapies

Unsupervised learning divides the research signature in neoadjuvant immunotherapy into the following five clusters: Cluster 1: 'Tumor microenvironment and cancer immunology', Cluster 2: 'Neoadjuvant immunotherapy clinical trials', Cluster 3: 'Neoadjuvant immunotherapy efficacy', Cluster 4: 'Balance of neoadjuvant immunotherapy efficacy and safety', and Cluster 5: 'Neoadjuvant immunotherapy in combination with other therapies' (Fig. 4A). Similarly, the research signatures in adjuvant

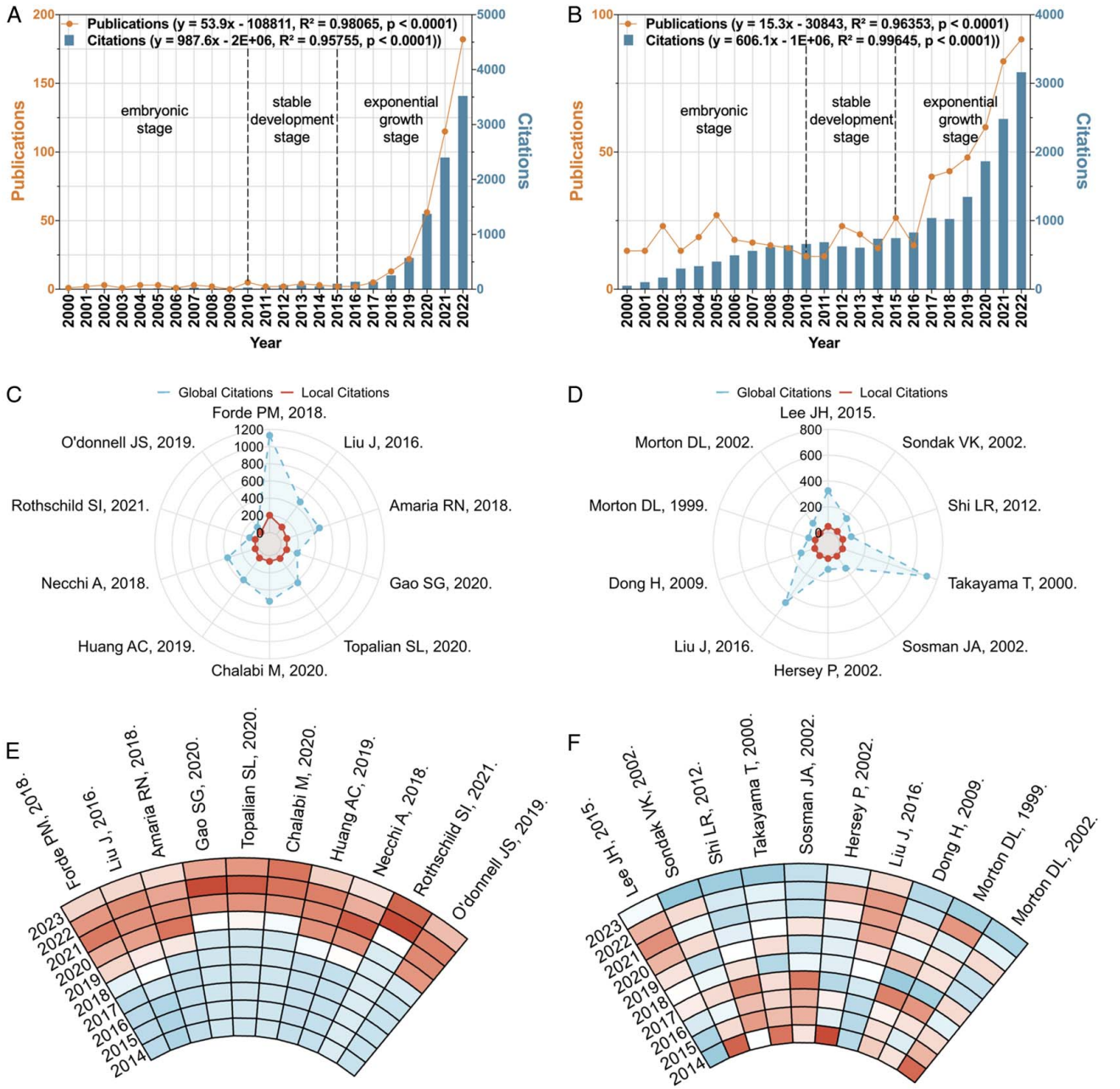

Figure 1. Visualization overview of metrological information in the field of neoadjuvant and adjuvant immunotherapies in oncology. (A) Three stages in the evolutionary patterns of neoadjuvant immunotherapy. (B) Three stages in the evolutionary patterns of adjuvant immunotherapy. Based on the metrological quantities and key events, the field of cancer immunotherapy was divided into three phases from 2000 to 2022: the embryonic stage, the stable development stage, and the exponential growth stage. (C) Global and local citations for the citation classics in the field of neoadjuvant immunotherapy. (D) Global and local citations for the citation classics in the field of adjuvant immunotherapy. (E) Annual citations of the citation classics in the field of neoadjuvant immunotherapy. (F) Annual citations of the citation classics in the field of adjuvant immunotherapy.

immunotherapy were divided into five clusters: Cluster 1: 'Tumor microenvironment and cancer immunology', Cluster 2: 'Adjuvant immunotherapy clinical trials', Cluster 3: 'Adjuvant immunotherapy strategies', Cluster 4: 'Adjuvant immunotherapy in combination with other therapies', and Cluster 5: 'Adjuvant immunotherapy efficacy' (Fig. 4B). The results of the temporal distribution of the research signatures demonstrated that Cluster 4 (APY = 2021.70 ± 0.70) and Cluster 2 (APY = 2017.54 ± 4.59) are emerging research clusters in neoadjuvant and adjuvant immunotherapies, respectively (Fig. 4C, D). For neoadjuvant immunotherapy, the core nodes were immunotherapy [Total Link Strength (TLS) = 2235, Occurrence Frequency (OF) = 260] in Cluster 1, open-label (TLS = 1862, OF = 186) in Cluster 2, neoadjuvant immunotherapy (TLS = 1002, OF = 130) in Cluster 3, surgery (TLS = 745, OF = 81) in Cluster 4, and chemotherapy (TLS = 1766, OF = 205) in Cluster 5 (Fig. 4E, G). The core nodes for adjuvant immunotherapy were immunotherapy (TLS = 2177, OF = 266) in Cluster 1, survival (TLS = 954, OF = 120) in Cluster

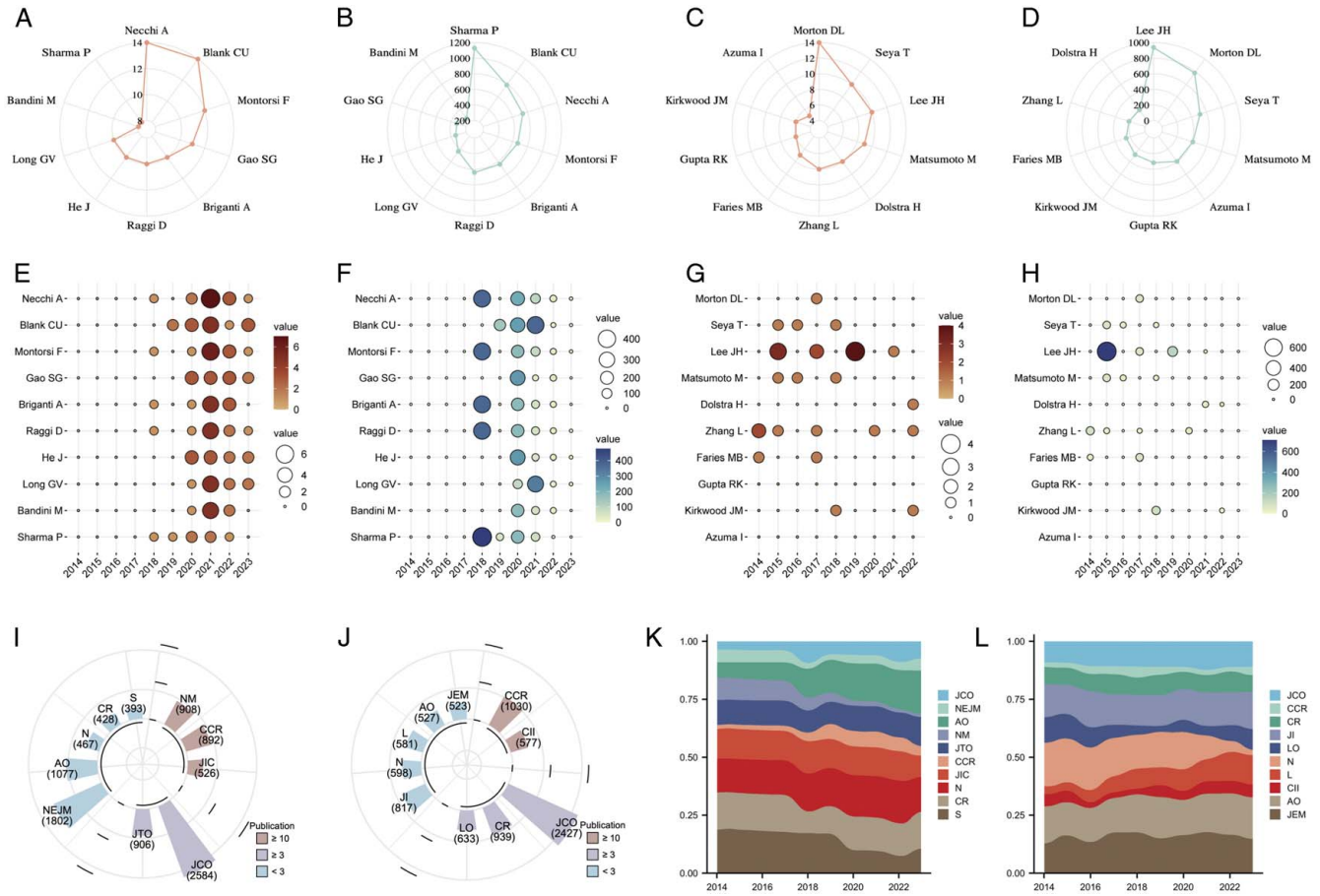

Figure 2. Metrological comparative investigation of the prolific scholars or journal leaders in neoadjuvant and adjuvant immunotherapies. (A) Total publications by the prolific scholars in neoadjuvant immunotherapy. (B) Total citations by the prolific scholars in neoadjuvant immunotherapy. (C) Total publications by the prolific scholars in adjuvant immunotherapy. (D) Total citations by the prolific scholars in adjuvant immunotherapy. (E) Annual publication volume by the prolific scholars in neoadjuvant immunotherapy. (F) Annual citation volume by the prolific scholars in neoadjuvant immunotherapy. (G) Annual publication volume by the prolific scholars in adjuvant immunotherapy. (H) Annual citation volume by the prolific scholars in adjuvant immunotherapy. (I) Citation ray diagrams for the journal leaders in neoadjuvant immunotherapy. Pretriple categorization by publication volume. AO, Annals of Oncology; CR, Cancer Research; CCR, Clinical Cancer Research; JIC, Journal for Immunotherapy of Cancer; JCO, Journal of Clinical Oncology; JTO, Journal of Thoracic Oncology; NM, Nature Medicine; NEJM, New England Journal of Medicine; N, Nature; S, Science. (J) Citation ray diagrams for the journal leaders in adjuvant immunotherapy. Pretriple categorization by publication volume. AO, Annals of Oncology; CR, Cancer Research; CCR, Clinical Cancer Research; CII, Cancer Immunology Immunotherapy; JEM, Journal of Experimental Medicine; JI, Journal of Immunology; JCO, Journal of Clinical Oncology; L, Lancet; LO, Lancet Oncology; N, Nature. (K) Proportional river chart of journal leaders in neoadjuvant immunotherapy. (L) Proportional river chart of journal leaders in adjuvant immunotherapy.

2, vaccines (TLS = 240, OF = 26) in Cluster 3, therapy (TLS = 729, OF = 97) in Cluster 4, and adjuvant immunotherapy (TLS = 1659, OF = 199) in Cluster 5 (Fig. 4F, H).

Burst status, temporal evolution, and regression curve of research signatures in neoadjuvant and adjuvant immunotherapies

For neoadjuvant immunotherapy, Pembrolizumab [Burst Intensity (BI) = 25), Esophageal squamous cell carcinoma (BI = 18), and Bladder cancer (BI = 16) had the highest burst intensities in the last 5 years (Fig. 5A). For adjuvant immunotherapy, Melanoma (BI = 68), Immune checkpoint inhibitors (BI = 35), and Hepatocellular carcinoma (BI = 33) showed the highest burst intensities in the last 2 years (Fig. 5C). For neoadjuvant immunotherapy, the research signatures with slope ≥ 2 are neoadjuvant immunotherapy (a = 3.783, $R^2 = 0.6715$, $P = 0.0069$), nonsmall-cell lung cancer (NSCLC) (a = 3.467, $R^2 = 0.6803$, $P = 0.0062$), neoadjuvant chemotherapy or radiotherapy (a = 2.383, $R^2 = 0.5928$, $P = 0.0152$), and pathological response (a = 2.300, $R^2 = 0.6475$, $P = 0.0089$). The research signatures with slope ≥ 1 are immune checkpoint inhibitors (a = 1.583, $R^2 = 0.5259$, $P = 0.0270$), surgery (a = 1.533, $R^2 = 0.7915$, $P = 0.0013$), bladder cancer (a = 1.317, $R^2 = 0.6342$, $P = 0.0102$), biomarkers (a = 1.267, $R^2 = 0.6505$, $P = 0.0086$) and pembrolizumab (a = 1.117, $R^2 = 0.7319$, $P = 0.0033$). The research signatures with slope ≥ 0.5 are melanoma (a = 0.8500, $R^2 = 0.7361$, $P = 0.0031$), head and neck cancer (a = 0.5667, $R^2 = 0.5352$, $P = 0.0251$), PD-L1 (a = 0.5500, $R^2 = 0.5876$, $P = 0.0160$), tumor microenvironment (a = 0.5333, $R^2 = 0.6857$, $P = 0.0058$), and clinical trials (a = 0.5167, $R^2 = 0.7430$, $P = 0.0028$). The research signatures with slope <0.5 are PD-1 (a = 0.4833, $R^2 = 0.6371$, $P = 0.0099$), colorectal cancer (a = 0.3833, $R^2 = 0.8097$, $P = 0.0009$), atezolizumab (a = 0.3000, $R^2 = 0.5283$, $P = 0.0265$), renal cell carcinoma (a = 0.2500, $R^2 = 0.6250$, $P = 0.0112$),

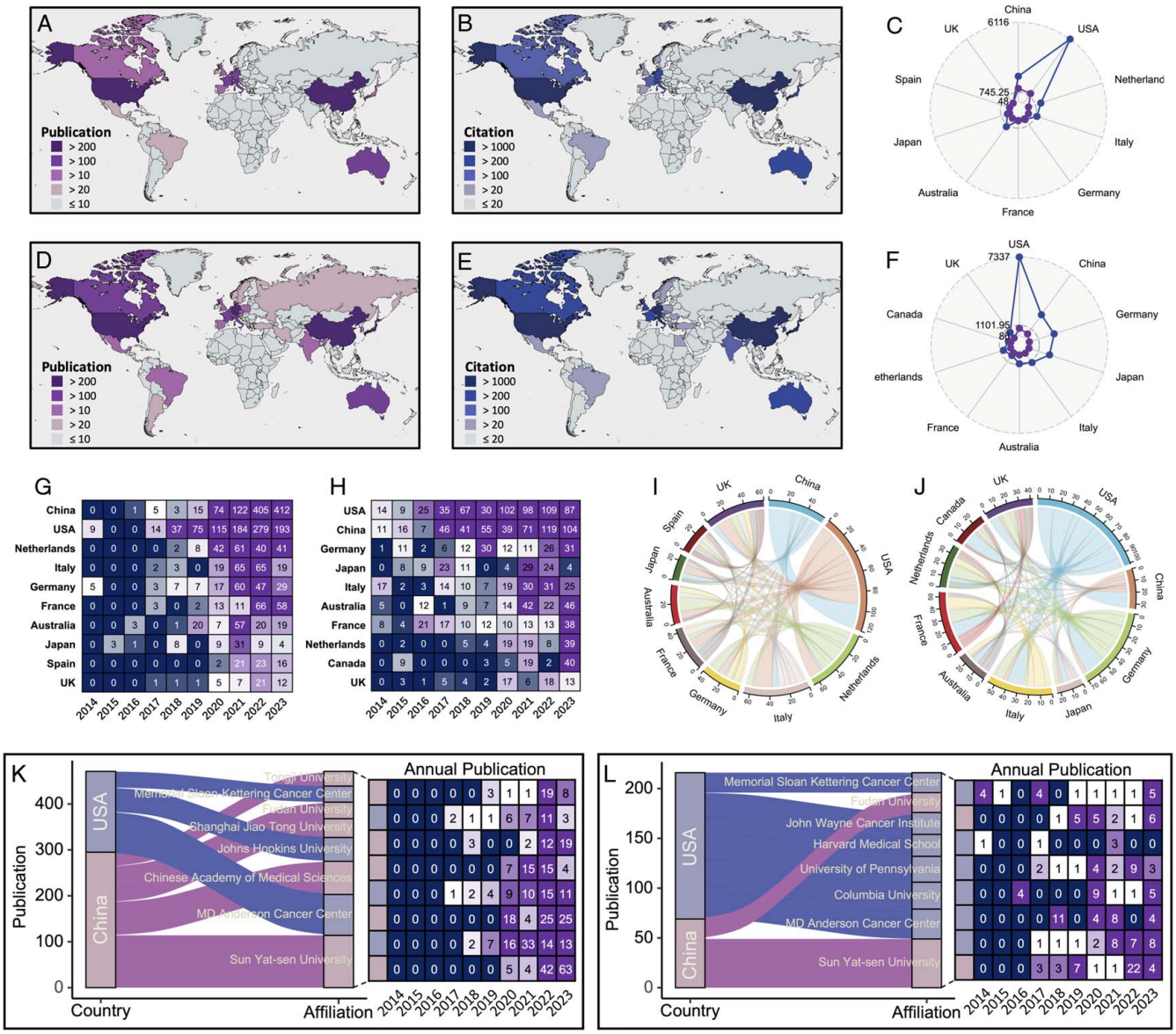

Figure 3. Spatial and temporal distribution and interactions of the prolific countries and affiliations in neoadjuvant immunotherapy and adjuvant immunotherapies. (A) Total publications by the prolific countries in neoadjuvant immunotherapy. (B) Total citations by the prolific countries in neoadjuvant immunotherapy. (C) Metrological comparison of publication and citation volume by the prolific countries in neoadjuvant immunotherapy. (D) Total publications by the prolific countries in adjuvant immunotherapy. (E) Total citations by the prolific countries in adjuvant immunotherapy. (F) Metrological comparison of publication and citation volume by the prolific countries in adjuvant immunotherapy. (G) Annual publications by the prolific countries in neoadjuvant immunotherapy. (H) Annual publications by the prolific countries in adjuvant immunotherapy. (I) Spatial interactions of the prolific countries in neoadjuvant immunotherapy. (J) Spatial interactions of the prolific countries in adjuvant immunotherapy. (K) National attribution and annual publications of the prolific affiliations in neoadjuvant immunotherapy. (L) National attribution and annual publications of the prolific affiliations in adjuvant immunotherapy.

toripalimab (a = 0.2500, $R^2 = 0.4561$, $P = 0.0459$), microsatellite instability (a = 0.1667, $R^2 = 0.7500$, $P = 0.0025$) (Fig. 5B). For adjuvant immunotherapy, the research signatures with slope ≥ 1 are adjuvant immunotherapy (a = 3.783, $R^2 = 0.8468$, $P = 0.0004$), and NSCLC (a = 1.333, $R^2 = 0.5941$, $P = 0.0151$). The research signatures with slope ≥ 0.5 are melanoma (a = 0.9833, $R^2 = 0.6593$, $P = 0.0079$), and PD-1 (a = 0.5333, $R^2 = 0.6857$, $P = 0.0058$). The research signatures with slope <0.5 are adjuvant chemotherapy (a = 0.4500, $R^2 = 0.4882$, $P = 0.0363$), prognosis (a = 0.4333, $R^2 = 0.5633$, $P = 0.0198$), tumor microenvironment (a = 0.4333, $R^2 = 0.5571$, $P = 0.0209$), recurrence (a = 0.3667, $R^2 = 0.7408$, $P = 0.0029$), esophageal cancer (a = 0.3333, $R^2 = 0.6977$, $P = 0.0051$), nivolumab (a = 0.3333, $R^2 = 0.6667$, $P = 0.0072$), metastasis (a = 0.3000, $R^2 = 0.5651$, $P = 0.0195$), and breast cancer (a = 0.2500, $R^2 = 0.6750$, $P = 0.0066$) (Fig. 5D).

Potentiality comparison investigation of research signatures in the field of neoadjuvant immunotherapy and adjuvant immunotherapies

Based on the degree of relevance and development, all research signatures were categorized into four quadrants: Motor Themes

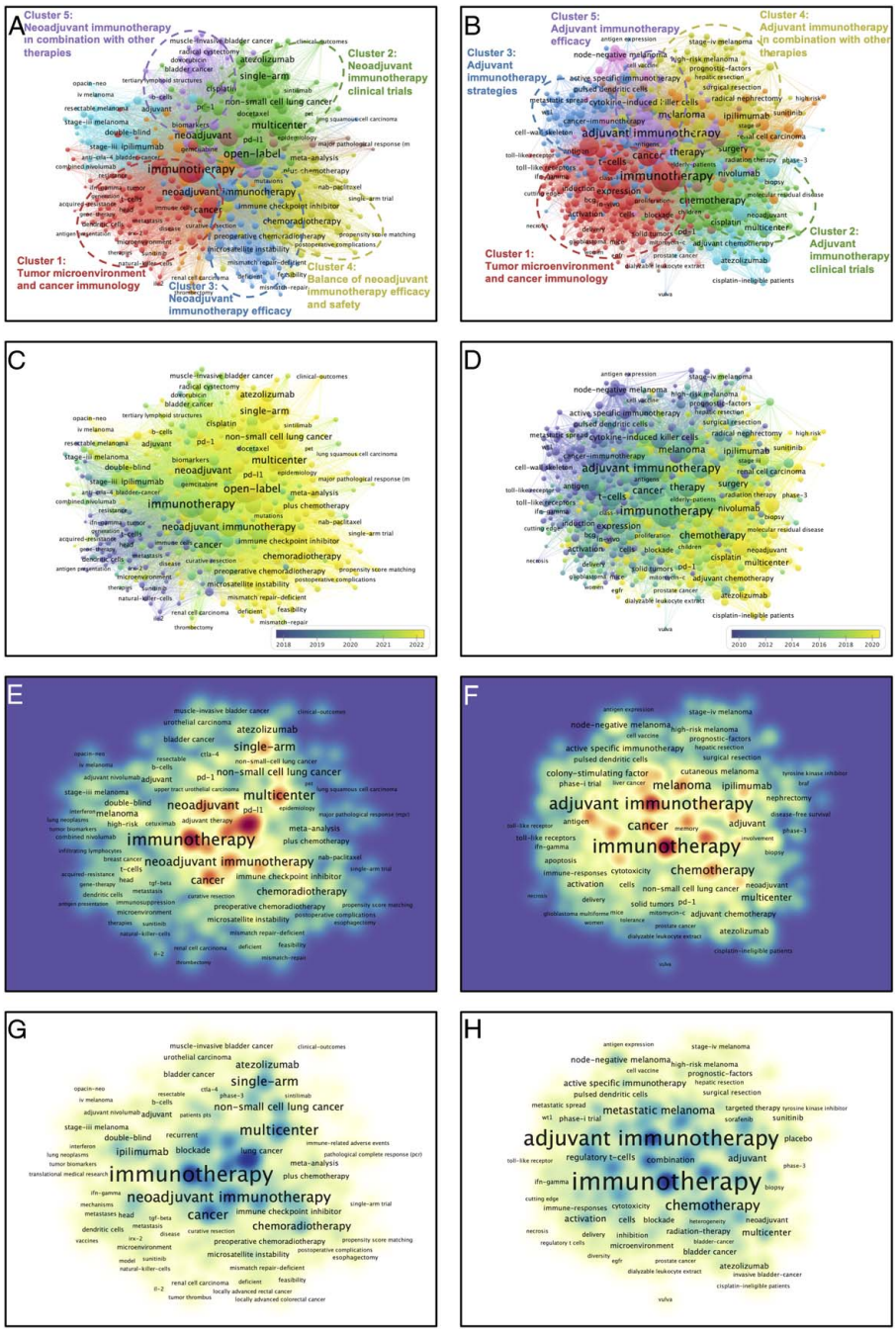

Figure 4. Comparative investigation of spatial and temporal networks of research signatures in the fields of neoadjuvant immunotherapy and adjuvant immunotherapies. (A) Unsupervised learning hierarchical clustering of research signatures in neoadjuvant immunotherapy. (B) Unsupervised learning hierarchical clustering of research signatures in adjuvant immunotherapy. (C) Temporal distribution pattern of research signatures in neoadjuvant immunotherapy. (D) Temporal distribution pattern of research signatures in adjuvant immunotherapy. (E) Spatial density network based on connection frequency for research signatures in neoadjuvant immunotherapy. (F) Spatial density network based on connection frequency for research signatures in adjuvant immunotherapy. (G) Spatial density network based on occurrence frequency for research signatures in neoadjuvant immunotherapy. (H) Spatial density network based on occurrence frequency for research signatures in adjuvant immunotherapy.

(Quadrant I, representing highly relevant and rapidly developing topics), Niche Themes (Quadrant II, representing relatively small areas of particular importance), Emerging or Declining Themes (Quadrant III, representing topics that are emerging or declining), and Basic Themes (Quadrant IV, representing topics that are broadly relevant but still not well-developed).

In the field of neoadjuvant immunotherapy, 'renal cell carcinoma, ipilimumab' [Relevance Percentage (RP) = 87.5%, Development Percentage (DP) = 100%], and 'overall survival, disease-free survival' (RP = 79.2%, DP = 70.8%) were identified as highly relevant and rapidly developing topics in Quadrant I. In Quadrant II, 'tumor biomarkers' (RP = 54.2%, DP = 91.7%),

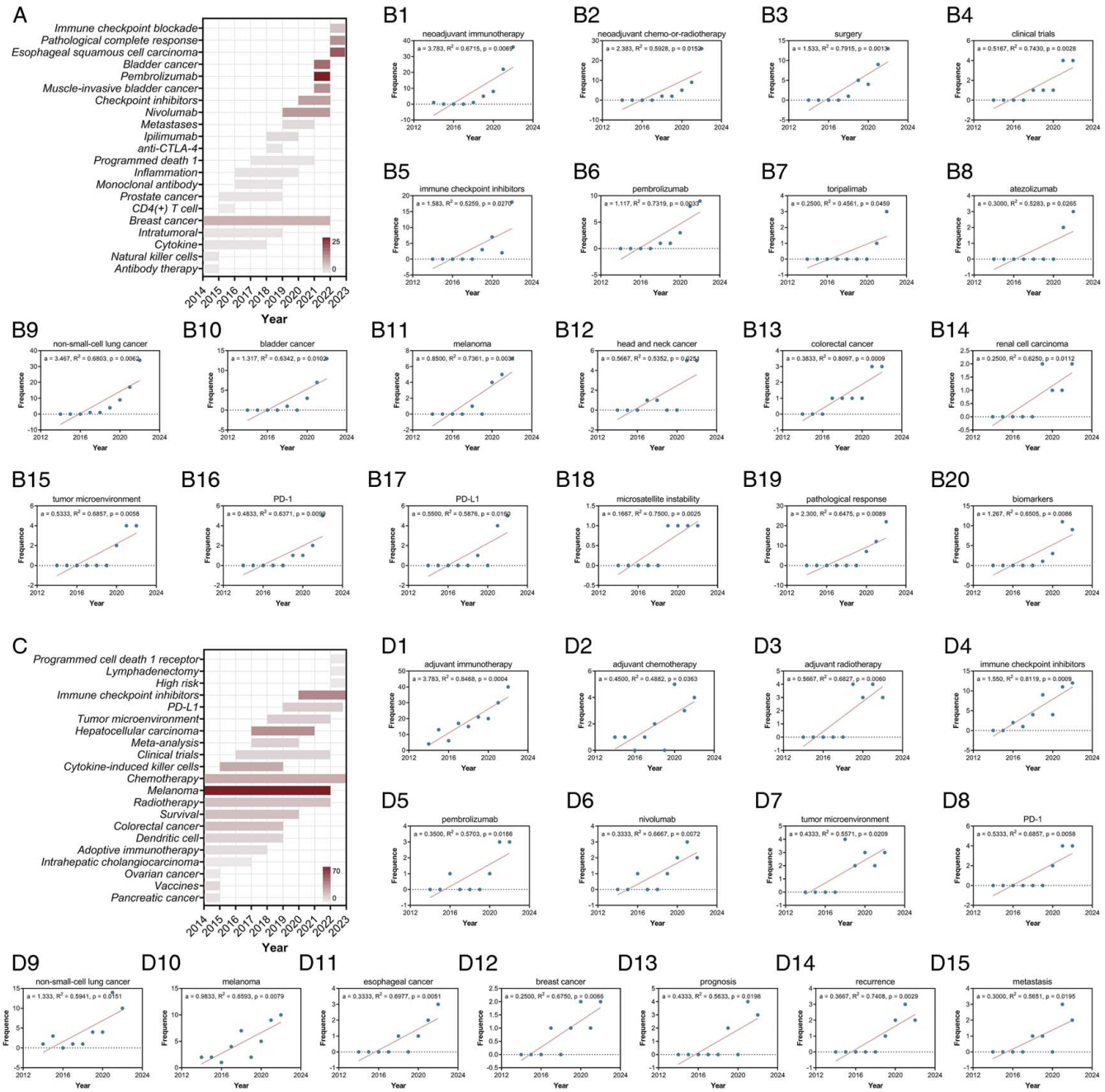

Figure 5. Burst status, temporal evolution, and regression curve of research signatures in neoadjuvant and adjuvant immunotherapies. (A) Burst status and temporal evolution of research signatures in neoadjuvant immunotherapy. (B) Populations of annual frequency-based regression models for research signatures in neoadjuvant immunotherapy. 'a' denotes the slope; 'R^2' denotes the goodness of fit ('$P < 0.05$' indicates statistical significance). (C) Burst status and temporal evolution of research signatures in adjuvant immunotherapy. (D) Populations of annual frequency-based regression models for research signatures in adjuvant immunotherapy.

'liquid biopsy' (RP = 22.9%, DP = 70.8%), and 'programmed cell death protein 1' (RP = 22.9%, DP = 70.8%) were identified as relatively small areas of particular importance. In Quadrant III, 'tislelizumab, cisplatin' (RP = 45.8%, DP = 43.8%) was identified as a topic that is emerging or declining. In Quadrant IV, 'neoadjuvant immunotherapy, NSCLC, immune checkpoint inhibitors, melanoma' (RP = 100%, DP = 37.5%), 'immune checkpoint inhibitor, safety, pathological complete response' (RP = 95.8%, DP = 8.33%), 'interleukin-2' (RP = 83.3%, DP = 25.0%), and 'MSI-H' (RP = 66.7%, DP = 50.0%) were identified as topics that are broadly relevant but still not well-developed (Fig. 6A). In the field of adjuvant immunotherapy, 'metastatic melanoma, immune therapy' (RP = 91.4%, DP = 91.4%), 'car-t' (RP = 82.9%, DP = 71.4%), and 'immunomodulation, nanoparticles' (RP = 74.3%, DP = 94.3%) were identified as highly relevant and rapidly developing topics in Quadrant I. In the Quadrant II, 'ovarian cancer, TIGIT' (RP = 28.6%, DP = 100%) was identified as a relatively small

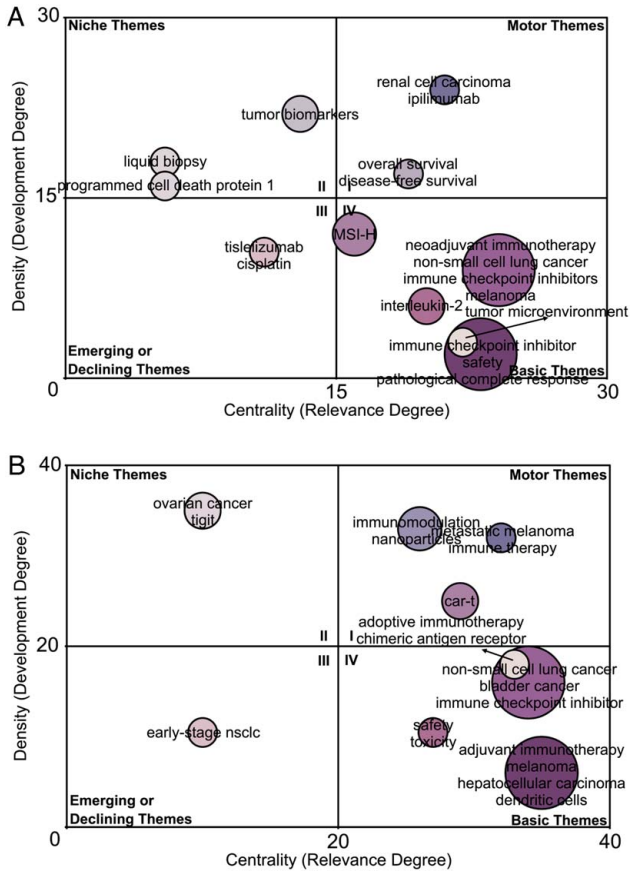

Figure 6. Potentiality comparison investigation of research signatures in neoadjuvant immunotherapy and adjuvant immunotherapies. (A) Potentiality discovery of research signatures in neoadjuvant immunotherapy. (B) Potentiality discovery of research signatures in adjuvant immunotherapy.

area of particular importance. In Quadrant III, 'early-stage NSCLC' (RP = 28.6%, DP = 30%) was identified as a topic that is emerging or declining. In Quadrant IV, 'adjuvant immunotherapy, melanoma, hepatocellular carcinoma, dendritic cells' (RP = 100%, DP = 17.1%), 'NSCLC, bladder cancer, immune checkpoint inhibitor' (RP = 97.1%, DP = 45.7%), 'adoptive immunotherapy, chimeric antigen receptor' (RP = 94.3%, DP = 51.4%), and 'safety, toxicity' (RP = 77.1%, DP = 30%) were identified as topics that are broadly relevant but still not well-developed (Fig. 6B).

Notably, research signatures in Quadrant IV have exceptionally high relevance to the field but are yet to be fully developed, highlighting their importance, and warranting further exploration.

Discussion

This cross-sectional study mainly aimed to comparatively analyze the global scientific landscapes of neoadjuvant and adjuvant immunotherapies in oncology using machine learning-based informatics analysis. Although the role of adjuvant immunotherapy in perioperative cancer patients should not be underestimated, considering the intervention stage and effect characteristics of these approaches, we hypothesized that neoadjuvant immunotherapy deserves more attention to leverage the body's anticancer immunity in a more integrated manner at an earlier intervention stage to achieve more robust control of cancer development and dissemination. Through unsupervised hierarchical clustering and times series analysis, we found that 'Balance of neoadjuvant immunotherapy efficacy and safety' and 'Adjuvant immunotherapy clinical trials' are the crucial emerging research populations in the neoadjuvant and adjuvant scenarios, respectively. Using the random-walk strategy-based Walktrap algorithm, we found that 'neoadjuvant immunotherapy, NSCLC, immune checkpoint inhibitors, melanoma' and 'adjuvant immunotherapy, melanoma, hepatocellular carcinoma, dendritic cells' are extremely relevant but still underdeveloped directions for this field that warrant further investigation.

Consistent with our findings, a bibliometric analysis solely on neoadjuvant immunotherapy reported that current research on neoadjuvant immunotherapy focuses on NSCLC, bladder cancer, melanoma, immunotherapy, immune checkpoint inhibitors, tumor microenvironments, pathological responses, and biomarkers. However, our results were validated using statistical and regression analyses[27]. Moreover, we identified promising research prospects for head and neck cancer, colorectal cancer, and pembrolizumab, toripalimab, and atezolizumab in neoadjuvant immunotherapy with statistically significant evidence. Notably, Jiang *et al.*[27] reported that breast cancer, radical cystectomy, and ipilimumab will be future research hotspots; however, our study found that these themes did occur with a specific frequency, but failed to gain further statistical support. The discrepancy in the above results may be attributed to extensive confounders in Jiang *et al.*'s findings owing to errors in their retrieval process, which were promptly addressed and experimentally confirmed in a follow-up study[28].

Through hierarchical clustering and time-series analysis, our study found that 'Balance of neoadjuvant immunotherapy efficacy and safety' is a crucial emerging research population in the neoadjuvant immunotherapy scenarios. Readers of this paper need to be aware that although immunotherapy efficacy is a key concern in current clinical research, the obsessive pursuit of efficacy is also irrational, as excessive immune activation leads to immune-inflammatory responses, autoimmune reactions, and other adverse events. The balance between efficacy and safety is crucial for patients and is a major concern in current clinical practice[29–32]. In addition, the results of the spatial and temporal networks, burst statuses, temporal evolution, regression curves, and potential discoveries of the research signatures all indicate that researchers are highlighting the exploration of immune checkpoint inhibitors, especially PD-1, PD-L1, and CTLA-4. However, in current clinical practice, these immune checkpoint inhibitors fail to yield absolute efficacy in all patients[33–35]. And readers need to take note that one of the principal challenges in immunotherapy is identifying individuals with optimal benefits. Yet, our study revealed that current research direction focused on exploring biomarkers or constructing predictive models based on healthcare big data generated from routine clinical procedures (e.g. radiological images, pathological images, medical history, and bioinformatics tests) may help predict the efficacy or toxicity of immunotherapy for patients as a strategy to achieve the purpose of treatment stratification[36–41]. Notably, comprehensive quantitative comparisons demonstrated a shift in focus after 2020 from adjuvant immunotherapy to that of neoadjuvant immunotherapy. Consequently, this qualitative finding will

facilitate appropriate decision-making for subsequent research and mitigate the risk of healthcare resources waste.

Nevertheless, this study had several potential limitations. First, to avoid excessive confounders and pursue solid findings, only the most authoritative high-quality database, the WOSCC, was used in this study, and nonpeer-reviewed documents were excluded. However, owing to the comprehensive and authoritative nature of the WOSCC, its data are sufficient to represent the entire research field of cancer immunotherapy. Future studies could attempt to integrate other databases, such as PubMed, Embase, and Scopus; however, duplicate data and confounding factors from other databases should be considered. Second, owing to limited space, a wealth of visualization results in this study were not adequately presented and discussed. Future studies validating these results are anticipated and may provide potential insights into the current cancer immunotherapy domain. Finally, this study did not directly confirm exactly which among the neoadjuvant immunotherapy or adjuvant immunotherapy would be most beneficial for perioperative patients with cancer, in particular. However, our study provides an essential theoretical basis for subsequent clinical trials of neoadjuvant and adjuvant immunotherapies from the perspective of informatics analysis, which will considerably boost researchers' confidence and facilitate them to implement proper decision-making. Future studies with the inclusion of multiple clinical factors and large-sample randomized controlled trials could comparatively assess the efficacy of neoadjuvant and adjuvant immunotherapies in perioperative patients with cancer to provide more definitive regimens for these patients.

Conclusion

This cross-sectional study provides the first comparative analysis of the global scientific landscape of neoadjuvant and adjuvant immunotherapies. The fields of neoadjuvant and adjuvant immunotherapies have witnessed promising developmental status and global collaboration over the last decade. Through hierarchical clustering and time-series analysis, we showed that the balance between immunotherapy efficacy and safety is crucial for patients and is a potential concern in current clinical practice. In addition, current research is focused on identifying biomarkers or constructing predictive models based on healthcare big data to predict immunotherapy efficacy or toxicity for patient stratification management. Comprehensive quantitative comparisons indicated that the focus in this field shifted considerably to neoadjuvant immunotherapy after 2020. This qualitative finding will aid in effective decision-making for subsequent research and avoid the wastage of healthcare resources.

Ethical approval

This study did not involve patients and therefore did not require ethical approval.

Consent

The study did not involve patients or volunteers and therefore did not require ethics committee approval and fully informed written consent.

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Author contribution

S.-B.G.: conceptualization, data curation, investigation, methodology, visualization, and writing – original draft; L.-S.H. and W.-J.H.: data curation, investigation, and validation; Z.-Z.Z.: data curation and validation; H.-Y.L. and X.-P.T.: conceptualization, project administration, supervision; and writing – review and editing.

Conflicts of interest disclosure

All authors declare that there is no potential commercial or financial interest in this study.

Research registration unique identifying number (UIN)

This study does not involve human participants, so this section is exempt.

Guarantor

Xiao-Peng Tian and Hui-Yan Luo.

Data availability statement

The data used in this study were obtained from public databases and are therefore inherently insensitive and available. All raw data used in this study can be obtained from the corresponding author for appropriate reasons.

Provenance and peer review

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