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Advancing the understanding of the role of apoptosis in lung cancer immunotherapy: Global research trends, key themes, and emerging frontiers

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ABSTRACT

Apoptosis is vital for improving the efficacy of lung cancer (LC) immunotherapy by targeting cancer cell elimination. Despite its importance, there is a lack of comprehensive bibliometric studies analyzing global research on apoptosis in LC immunotherapy. This analysis aims to address this gap by highlighting key trends, contributors, and future directions. A total of 969 publications from 1996 to 2024 were extracted from the Web of Science Core Collection. Analysis was conducted using VOSviewer, CiteSpace, and the R package 'bibliometrix.' The study included contributions from 6,894 researchers across 1,469 institutions in 61 countries, with research published in 356 journals. The volume of publications has steadily increased, led by China and the United States, with Sichuan University as the top contributor. The journal *Cancers* published the most articles, while *Cancer Research* had the highest co-citations. Yu-Quan Wei was the leading author, and Jemal, A. was the most frequently co-cited. Key research themes include "cell death mechanisms," "immune regulation," "combination therapies," "gene and nanomedicine applications," and "traditional Chinese medicine (TCM)." Future research is likely to focus on "coordinated regulation of multiple cell death pathways," "modulation of the tumor immune microenvironment," "optimization of combination therapies," "novel strategies in gene regulation," and the "integration of TCM" for personalized treatment. This is the first bibliometric analysis on the role of apoptosis in LC immunotherapy, providing an landscape of global research patterns and emerging therapeutic strategies. The findings offer insights to guide future research and optimize treatment approaches.

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Introduction

Lung cancer (LC) remains the leading cause of cancer-related mortality worldwide. Treatment options include surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy.[1,2] Surgery is suitable for early-stage non-small cell lung cancer (NSCLC), but due to late diagnosis in most cases, advanced-stage patients often rely on chemotherapy and radiotherapy, which are limited by systemic toxicity and drug resistance.[3,4] Targeted therapies (e.g., *EGFR* and *ALK* inhibitors) have shown promise but are often limited by tumor heterogeneity and resistance. Likewise, immune checkpoint inhibitors (ICIs), such as programmed death-1 (PD-1)/programmed cell death 1 ligand 1 (PD-L1) inhibitors, show limited efficacy and adverse effects in a significant number of patients.[5,6]

The tumor's ability to evade apoptosis limits response to immunotherapy, underscoring the critical role of apoptosis in LC treatment. Apoptosis, a programmed cell death process, involves both intrinsic (mitochondrial) and extrinsic (death receptor) pathways. Intrinsic apoptosis can be triggered by genetic damage or stress, leading to the release of molecules like cytochrome c, which activates caspase-3, resulting in cell death.[7] While traditionally viewed as separate mechanisms, recent research has revealed significant crosstalk between intrinsic and extrinsic apoptotic pathways in LC, with implications for immunotherapy response.[8–11] The extrinsic pathway, initiated by immune cell-derived death ligands such as *Fas* ligand (FasL) and *TNF*-related apoptosis-inducing ligand (TRAIL) binding to their corresponding receptors on tumor cells, can activate the intrinsic pathway through BH3 interacting domain death agonist (Bid) cleavage, amplifying the apoptotic signal through mitochondrial outer membrane permeabilization.[12–14] This amplification is particularly relevant in LC cells, which often require this mitochondrial amplification loop for effective apoptosis execution following immunotherapy.[12] Balancing pro- and anti-apoptotic *BCL-2* family proteins can enhance anti-tumor effects, and *BCL-2* inhibitors have been shown to improve ICIs' efficacy.[15,16] The extrinsic pathway, mediated by death receptors (e.g., *Fas*, *TNF* receptors), also activates apoptosis, and targeting these receptors can enhance immunotherapy effectiveness for resistant LC.[17,18]

Dysregulation of apoptotic pathways plays a multifaceted role in immunotherapy resistance in LC. Previous studies have revealed that tumor cells develop specific mechanisms to evade apoptosis-mediated immune clearance, including downregulation of death receptors, increased expression of decoy receptors, and alterations in downstream signaling components.[19–21] LC

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cells frequently develop simultaneous resistance to both apoptotic pathways, with intrinsic pathway blockade (via *BCL-2* upregulation) complemented by extrinsic pathway alterations (via *c-FLIP* upregulation and death receptor downregulation), creating a formidable barrier to immunotherapy-induced cell death.[13,22] This dual-pathway resistance is particularly pronounced in NSCLC subtypes with high mutational burden, where immune effector cells can recognize tumor antigens but fail to induce apoptosis despite successful immune synapse formation.[23,24] In particular, the upregulation of anti-apoptotic proteins like X-linked inhibitor of apoptosis protein (XIAP) and *Survivin* has been shown to directly impair cytotoxic T-lymphocyte (CTL)-mediated tumor cell killing, a key mechanism of ICI action.[25,26] Furthermore, tumor-derived exosomes containing microRNAs that target pro-apoptotic factors have been identified as important mediators of immunotherapy resistance in NSCLC patients.[27–29]

Tumor cells further evade immune surveillance by upregulating anti-apoptotic proteins like *BCL-2* and suppressive factors like *TGF-β* and *IL-10*, reducing immunotherapy efficacy. The coordinated dysregulation of both apoptotic pathways creates a unique challenge in LC immunotherapy. ICI therapy primarily enhances extrinsic apoptosis through restored immune cell cytotoxicity, but this effect is often neutralized when the intrinsic pathway is concurrently inhibited.[30,31] Recent studies demonstrate that successful immunotherapy in LC requires competent signaling in both pathways, with genetic alterations in either pathway sufficient to confer treatment resistance.[32] Recent evidence demonstrates that activated *BCL-2* not only prevents tumor cell death but also modulates the tumor microenvironment (TME) by inhibiting dendritic cell (DC) maturation and reducing T-cell priming, directly compromising ICI efficacy.[33–37] Moreover, *BCL-2*-mediated resistance creates an immunosuppressive TME characterized by increased regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), further diminishing anti-tumor immune responses.[38,39] Therefore, enhancing apoptotic pathways is a key strategy to improve treatment outcomes. Targeting *BCL-2* and related pathways has become a promising area of research for overcoming immunotherapy resistance. Emerging research from 2020–2024 has shown that dual targeting of apoptotic pathways and immune checkpoints can synergistically overcome resistance mechanisms and restore immunosurveillance in LC.[9,40–43]

Despite growing research interest in apoptosis in LC immunotherapy, systematic bibliometric analysis is still lacking. This analysis is needed to comprehensively assess apoptosis's impact in this context, identify key trends, and determine future research directions. This study aims to fill this gap by analyzing global literature from 1996 to 2024, focusing on:

(1) What are the main trends and emerging topics in apoptosis research in LC immunotherapy?
(2) Which countries and institutions have leading roles in this field?
(3) How do international collaborations and citation networks influence research on apoptosis in LC immunotherapy?
(4) What specific effects does apoptosis have on LC immunotherapy?
(5) Which areas have the greatest potential to become future research hotspots?

Using advanced bibliometric tools like VOSviewer and CiteSpace, this study aims to map out key areas in apoptosis research, providing a foundation for future studies and enhancing LC treatment strategies to improve patient outcomes. This bibliometric analysis directly connects to real-world clinical challenges in LC immunotherapy, including treatment resistance, patient response heterogeneity, and lack of reliable biomarkers. By identifying research hotspots and emerging strategies, this study aims to guide future investigations toward solutions for these pressing clinical problems, ultimately improving patient outcomes through more targeted therapeutic approaches.

Methods

Publication search

A comprehensive search of the Web of Science Core Collection (WoSCC) database was carried out to identify studies on the role of apoptosis in LC immunotherapy, covering the period from January 1, 1990, to September 28, 2024. Details regarding the specific search terms and strategies are available in Supplementary Table S1. WoSCC was chosen due to its extensive collection of high-quality, peer-reviewed journals, making it well-suited for bibliometric analyses. The detailed metadata and citation features provided by WoSCC improved the precision of the analysis.

Inclusion criteria

(1) Only articles and review papers published in English were considered.
(2) Studies specifically addressing the role of apoptosis in LC immunotherapy were included.

Exclusion criteria

Publications such as editorials, letters, and book chapters were excluded.

Literature screening process

During the literature screening process, we focused on apoptosis in tumor cells within the context of enhancing immunotherapy. Studies primarily examining immune cell apoptosis, particularly its immunosuppressive effects, were excluded unless their relevance to immunotherapy efficacy was explicitly demonstrated. The initial search retrieved 978 records. After limiting the results to English-language publications, 976 records remained. Screening titles and abstracts excluded 7 records that did not meet the inclusion criteria, resulting in a total of 969 studies. These comprised 755 research articles and 214 review papers (see Supplementary Figure S1).

Data analysis

We performed the bibliometric analysis using VOSviewer (version 1.6.19) and CiteSpace (version 6.2 R3) for visualization purposes.

VOSviewer was used to create visual networks that illustrate the relationships and influence among countries, institutions, journals, researchers, and publications.[44] These networks were constructed based on citation data, co-citation patterns, bibliographic coupling, and co-authorship connections. Nodes in the visualizations represented elements such as keywords, authors, or regions, while their size and color indicated the quantity and category. Lines connecting nodes depicted relationships like collaboration or co-citation links.

CiteSpace was employed to generate dual-map overlays, which emphasized citation bursts in references and sources, as well as identifying the strongest citation bursts among keywords, references, countries, and institutions.[45,46]

The R package bibliometrix (version 4.3.1) was also used to produce global distribution maps and thematic maps.[47] For quantitative data analysis, Microsoft Office Excel 2021 was used to ensure accurate management and processing of publication data.

Result

Quantitative analysis of publications

This analysis includes 969 publications by 6,894 researchers from 1,469 institutions in 61 countries, published across 356 journals, spanning 1996 to 2024. The earliest study appeared in 1996, with annual publications ranging from 1 to 5 until 2004. From 2005 to 2014, annual output increased to 8–19 articles. A significant rise in publications occurred after 2015, as shown in Figure 1(a). Projections suggest a continued increase in publication output, reaching 180 in 2024, 218 in 2025, and 262 in 2026, with an average annual growth rate of 20.46% from 2024 to 2026. These trends reflect expanding research interest in this domain.

Country and institution

Research on the role of apoptosis in LC immunotherapy involves contributions from 1,469 institutions across 61 countries. As illustrated in Figures 1(b-d), China, the United States, and Japan lead this research, with China publishing the most papers (n = 560) (Table 1). Although China ranks first in both publication count (n = 560) and total citations (14,670), the United States has the highest average citations per publication (48.89) and a centrality index of 0.51, highlighting its greater research impact and global collaboration. This global research effort reflects the growing recognition that understanding apoptotic mechanisms is crucial for overcoming immunotherapy resistance in LC. The blockade of immune checkpoints, particularly the application of cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and PD1 antibodies proposed by the Johns Hopkins University School of Medicine in the United States, demonstrates the potential to activate antitumor immunity in LC immunotherapy, potentially leading to durable clinical responses.[48] This pioneering work established the foundation for targeting immune checkpoint pathways that regulate T cell-mediated apoptosis of tumor cells.

Japan, Germany, and South Korea contribute moderately, with Germany's centrality index (0.24) indicating active international collaboration. A study conducted by the Lung Clinic Grosshansdorf in Germany, in collaboration with multiple institutions, demonstrated that in patients with advanced NSCLC with at least 50% PD-L1 expression, the use of *pembrolizumab* immunotherapy significantly prolonged progression-free survival and overall survival, while also showing a lower incidence of treatment-related adverse events compared to platinum-based chemotherapy, highlighting the potential of immunotherapy in overcoming tumor cell apoptosis resistance.[49] This breakthrough research demonstrates how modulating the PD-1/PD-L1 axis not only enhances T cell activity but also counteracts the apoptosis resistance mechanisms that LC cells develop to evade immune surveillance.

All of the top 10 contributing institutions are based in China (Figure 2, Table 1). Sichuan University has the highest publication count (n = 28), while Fudan University leads in total citations (1,664) and centrality (0.1), reflecting its strong academic influence and collaborations. A study from Fudan University in Shanghai demonstrated that tryptophan and its metabolic inhibitors promote apoptosis of cancer cells by reducing PD-1 expression and enhancing the cytotoxicity of CD8+ T cells, suggesting that combining tryptophan supplementation with indoleamine 2,3-dioxygenase (*IDO*) inhibitors and PD-1 blockade may enhance immunotherapeutic efficacy in LC treatment.[50] This research elucidates a key metabolic pathway connecting immune checkpoint expression with apoptotic signaling, representing a novel approach to overcome LC cell resistance to immunotherapy-induced cell death. Sun Yat-sen University and Nanjing Medical University also show significant impact, with high citations and centrality values. Research conducted at Sun Yat-sen University revealed that immunization with LC cell extracts combined with TNBS effectively induces specific CD8(+) CD196(+) T cells, which in turn suppress LC growth and facilitate the apoptosis of cancer cells, underscoring the promise of LC-specific immunotherapy.[51] This approach demonstrates how targeted immunotherapy can activate cytotoxic T cells to directly trigger apoptotic pathways in LC cells, bypassing multiple resistance mechanisms. In addition, a study from Nanjing Medical University has underscored the critical role of NADPH oxidase 4 (*NOX4*) in acquired resistance to *EGFR* tyrosine kinase inhibitors (TKIs) in LC. The research revealed that *NOX4* regulates the expression of the transcription factor YY1 and interleukin-8 (*IL-8*), which are essential for tumor cell resistance and immune evasion. Notably, elevated levels of *NOX4* and *IL-8* were linked to poorer responses to anti-PD-L1 therapy in LC patients. This finding highlights the complex interplay between oxidative stress pathways, apoptosis regulation, and immune checkpoint signaling, suggesting that targeting *NOX4* could sensitize LC cells to both TKI-induced and immunotherapy-mediated apoptosis. This suggests that *NOX4* and *IL-8* may serve as promising new biomarkers and therapeutic targets for overcoming TKI resistance and improving the effectiveness of immunotherapy in LC treatment.[52] Figure 2 underscores the

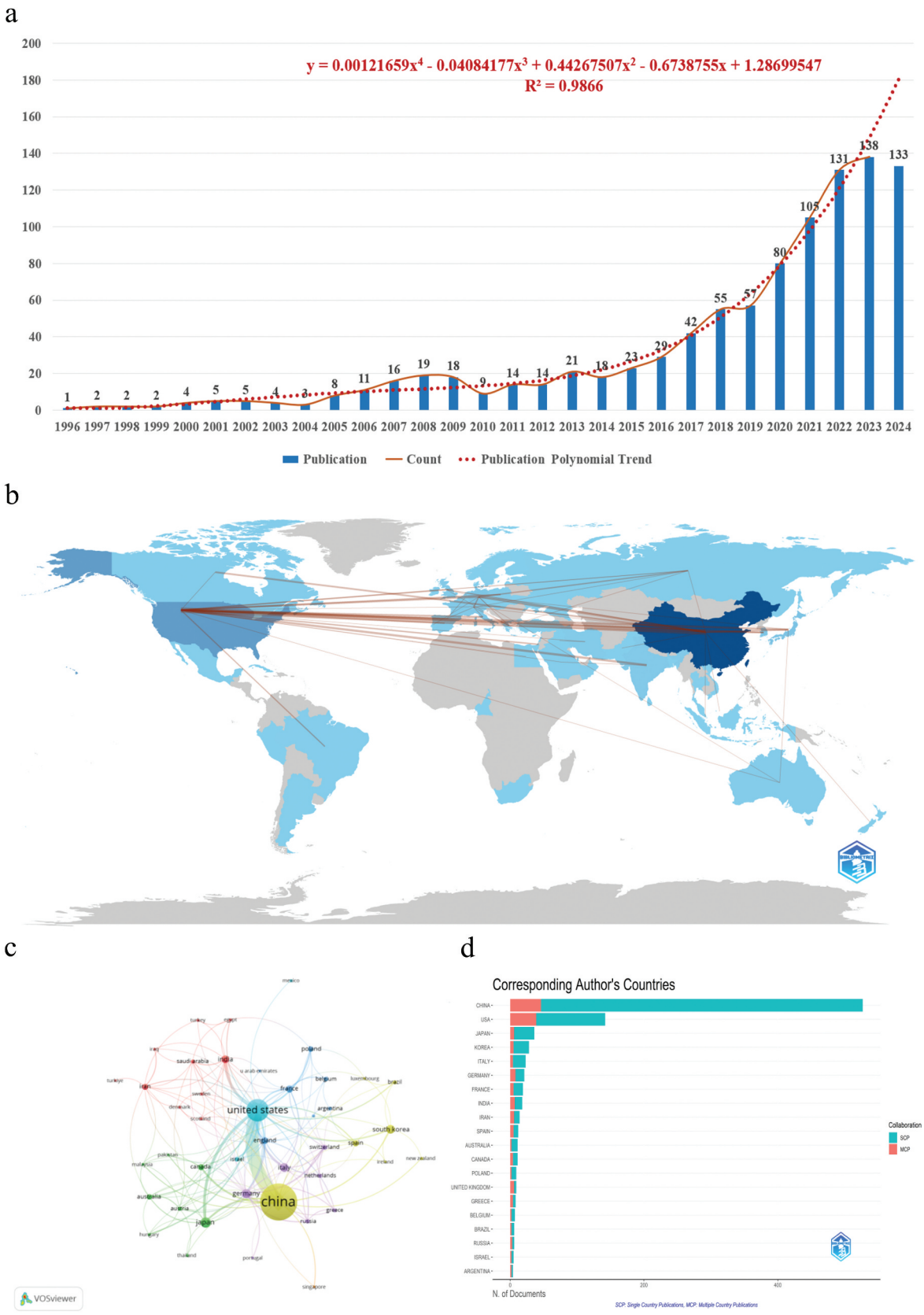


Figure 1. (a) Annual research output on the role of apoptosis in lung cancer immunotherapy. The orange curve indicates the annual publication trend. The red dotted trend line is fitted to the number of publications using a quadratic polynomial model. (b) The geographical spread of contributions. (c) Cooperation network of different countries. (d) A geospatial map illustrating the countries of corresponding authors.

Table 1. Top 10 countries and organization on the research of the role of apoptosis in lung cancer immunotherapy.

Rank	Country	Counts	Citations	Average Citation/ Publications	Total Link Strength	Centrality	Organization	Counts	Citations	Total Link Strength	Centrality
1	China	560	14670	26.20	100	0.36	Sichuan University (China)	28	767	2	0.01
2	United States	203	9925	48.89	125	0.51	Fudan University (China)	24	1664	10	0.1
3	Japan	44	1246	28.32	23	0.02	Tongji University (China)	24	507	12	0.04
4	Germany	35	1111	31.74	38	0.24	Shanghai Jiao Tong University (China)	23	321	18	0.06
5	South Korea	33	1165	35.30	13	0.02	Sun Yat-sen University (China)	23	1331	11	0.09
6	Italy	30	804	26.80	15	0.01	Nanjing Medical University (China)	21	418	18	0.11
7	India	25	610	24.40	22	0.10	Shandong University (China)	18	393	5	0.01
8	France	23	854	37.13	18	0.08	Zhengzhou University (China)	18	793	7	0.03
9	England	20	497	24.85	25	0.18	Central South University (China)	17	303	6	0.01
10	Iran	16	241	15.06	15	0.15	Chinese Academy of Sciences (China)	15	342	7	0.01

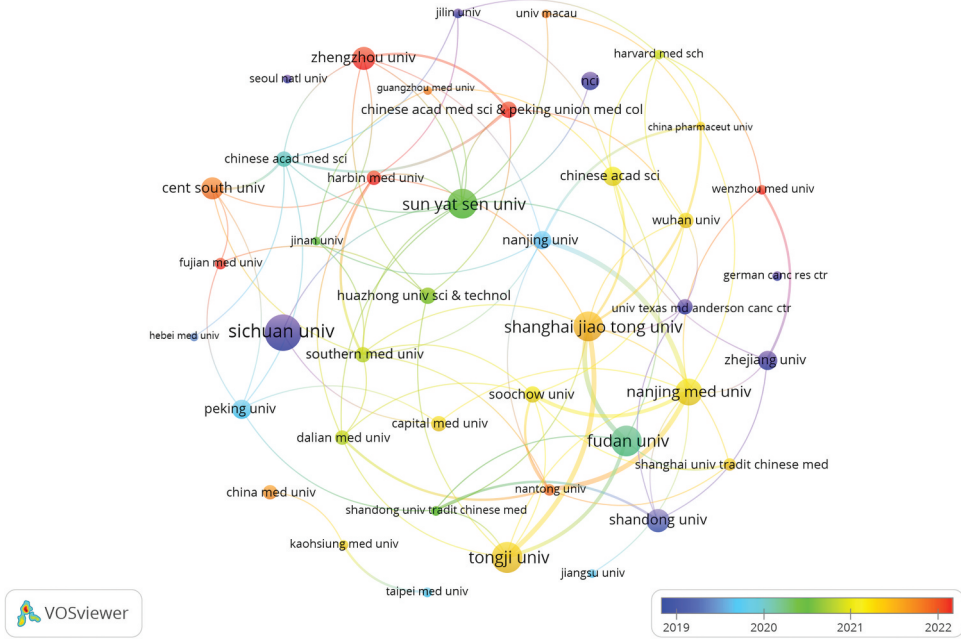


Figure 2. The visualization of institutions on research of the role of apoptosis in lung cancer immunotherapy.

critical role of both international and domestic partnerships, revealing how collaborative networks have accelerated discoveries in apoptosis-related immunotherapeutic targets. These collaborations take various forms, including multinational co-authorship networks, multicenter clinical trials, and cross-institutional technology sharing. A prominent example is the international KEYNOTE-042 trial (NCT02220894), which involved multiple countries and established the efficacy of *pembrolizumab* in inducing immunogenic cell death (ICD) in PD-L1-positive NSCLC patients.[53,54] Similarly, the CheckMate 227 trial represents a collaborative effort across multiple countries, demonstrating that the combination of *nivolumab* and *ipilimumab* enhances T-cell-mediated tumor cell apoptosis, regardless of PD-L1 expression levels.[55,56] Additionally, cross-institutional partnerships between Fudan University and Memorial Sloan Kettering Cancer Center have advanced the understanding of how tumor cell-intrinsic apoptotic resistance mechanisms can be overcome through the combined targeting of both death receptor and mitochondrial apoptotic pathways in immunotherapy-resistant LC models.[57,58]

Top journals and co-cited journals

Publications on the role of apoptosis in LC immunotherapy are distributed across 356 journals, reflecting the interdisciplinary and diverse nature of this field. As presented in Table 2, the top 10 journals significantly contribute to the overall output. Leading the list is *Cancers* with 41 articles, followed by *Frontiers in Immunology* (26 papers), *Cancer Immunology Immunotherapy* (23 papers), *Frontiers in Oncology* (21 papers), and the *International Journal of Molecular Sciences* (21 papers). *Cancer Research*, with an impact factor (IF) of 12.5, stands out as a key journal for high-impact publications. Similarly, the *Journal for Immunotherapy of Cancer* holds considerable influence with an IF of 10.3, particularly in integrating research on apoptosis in LC immunotherapy. The citation network map (Figure 3(a)) demonstrates the interconnectivity among these journals, forming clusters that facilitate knowledge exchange within the research ecosystem.

The influence of these journals is further reinforced by their co-citations. As seen in Table 2, 40% of the top 10 co-cited journals have been referenced over 1,000 times. *Cancer Research* leads with 2,255 co-citations, followed by *Clinical*

Table 2. Top 10 journals and co-cited journals on the research of the role of apoptosis in lung cancer immunotherapy.

Rank	Journal	Counts	Citations	IF[a]	Q[b]	Co-cited journal	Co-citation	IF[a]	Q[b]
1	Cancers	41	694	4.5	1	Cancer Research	2255	12.5	1
2	Frontiers in Immunology	26	260	5.7	1	Clinical Cancer Research	1523	10	1
3	Cancer Immunology Immunotherapy	23	568	4.6	1	Nature	1307	50.5	1
4	Frontiers in Oncology	21	229	3.5	2	Journal of Immunology	1076	3.6	2
5	International Journal of Molecular Sciences	21	818	4.9	1	Proceedings of the National Academy of Sciences of the USA	947	9.4	1
6	Cancer Research	18	2202	12.5	1	Journal of Clinical Oncology	903	42.1	1
7	Oncoimmunology	17	572	6.5	1	Cell	869	45.5	1
8	International Immunopharmacology	16	240	4.8	1	Oncogene	798	6.9	1
9	Journal for Immunotherapy of Cancer	15	572	10.3	1	PLOS ONE	769	2.9	1
10	Oncotarget	15	392	N/A	N/A	New England Journal of Medicine	731	96.2	1

[a]The impact factor of the journal are obtained from Journal Citation Reports 2023.
[b]The quartile of the journal are obtained from Journal Citation Reports 2023.
N/A: Not Applicable.

Cancer Research (1,523 co-citations) and *Nature* (1,307 co-citations). Although high-impact journals like *New England Journal of Medicine* (IF 96.2), *Cell* (IF 45.5), and *Journal of Clinical Oncology* (IF 42.1) publish fewer articles specifically on apoptosis in LC immunotherapy, their foundational contributions across related fields are noteworthy. The co-citation network (Figure 3(b)) underscores the role of these journals in shaping research trends. *Cancer Research* shows strong co-citation links with *Clinical Cancer Research*, *Nature*, *Journal of Clinical Oncology*, and *New England Journal of Medicine*, highlighting their collaborative contributions to advancing understanding in this area.

The dual-map overlay of journals highlights the citation relationships between journals and their co-cited sources (16). Figure 4 shows two major citation pathways: the orange path represents prominent citations from articles in the "Molecular/Biology/Immunology" sections to literature in "Molecular/Biology/Genetics," while the green path depicts significant citations from the "Medicine/Medical/Clinical" sections to literature within "Molecular/Biology/Genetics."

Top authors and co-cited authors

The progress in understanding the role of apoptosis in LC immunotherapy is largely due to the work of 6,894 authors. Among the top 10 most prolific researchers, half have authored at least 6 publications, highlighting their crucial role in advancing this field (Table 3). As shown in Figure 5(a), Yu-Quan Wei leads with the most publications, represented by the largest node, signifying his impact in this research area. Li Zhang and Li Wang also follow closely, contributing significantly to the body of knowledge. Notably, Xing-Xing Fan has formed key collaborations in recent years with prominent researchers, including Ju-Min Huang, Chun Xie, Elaine Lai-Han Leung, Ze-Bo Jiang, Qi-Biao Wu, Mei-Fang Wang, Ya-Jia Xie, and Xiao-Jun Yao. These collaborations span several countries, promoting international cooperation and strengthening the global research network.

Additionally, 80% of the top authors have been co-cited more than 80 times, underlining the influence of their work (Table 3). Jemal, A. stands out as the most co-cited author with 124 co-citations, showcasing his foundational contributions to the field. Siegel, R.l. follows with 113 co-citations, indicating the significant impact of their research on the current understanding of apoptosis in LC immunotherapy. The co-citation network, depicted in Figure 5(b), illustrates strong interconnections among these key researchers. Authors such as Galluzzi, I., Jemal, A., Kroemer, G., and Garg, A.D. are frequently co-cited, indicating their pivotal roles in fostering collaboration and pushing the boundaries of research in this domain.

Top co-cited references

The top 10 co-cited references, with 60% cited over 30 times (Supplementary Table S2), serve as foundational studies that have significantly shaped the understanding of the role of apoptosis in LC immunotherapy. The co-citation network (Figure 6(a)) reveals strong interconnections among these key works. For example, "Pardoll DM, 2012, *Nat Rev Cancer*" is frequently co-cited with "Dong HD, 2002, *Nat Med*," "Reck M, 2016, *New Engl J Med*." and "Topalian SL, 2012, *New Engl J Med*."[48,49,59,60] These studies have emerged as intellectual bridges connecting diverse aspects of apoptosis research in LC immunotherapy, demonstrating exceptional influence across multiple research domains. Pardoll et al presented a foundational conceptual framework that links basic immunology with clinical applications, cited extensively in studies ranging from mechanistic apoptosis research to clinical trial design. This study established the rationale that blocking immune checkpoints can reverse tumor-induced T-cell dysfunction and enhance antitumor immunity, creating a paradigm shift in cancer treatment approaches.[48] Dong et al offered a critical mechanistic bridge between tumor biology and immunology, revealing how cancer cells exploit PD-L1 expression to directly induce apoptosis in tumor-reactive T cells.[59] This seminal work is highly cited across TME studies, apoptosis mechanism research, and biomarker development, demonstrating its cross-disciplinary impact on understanding how LC evades immune surveillance through manipulation of apoptotic pathways. Clinical research studies conducted by Reck M et al.[49] and Topalian et al[60] have transformed the theoretical understanding of immune checkpoint inhibition into practical therapeutic approaches. These

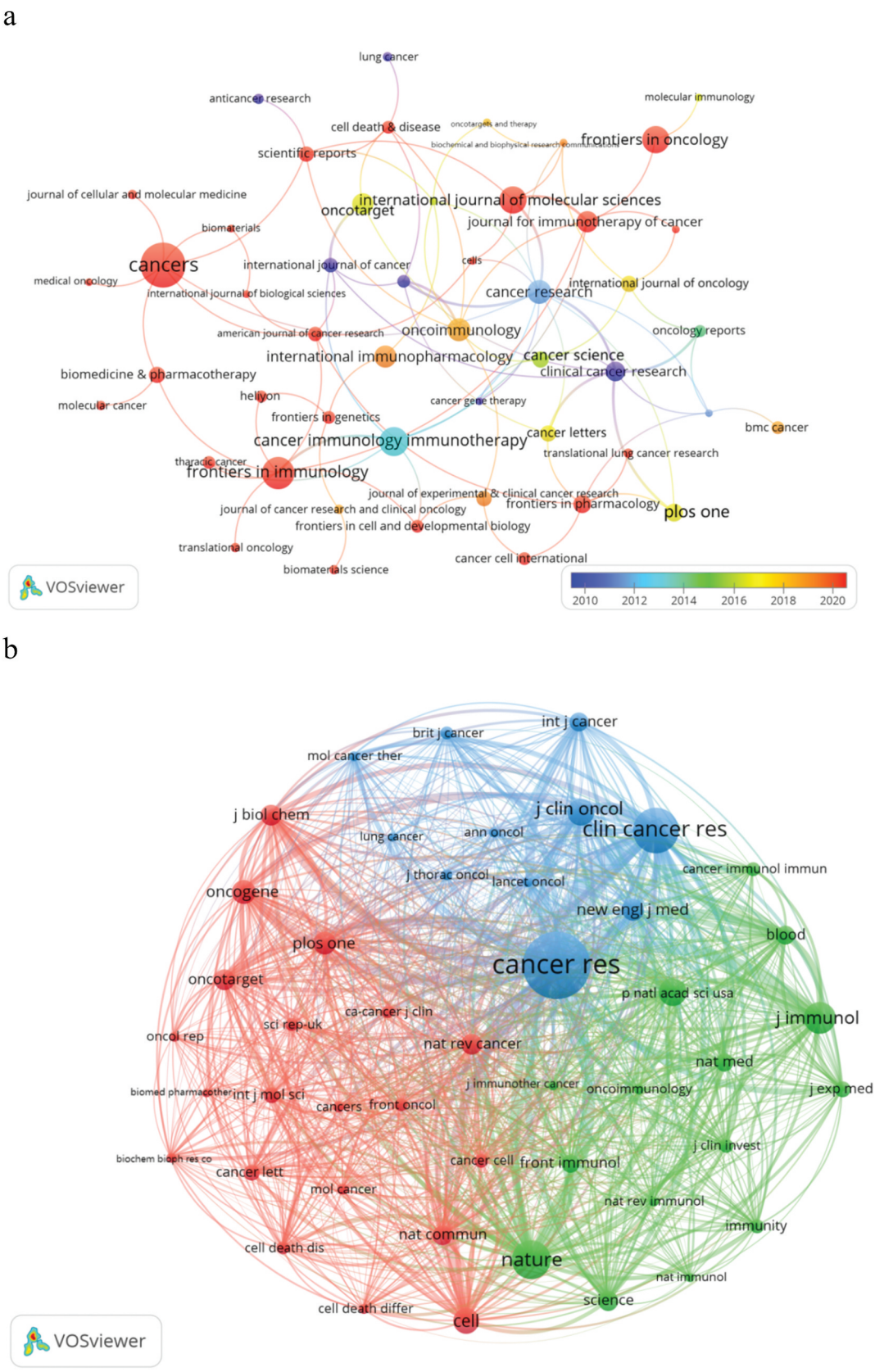


Figure 3. The visualization of journals (a) and co-cited journals (b) on research of the role of apoptosis in lung cancer immunotherapy.

papers are uniquely cited across translational science, clinical oncology, and drug development fields. Notably, Topalian et al established the relationship between PD-L1 expression and clinical response, creating a critical link between biomarker research and personalized immunotherapy approaches that has influenced study designs across multiple cancer types beyond LC. This cross-disciplinary citation pattern highlights how breakthroughs in understanding the

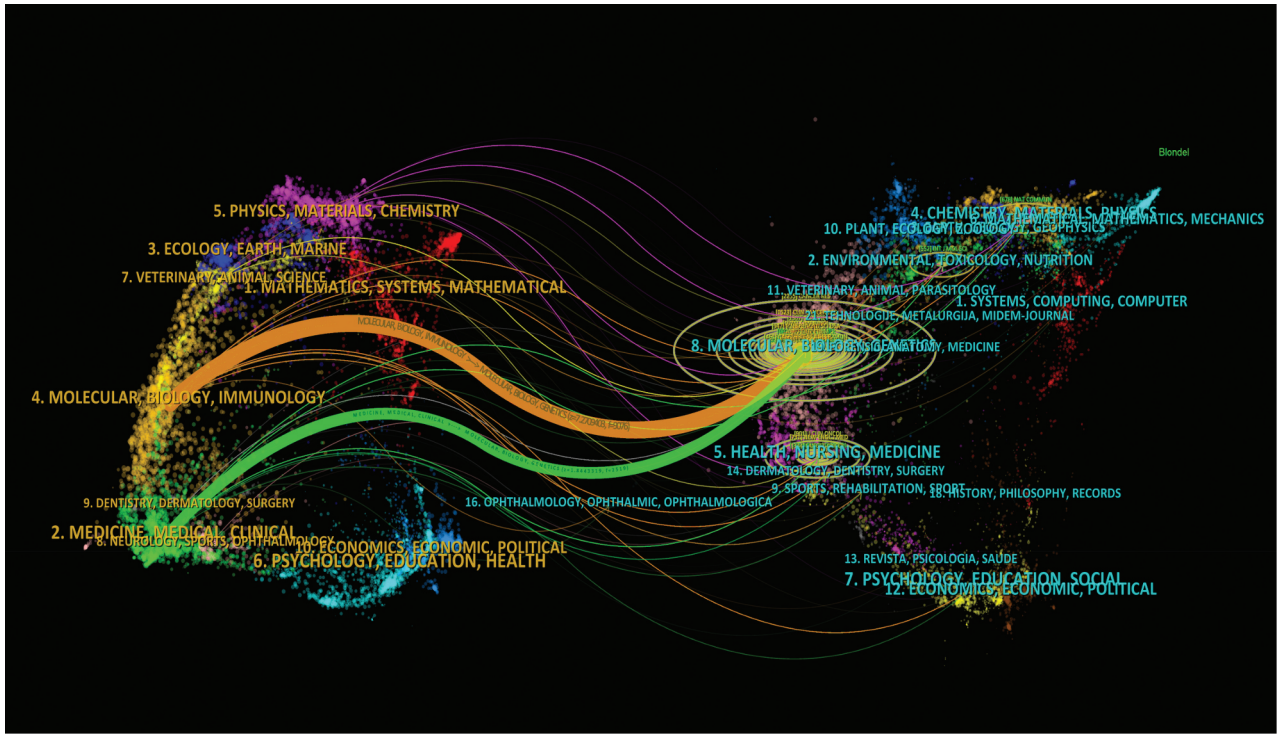


Figure 4. The dual-map overlay of journals on research of the role of apoptosis in lung cancer immunotherapy.

Table 3. Top 10 authors and co-cited authors on the research of the the role of apoptosis in lung cancer immunotherapy.

Rank	Author	Counts	Citations	H-index	Co-cited Authors	Citations
1	Wei, Yu-Quan	8	916	9	Jemal, A.	124
2	Zhang, Li	7	354	4	Siegel, R.l.	113
3	Wang, Li	7	125	3	Zhang, Y.	89
4	Yang, Yang	7	133	2	Galluzzi, L.	87
5	Zhang, Wei	7	356	3	Herbst, R.S.	84
6	Zhang, Yi	6	72	2	Wang, Y.	82
7	Liu, Yu	6	56	4	Hanahan, D.	78
8	Wang, Wei	6	257	3	Reck, M.	78
9	Yang, Li	6	149	2	Topalian, S.L.	74
10	Zhang, Yan	6	213	3	Wang, J.	74

interplay between apoptosis and immune checkpoint regulation have catalyzed a convergence of previously separate research domains, accelerating therapeutic innovation through integrated knowledge from molecular biology, immunology, and clinical oncology.

Reference with citation bursts

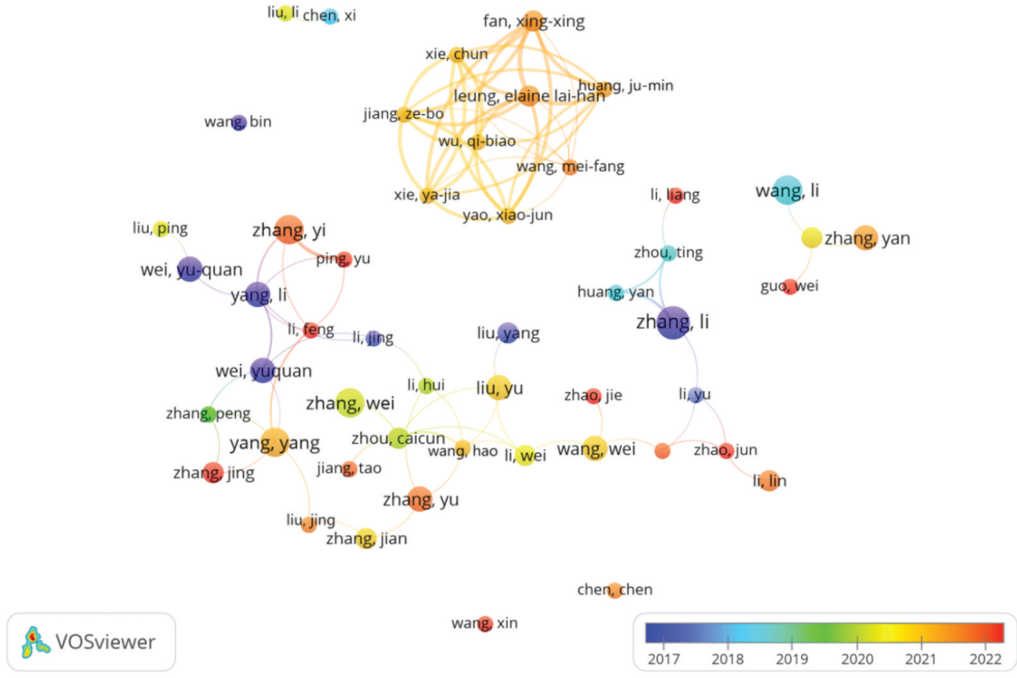
References with citation bursts are those that experience a rapid surge in citations within a particular timeframe and research domain, signifying their growing relevance. Using CiteSpace, we constructed a network showcasing references with the strongest citation bursts, highlighting the top 20 with red bars (Figure 6(b)). Topping the list is "Borghaei H, 2015, *NEW ENGL J MED*" with the highest citation burst strength (6.79).[61] This is followed by "Reck M, 2016, *NEW ENGL J MED*" (strength 6.29)[49]and "Jiang P, 2018, *NAT MED*" (strength 5.99).[62] These references collectively underscore the pivotal role of apoptosis in LC immunotherapy. ICIs, such as *Nivolumab* and *Pembrolizumab*, enhance T-cell activity by removing inhibitory pathways, thus promoting tumor cell apoptosis, improving therapeutic outcomes, and extending patient survival. Computational tools like the tumor immune dysfunction and exclusion model also provide insights into T-cell dysfunction and its impact on apoptosis, helping optimize immunotherapy strategies. In summary, apoptosis is a central mechanism in LC immunotherapy, vital for both direct tumor eradication by T-cells and overall treatment enhancement, and will continue to be a crucial focus for future research and clinical use.

Keyword analysis

Keyword analysis, thematic development, and future research directions

The keyword co-occurrence analysis identified seven major clusters of research focus related to apoptosis in LC immunotherapy (Figure 7(a), Supplementary Table S3). These clusters encompass: (1) different types of cell death mechanisms; (2) CD8+ T cell activation and immune evasion; (3) combination therapy approaches; (4) gene regulation and

a



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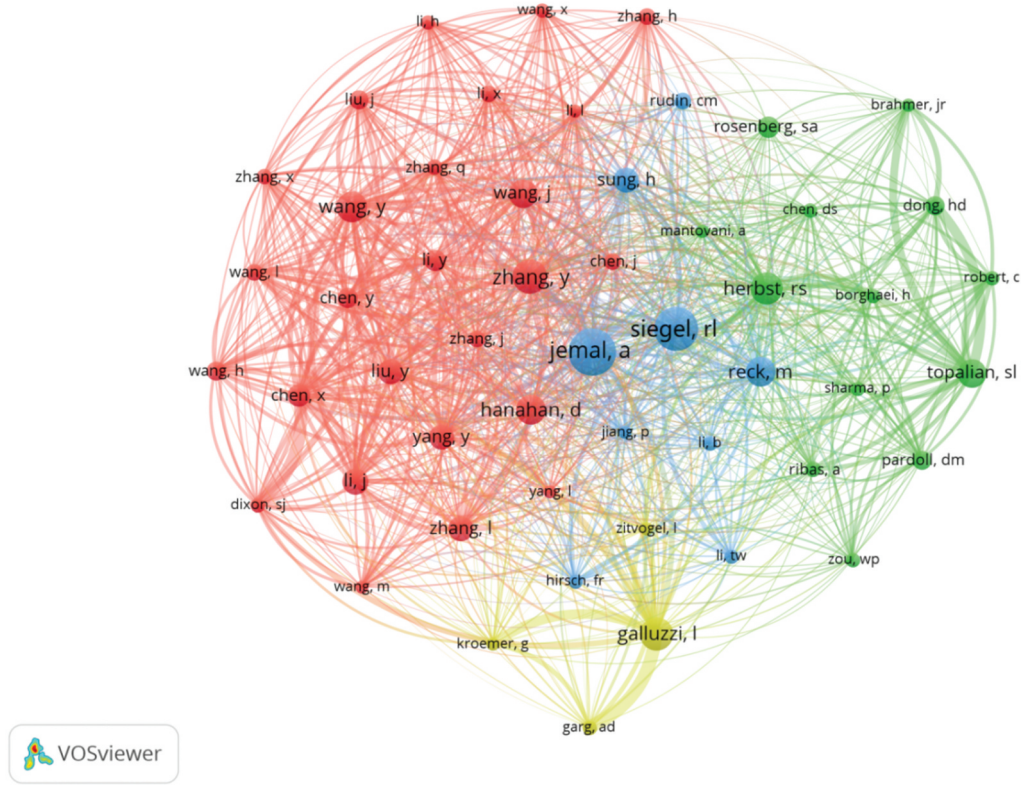

Figure 5. The visualization of authors (a) and co-cited authors (b) on research of the role of apoptosis in lung cancer immunotherapy.

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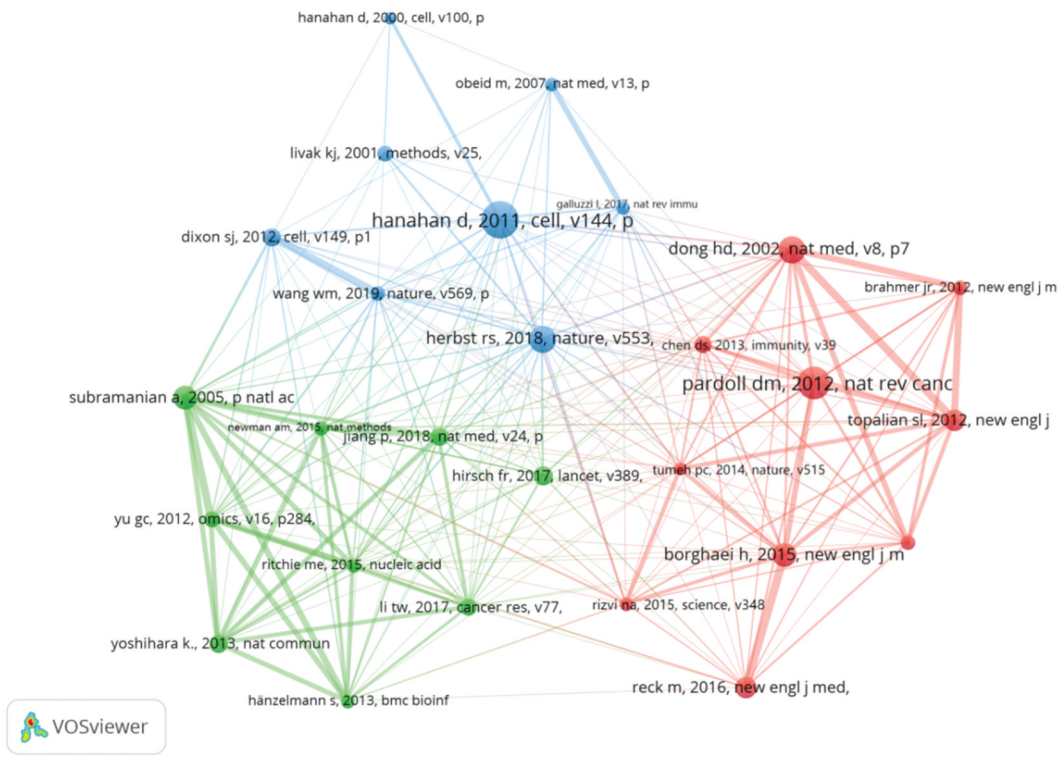

b

Top 20 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2010 - 2024
Fang J, 2011, ADV DRUG DELIVER REV, V63, P136, DOI 10.1016/j.addr.2010.04.009, DOI	2011	9.88	2012	2016	
Barenholz Y, 2012, J CONTROL RELEASE, V160, P117, DOI 10.1016/j.jconrel.2012.03.020, DOI	2012	8.94	2013	2017	
Mura S, 2013, NAT MATER, V12, P991, DOI 10.1038/NMAT3776, DOI	2013	11.45	2015	2018	
Lv SX, 2014, BIOMATERIALS, V35, P6118, DOI 10.1016/j.biomaterials.2014.04.034, DOI	2014	10.57	2015	2019	
Blanco E, 2015, NAT BIOTECHNOL, V33, P941, DOI 10.1038/nbt.3330, DOI	2015	11.9	2016	2020	
Jiang L, 2015, BIOMATERIALS, V52, P126, DOI 10.1016/j.biomaterials.2015.02.004, DOI	2015	9.5	2016	2020	
Maeda H, 2013, ADV DRUG DELIVER REV, V65, P71, DOI 10.1016/j.addr.2012.10.002, DOI	2013	11.54	2017	2018	
Sun TM, 2014, ANGEW CHEM INT EDIT, V53, P12320, DOI 10.1002/anie.201403036, DOI	2014	9.75	2017	2019	
Kuzmov A, 2015, J CONTROL RELEASE, V219, P500, DOI 10.1016/j.jconrel.2015.07.024, DOI	2015	9.16	2017	2020	
Wilhelm S, 2016, NAT REV MATER, V1, P0, DOI 10.1038/natrevmats.2016.14, DOI	2016	13.99	2018	2021	
Shi JJ, 2017, NAT REV CANCER, V17, P20, DOI 10.1038/nrc.2016.108, DOI	2017	10.87	2018	2022	
Patra JK, 2018, J NANOBIOTECHNOL, V16, P0, DOI 10.1186/s12951-018-0392-8, DOI	2018	15.51	2020	2024	
Senapati S, 2018, SIGNAL TRANSDUCT TAR, V3, P0, DOI 10.1038/s41392-017-0004-3, DOI	2018	11.73	2020	2024	
Din FU, 2017, INT J NANOMED, V12, P7291, DOI 10.2147/IJN.S146315, DOI	2017	10.45	2020	2022	
Herbst RS, 2018, NATURE, V553, P446, DOI 10.1038/nature25183, DOI	2018	9.04	2020	2024	
Mangal S, 2017, ACTA PHARMACOL SIN, V38, P782, DOI 10.1038/aps.2017.34, DOI	2017	8.77	2021	2022	
Sung H, 2021, CA-CANCER J CLIN, V71, P209, DOI 10.3322/caac.21660, DOI	2021	30.76	2022	2024	
Mitchell MJ, 2021, NAT REV DRUG DISCOV, V20, P101, DOI 10.1038/s41573-020-0090-8, DOI	2021	16.66	2022	2024	
Yao YH, 2020, FRONT MOL BIOSCI, V7, P0, DOI 10.3389/fmolb.2020.00193, DOI	2020	10.2	2022	2024	
Siegel RL, 2022, CA-CANCER J CLIN, V72, P7, DOI 10.3322/caac.21708, DOI	2022	9.85	2022	2024	

Figure 6. (a) The visualization of co-cited references on research of the role of apoptosis in lung cancer immunotherapy. (b) Top 20 references with strong citation bursts. A red bar indicates high citations in that year.

nanomedicine; (5) signaling pathways and cell types; (6) immunosuppression factors; and (7) traditional Chinese medicine (TCM) applications.

Citation burst analysis revealed the top 20 keywords with the strongest citation bursts over time (Figure 7(b)). The keywords with the highest burst strengths were "dendritic cells" (strength 8.14), "antigen" (strength 5.88), and "induction" (strength 5.51). Recent periods (2021–2024) showed notable citation bursts for terms including "lymphocytes," "PD-L1 expression," "growth factor receptor," "metastatic lung cancer," and "cells," indicating shifting research priorities in recent years.

Timeline visualization (Figure 7(c)) demonstrated emerging trends toward diverse research areas including "microRNA," "ferroptosis," "immune infiltration," "tumor immune microenvironment (TIME)," "TCM," and "immune checkpoint inhibitor," reflecting the evolution of research interests in this field.

The thematic map (Figure 7(d)) identified both mature and emerging research themes. The bottom-right quadrant highlighted significant yet underexplored themes including immune evasion mechanisms, antigen presentation pathways, photodynamic therapy, alternative cell death mechanisms (ferroptosis, pyroptosis, necroptosis), and the role of MDSCs. These areas represent potential opportunities for future research development in apoptosis and LC immunotherapy.

Discussion

Relevance to clinical challenges in LC treatment

This bibliometric analysis of apoptosis in LC immunotherapy directly addresses several critical challenges faced in clinical practice. Despite advances in ICIs therapy, treatment resistance remains a significant obstacle, with many patients showing initial response followed by progression. Our findings highlight emerging research focused on overcoming resistance mechanisms related to dysregulated apoptotic pathways, particularly through combination strategies targeting both immune checkpoints and anti-apoptotic proteins. Patient heterogeneity represents another major challenge, as evidenced by the variable response rates to immunotherapy. The research clusters identified in our analysis, particularly those focusing on biomarker development and precision targeting of genetic alterations (such as *EGFR*, *ALK*, and *KRAS*), offer promising directions for patient stratification. Additionally, the economic burden of these advanced therapies necessitates better patient selection strategies. Our identification of key research hotspots and emerging themes provides a roadmap for investigators to develop more targeted approaches that address these pressing clinical challenges, ultimately improving treatment outcomes while optimizing resource utilization. The growth in collaborative networks, as revealed in our analysis, further suggests that global research efforts are increasingly directed toward solving these real-world problems through multidisciplinary approaches.

General information

This study provides the first comprehensive bibliometric analysis of apoptosis in LC immunotherapy, highlighting significant research growth since 2015. The steady increase in publications reflects the growing importance of apoptosis and strong global collaboration, signaling its evolution into a critical cancer research field.

The analysis shows a disparity between publication volume and research impact. While China leads in publication count ($n = 560$), the United States achieves higher citation rates (48.89 citations per publication compared to China's 26.20) despite fewer papers ($n = 203$), with the strongest citation burst (strength = 13.76) (Supplementary Figure S2). It is important to note that our citation analysis included all citations without excluding self-citations, which is consistent with standard bibliometric methodology but may influence the comparative analysis to some extent. This citation gap may be attributed to several factors. First, differences in research quality, as reflected by methodological rigor, novelty, and clinical relevance, may contribute significantly to citation disparities. Second, publication language preferences and English language proficiency may affect how papers are received internationally, as English-language proficiency can impact clarity of communication and manuscript acceptance in high-impact journals. Third, historical research establishment plays a role – U.S. institutions generally have longer-established research programs in cancer immunology, providing advantages in research infrastructure, funding stability, and international recognition. Finally, international collaboration patterns differ notably, with U.S. institutions demonstrating higher centrality indices (0.51 for the U.S. *vs*. 0.29 for China), indicating their more central position in global research networks. This is particularly important as internationally collaborative papers typically receive more citations than single-country publications. To address this disparity, Chinese institutions could benefit from emphasizing quality over quantity in research output, increasing international collaborations (especially with established research centers), focusing on novel and clinically significant questions, and improving English-language scientific communication. Strengthening global partnerships and focusing on impactful studies could help bridge this gap between publication quantity and research influence.

All of the top 10 institutions by publication volume and citations are in China. However, leading institutions from China and the United States, such as Zhengzhou University, Sichuan University, National Institutes of Health, and the University of Texas System, show rapid recognition (Supplementary Figure S3). To enhance their broader research impact, these institutions should focus on stronger international collaborations and high-quality output.

In terms of journal influence, *Cancers* leads in volume, while *Cancer Research* ranks highest in co-citations, illustrating a distinction between publication quantity and sustained influence. High-impact journals like *Nature* play a key role in advancing apoptosis research in LC immunotherapy, suggesting that targeting influential journals can be more beneficial for researchers than merely increasing publication numbers. Notably, high-impact journals such as *New England Journal of*

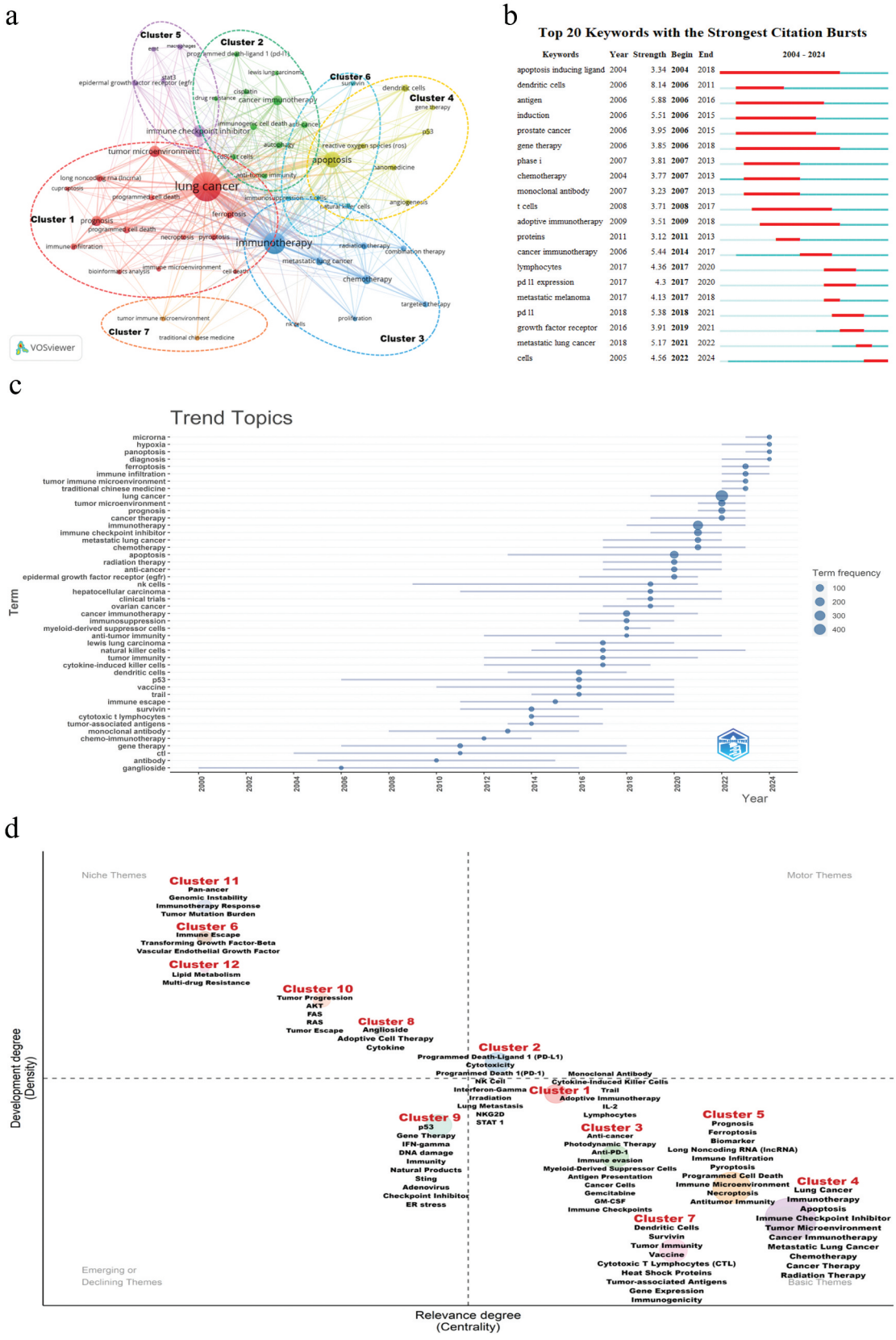

Figure 7. Keywords visualization analysis. (a) Keyword cluster analysis. (b) Top 20 keywords with strongest citation bursts. (c) Topic trend on the role of apoptosis in lung cancer immunotherapy. (d) Thematic map: the horizontal axis represents mediating centrality, indicating the theme's relevance to the field, while the vertical axis represents density, showing how well the theme has developed. Quadrant 1 (top right) represents MOTOR themes, which are both important and well-developed. Quadrant 2 (top left) represents HIGHLY DEVELOPED and INDIVIDUAL themes – those that are well-developed but less relevant to the current domain. Quadrant 3 (bottom left) includes EMERGING or DECLINING themes, which are underdeveloped and may be either gaining or losing relevance. Quadrant 4 (bottom right) represents BASIC and TRANSVERSAL themes, which are important to the field but not yet well-developed.

Medicine, *Cell*, and *Journal of Clinical Oncology* contribute fewer articles on apoptosis in LC immunotherapy despite their significant influence. Future studies in this field should target these prestigious journals to enhance research visibility, accelerate knowledge translation into clinical practice, and strengthen the impact of apoptosis research in oncology.

Hotspots and frontiers

Highly co-cited references have been instrumental in shaping the academic understanding of the role of apoptosis in LC immunotherapy (Supplementary Table S2). As depicted in Figure 7(c), the keywords with the strongest citation burst analysis reflect an increasing focus on improving LC immunotherapy efficacy. This has been pursued through approaches like regulating the TIME,[63] targeting key receptors such as *EGFR*,[52] and enhancing cell apoptosis.

Keyword analysis provides vital insights into the core areas of this field. Figure 7(a) identifies seven key themes in apoptosis in LC immunotherapy: (1) interaction between multiple cell death mechanisms and immunotherapy; (2) anti-tumor immunity and immune evasion; (3) combination therapies promoting apoptosis; (4) gene regulation and nanomedicine applications; (5) signaling pathways and specific cell types; (6) immunosuppression and apoptosis; and (7) the use of TCM in apoptosis. Future research directions are expected to include "coordinated regulation of multiple cell death pathways," "modulation of the TIME," "optimization of combination therapies," "novel strategies in gene regulation," and "integration of TCM" to achieve more personalized and effective treatment outcomes (Figure 7 (c-d)). Beyond these themes, several emerging therapeutic approaches and biomarkers show particular promise for combination with apoptosis-targeting strategies in LC immunotherapy. Circulating tumor DNA (ctDNA) analysis for monitoring apoptotic responses represents an emerging biomarker strategy, with studies demonstrating that decreases in ctDNA levels correlate with successful induction of tumor cell apoptosis during immunotherapy.[64,65] Novel ICIs targeting *LAG-3*, *TIM-3*, and *TIGIT* are being investigated to overcome resistance mechanisms related to defective apoptotic signaling in T cells.[66,67] Metabolic interventions targeting ferroptosis inducers have shown synergistic effects with apoptosis-promoting immunotherapies by circumventing anti-apoptotic defense mechanisms.[68,69] Additionally, epigenetic modifiers such as histone deacetylase (HDAC) inhibitors that can upregulate death receptors and pro-apoptotic proteins offer promising combination strategies to sensitize resistant LC cells to immunotherapy-induced apoptosis.[70–72]

Multidimensional regulatory mechanisms of apoptosis and their comprehensive application in LC immunotherapy

Interactions between apoptosis and other cell death mechanisms in LC immunotherapy

In LC immunotherapy, the synergy between apoptosis and other cell death mechanisms is crucial for enhancing treatment efficacy. Alongside apoptosis, pyroptosis, ferroptosis, and necroptosis also play key roles.[73] Pyroptosis promotes immune cell infiltration by releasing pro-inflammatory cytokines like *IL-1β* and *IL-18*, boosting immunotherapy effectiveness, although excessive inflammation may cause toxicity, requiring precise regulation.[74]

Ferroptosis, which involves disrupted iron metabolism and lipid peroxidation, complements apoptosis and enhances tumor sensitivity to immunotherapy, especially when combined with immune checkpoint inhibitors.[73] Necroptosis, activated via *RIPK1* and *RIPK3* signaling, releases immune-stimulating signals that further amplify immune responses, enhancing the effects of apoptosis.[73]

Neutrophils also contribute to tumor immunity by directly killing tumor cells through *ROS* and apoptosis-inducing factors, while also enhancing T cell activation via antigen presentation.[74] Integrating these pathways can help overcome resistance and enhance immune targeting of tumors, ultimately improving the efficacy of LC immunotherapy.

In conclusion, the coordinated activation of apoptosis, pyroptosis, ferroptosis, and necroptosis offers promising strategies for LC immunotherapy. This multidimensional approach strengthens the immune response and counters resistance to single treatment methods, suggesting that future immunotherapy designs should focus on integrating these pathways to improve treatment outcomes. Further research is needed to understand their application in specific therapeutic contexts and their impact on patient outcomes.

Enhancing apoptosis by activating anti-tumor immunity and overcoming immune evasion in LC immunotherapy

Immunosuppressive factors in the TME, such as *IL-10*, *IDO*, and *TGF-β*, hinder immune activity, allowing tumor cells to evade surveillance. Targeting tumor-associated macrophages (TAMs) can reduce their suppressive functions, thereby enhancing anti-tumor immunity. Studies show that inhibiting TAMs, especially in combination with ICIs, alleviates immunosuppression and boosts tumor-killing effects.[75]

ICIs, such as PD-1/PD-L1 and CTLA-4 inhibitors, block immune escape pathways, enabling T cells to recognize and eliminate tumor cells effectively. The activation of CD8+ T cells is crucial, requiring co-stimulatory signals like CD28. DCs are also key to antigen presentation, and therapeutic vaccines can enhance DC function, improving T cell activation and promoting apoptosis.[76,77]

Tumor cells further evade immune detection by upregulating *FasL* to induce T cell apoptosis or suppressing T cell activity via CTLA-4. Targeting these escape mechanisms is critical for enhancing therapeutic efficacy.[7] While our study focused on apoptosis in tumor cells, we acknowledge that immune cell apoptosis may also play a role in modulating the TIME. Excessive apoptosis in immune cells, such as effector T cells or DCs, could dampen anti-tumor responses and weaken immunotherapy efficacy. Future research should focus on minimizing immune cell apoptosis. It should also enhance pro-apoptotic effects on tumor cells. This will help achieve a balance between immune activation and tumor elimination. Additionally, keywords such as "TIME" suggest the critical role of modulating TIME components. Future research should prioritize strategies to suppress immunosuppressive cells (e.g., Tregs and MDSCs) while enhancing cytotoxic T cells and NK

cell activity. Specifically, targeting cytokines like *IL-10* and *TGF-β* or shifting macrophages from a pro-tumor M2 phenotype to an anti-tumor M1 phenotype may offer promising therapeutic opportunities. ICIs not only block immune checkpoints but also promote apoptosis by activating both the intrinsic mitochondrial pathway (e.g., increasing mitochondrial permeability) and the extrinsic death receptor pathway (e.g., activating *Fas*). Combining ICIs with anti-angiogenic drugs or metabolic regulators can further disrupt tumor growth, strengthen immune responses, and enhance apoptosis.[15,16,75] By simultaneously boosting anti-tumor immunity and inhibiting immune evasion, LC immunotherapy can significantly enhance apoptosis, improving treatment outcomes and patient prognosis.

Combination therapies enhancing apoptosis in LC immunotherapy

Combining ICIs like *Nivolumab* with chemotherapy has shown encouraging results in clinical trials. In the CheckMate 816 trial, patients treated with *Nivolumab* and chemotherapy had significantly higher complete response rates compared to chemotherapy alone, with enhanced tumor apoptosis and longer event-free survival, while maintaining a favorable safety profile.[78] Emerging strategies, such as using oncolytic viruses like the measles virus with *Atezolizumab*, also show promise. Injecting the virus directly into tumors and administering ICIs systemically has been shown to enhance immune response and induce apoptosis, offering hope for patients unresponsive to monotherapies.[79,80] Another synergistic approach is combining platinum-based chemotherapy with *Pembrolizumab*. This not only directly damages tumor cells but also boosts T cell-mediated apoptosis, thereby increasing overall treatment efficacy.[81]

In conclusion, combination therapies involving ICIs, chemotherapy, and innovative approaches like oncolytic viruses activate multiple immune mechanisms. This multi-faceted strategy strengthens anti-tumor responses, improves treatment outcomes, and ultimately enhances the prognosis for LC patients.

Application of gene regulation and nanomedicine in inducing apoptosis for LC immunotherapy

Clustered regularly interspaced short palindromic repeats (*CRISPR*) gene-editing technology offers new opportunities for LC immunotherapy. Using the *CRISPR/Cas9* system, autologous T cells can be genetically modified to knock out endogenous T cell receptors (TCRs) and PD-1 protein. These modified T cells, reintroduced into patients, have shown significant therapeutic effects in various cancers, marking a new phase in cancer immunotherapy. By modulating apoptosis-related genes, *CRISPR* technology can enhance tumor cell apoptosis and improve treatment outcomes.[82]

Nanomedicine also shows promise, particularly in targeted drug delivery and modulating TAMs. Nanoparticles, due to their unique properties, can precisely deliver agents like siRNA or miRNA to tumor sites, reducing systemic toxicity while enhancing therapeutic efficacy. Furthermore, nanomedicine can reprogram TAMs from a pro-tumor M2 phenotype to an anti-tumor M1 phenotype, boosting immune responses and promoting tumor cell apoptosis.[83–85]

In summary, *CRISPR* gene-editing and nanomedicine offer powerful tools for enhancing apoptosis in LC immunotherapy. *CRISPR* allows precise modulation of apoptosis-related genes, while nanomedicine ensures targeted delivery, maximizing efficacy while minimizing side effects. This combination holds great potential for improving therapeutic outcomes in LC patients.

Impact of signaling pathways and cell types on apoptosis in LC immunotherapy

The fifth thematic cluster identified in our analysis encompasses both signaling pathways and specific cell types involved in apoptosis regulation during LC immunotherapy. This co-clustering occurs because certain cell types are characterized by distinct signaling pathway activities that influence apoptotic responses. The "specific cell types" in this context primarily refer to specialized immune effector cells {such as Chimeric antigen receptor T (CAR-T) cells} and tumor cell subpopulations with unique signaling profiles that affect their susceptibility to apoptosis. These cell types and their associated signaling pathways are grouped together in our analysis because they demonstrate high co-occurrence in the literature, reflecting their functional interconnection in determining apoptotic outcomes during immunotherapy.

BCL-2 family proteins are key regulators of apoptosis. The *BCL-2* protein inhibits apoptosis by forming heterodimers with *BCL-2*-associated X protein (*BAX*) and regulating mitochondrial permeability, primarily through its BH4 domain. Targeting *BCL-2*-related signaling pathways can enhance apoptotic responses, improving the efficacy of immunotherapy.[86,87]

CAR-T cell therapy also plays a significant role in inducing apoptosis. Although the tumor microenvironment often reduces CAR-T cell effectiveness, "armored" CAR-T cells that secrete specific cytokines have demonstrated increased tumor-killing ability in challenging environments, showing promise for treating solid tumors.[88]

The *PI3K/AKT* and *MAPK* pathways are also critical in regulating apoptosis. Inhibiting *PI3K/AKT* enhances tumor sensitivity to immunotherapy, while activating *MAPK* boosts immune response by upregulating pro-apoptotic proteins. Targeting these pathways can improve resistance issues and maximize apoptotic effects.[89–91]

In conclusion, enhancing LC immunotherapy efficacy involves targeting *BCL-2* proteins, optimizing CAR-T cells, and regulating key signaling pathways, thus offering patients more effective therapeutic options.

Regulation of immunosuppression and its effect on apoptosis in LC immunotherapy

Tregs and MDSCs play significant roles in immune suppression within the TME, reducing the effectiveness of LC immunotherapy. Tregs release inhibitory cytokines like *IL-10* and *TGF-β*, which weaken effector T cell activity and decrease tumor cell apoptosis.[92] Reducing Tregs or inhibiting their function can promote T cell activation, enhance apoptosis, and improve treatment efficacy.

Similarly, MDSCs release suppressive molecules, including *IDO* and arginase, which inhibit T cells and NK cells, thereby reducing apoptosis. Targeting MDSCs to inhibit their expansion

can mitigate their immunosuppressive effects and enhance apoptosis in tumor cells.[92]

ICIs, such as PD-1/PD-L1 inhibitors, also play a crucial role by blocking PD-L1's interaction with PD-1, which in turn enhances T cell cytotoxicity and promotes apoptosis.[93–95] Additionally, our analysis highlighted the intersection of ICIs (e.g., PD-1/PD-L1 inhibitors) and apoptotic pathways as a pivotal research area. We suggest exploring how ICIs can synergize with pro-apoptotic agents, such as *BCL-2* inhibitors, to overcome resistance and enhance anti-tumor immune responses. By understanding these synergistic mechanisms, therapeutic strategies can be further optimized to boost immune activity and improve patient outcomes.

In conclusion, regulating immunosuppressive elements like Tregs and MDSCs, alongside using ICIs, can significantly boost apoptosis in LC immunotherapy, enhancing overall treatment effectiveness.

Regulation of apoptosis in the TIME by TCM in LC immunotherapy

Astragalus polysaccharide (APS), a TCM component, plays a crucial role in modulating TAMs and enhancing apoptosis in LC. APS promotes M1 polarization of TAMs, reducing the immunosuppressive M2 phenotype, and enhances anti-tumor immune responses by activating TLR4, *NF-κB*, and the Notch signaling pathway, thereby boosting nitric oxide (NO), *TNF-α*, and M1 markers like *iNOS* and *IL-6*.[96]

APS also enhances the activity of DCs, promoting the maturation and increased secretion of *IL-12*, which in turn activates CD8+ T cells and improves antigen presentation, ultimately enhancing cancer cell apoptosis.[97]

Furthermore, APS inhibits pro-survival pathways such as *PI3K/AKT/mTOR* and *JAK/STAT3*, thereby increasing pro-apoptotic factors and decreasing anti-apoptotic proteins. This multifaceted action improves the effectiveness of LC immunotherapy, reduces tumor resistance, and enhances treatment outcomes.[96]

Future directions for enhancing apoptosis in LC immunotherapy

Coordinated regulation of cell death pathways and immune microenvironment modulation

Enhancing apoptosis in LC immunotherapy requires integrating multiple synergistic cell death mechanisms, such as apoptosis and ICD. ICD activates the immune system by releasing immunostimulatory damage-associated molecular patterns (DAMPs), increasing tumor antigen expression, and boosting T cell-mediated apoptosis.[98]

Regulating the TIME is also essential. Balancing anti-tumor and pro-tumor components within TIME influences treatment outcomes. Targeting immunosuppressive cells like Tregs and MDSCs can enhance effector T cell and NK cell activity, thereby promoting tumor cell apoptosis.[99]

Integrating multiple cell death pathways with TIME regulation can improve immunotherapy efficacy, overcoming the limitations of single approaches. Future research should focus on combining ICD inducers with ICIs to optimally activate immune mechanisms and enhance apoptotic responses. The mechanisms of apoptosis in immunotherapy can be categorized into three key areas: (1) Direct mechanisms, where apoptosis directly enhances T cell and NK cell cytotoxicity to eliminate tumor cells; (2) Indirect mechanisms, where apoptosis modulates the TIME by suppressing Tregs and MDSCs, or altering cytokine profiles such as *IL-10* and *TGF-β*; and (3) Resistance reversal mechanisms, where apoptosis targeting anti-apoptotic pathways, such as *BCL-2* family proteins, can overcome ICIs resistance. Future research should focus on further categorizing the mechanisms of apoptosis in immunotherapy, particularly identifying which pathways are most synergistic with ICIs or other immunotherapeutic strategies. Understanding these mechanisms will help refine treatment combinations and improve therapeutic efficacy.

Novel strategies in gene regulation, combination therapy, and TCM

Gene regulation strategies, such as *CRISPR/Cas9*, are gaining prominence in LC immunotherapy by precisely modifying genes like PD-1 to enhance T cell activation and anti-tumor efficacy.[100] Introducing specific genes into the TME using viral vectors is also emerging as a frontier in gene therapy.[101]

Combination therapies, including ICIs with chemotherapeutic agents like cyclophosphamide and oxaliplatin, have shown notable synergy. These agents induce ICD, releasing DAMPs to enhance immune responses, thereby promoting tumor cell apoptosis and overcoming immune evasion.[102,103] Keywords such as "combination therapy" indicate significant potential in optimizing multimodal approaches. We suggest prioritizing combinations of ICIs with chemotherapeutic agents, apoptosis-inducing drugs, or nanomedicine-based delivery systems to achieve synergistic effects. For example, nanotechnology could be leveraged to deliver apoptosis-inducing agents precisely to tumor sites while minimizing systemic toxicity.

TCM, such as *Astragalus polysaccharide*, has unique potential in regulating immunity and promoting apoptosis. TCM enhances anti-tumor responses by modulating TAMs and DCs, increasing pro-apoptotic factor expression, and working synergistically with other therapies to improve treatment efficacy and reduce side effects.[104,105]

In summary, gene regulation, combination therapies, and TCM offer varied and promising strategies for inducing apoptosis and improving outcomes in LC treatment. Future research should focus on optimizing these approaches to maximize immune response and advance personalized medicine.

Precision targeting of key genetic pathways

Targeting key genetic mutations like *KRAS*, *EGFR*, *ALK*, and *ROS1* is essential for promoting apoptosis in LC immunotherapy.[106–108] Recent advancements include targeted therapies for *KRAS* G12C mutations, such as sotorasib, which reduce tumor cell proliferation, enhance sensitivity to immunotherapy, and promote apoptosis.[106] *EGFR* mutations in NSCLC respond well to TKIs like osimertinib, which inhibit tumor growth and support immune-mediated apoptosis. Studies are exploring combining these inhibitors with ICIs for better outcomes.[106] Similarly, *ALK* and *ROS1* inhibitors, such as *crizotinib*, are effective in targeting fusion gene activations, suppressing tumor growth, and inducing apoptosis.

These agents, when used with immunotherapy, can potentially overcome resistance.[108]

In summary, precise targeting of *KRAS*, *EGFR*, *ALK*, and *ROS1* pathways enhances apoptosis and improves LC treatment efficacy, especially in patients unresponsive to conventional therapies.

Development of underexplored themes in apoptosis regulation

Future research should explore under-investigated aspects of apoptosis regulation in LC immunotherapy (Figure 7(d)). Key areas include:

Immune Evasion Mechanisms: Elucidating specific immune evasion processes, such as *FasL*-induced T cell apoptosis, and identifying new regulatory molecules could improve targeted strategies to enhance apoptosis.[109]

Photodynamic Therapy (PDT): Combining PDT with ICIs shows potential for inducing apoptosis by generating ROS. Further research is needed to optimize PDT conditions for maximal synergy with immunotherapy.[110–112]

Synergistic Cell Death Mechanisms: Investigating the integration of ferroptosis, pyroptosis, necroptosis, and apoptosis can improve tumor sensitivity to treatment and overcome resistance, thereby enhancing anti-tumor immunity.[113,114] Ferroptosis (iron-dependent lipid peroxidation) and pyroptosis (inflammasome-mediated cell death) offer unique opportunities to complement apoptosis in immunotherapy. For instance, ferroptosis can enhance tumor sensitivity to ICIs, while pyroptosis promotes immune cell infiltration. Understanding how these mechanisms interact with apoptosis could lead to more effective combination therapies.

Role of DCs: Enhancing DC maturation through pathways like *NF-κB* or *JAK/STAT* can improve their function in antigen presentation and boost CD8+ T cell activation, thereby promoting apoptosis.[48,115]

Nonimmune Cells in the Tumor Microenvironment: While current research predominantly focuses on immune cells like T cells and NK cells, the potential roles of nonimmune stromal cells in regulating apoptosis remain underexplored. Cancer-associated fibroblasts (CAFs) can modulate tumor cell apoptosis through secretion of various growth factors and cytokines, while tumor-associated endothelial cells may influence apoptotic signaling through angiocrine factors.[116–119] Future studies should investigate how these nonimmune cellular components affect apoptotic pathways and immune cell function, potentially revealing novel therapeutic targets that could enhance immunotherapy efficacy by modulating the broader tumor microenvironment beyond immune cell interactions. Exploring these underdeveloped areas will provide critical insights into improving apoptotic responses and overcoming resistance, leading to better outcomes in LC immunotherapy.

Future challenges and emerging technological opportunities in the role of apoptosis for LC immunotherapy

Challenges in translating apoptosis induction to clinical applications for LC immunotherapy

Heterogeneity and Resistance: The heterogeneity of LC and tumor resistance to treatment are major challenges in current immunotherapy. Tumor cells can significantly inhibit apoptosis and reduce treatment efficacy by upregulating anti-apoptotic proteins such as *BCL-2* and *MCL-1*.[120,121] Future research should focus on developing combination therapies that target multiple anti-apoptotic proteins to enhance the induction of apoptosis.

Complexity of the Immune Microenvironment: Immunosuppressive factors within the TME, such as *TGF-β* and *IL-10*, limit the ability of immune cells to induce apoptosis in tumor cells.[122] Inhibiting the expression or function of these immunosuppressive factors remains challenging, as they may play different roles at various stages of tumor progression. Therefore, future studies should aim to better understand the dynamic regulatory mechanisms of these factors to enable timely intervention and optimize apoptotic responses.

Specificity of Targeting Apoptotic Pathways: Effective induction of apoptosis requires specific targeting of tumor cells while minimizing damage to normal cells. Many apoptosis-inducing agents can have adverse effects on normal cells, leading to systemic toxicity.[18,123] Future technologies need to address the issue of targeting specificity, developing drugs that can recognize tumor-specific markers to minimize the impact on normal cells.

Emerging technological opportunities for enhancing apoptosis in LC immunotherapy

Gene Editing and Precision Targeting Technologies: Gene editing tools such as *CRISPR-Cas9* offer new possibilities for enhancing apoptosis in LC immunotherapy. *CRISPR* technology can specifically regulate apoptosis-related genes, for instance, by knocking out anti-apoptotic genes like *BCL-2* to enhance apoptotic responses.[124] Additionally, editing regulatory genes of immune checkpoints can boost T cell function and enhance their cytotoxic effects on tumors.

Nanodrug Delivery Systems: Nanotechnology offers significant advantages in the precise delivery of apoptosis-inducing drugs. Nanoparticles can accurately deliver agents such as siRNA or miRNA to tumor sites, increasing drug concentration at the target location while reducing toxicity to normal tissues.[125,126] In the future, the development of targeted nanocarriers may further enhance tumor cell apoptosis while significantly minimizing side effects.

Personalized Medicine and Biomarker Application: Personalized medicine and precision oncology offer opportunities for enhancing apoptotic responses. By integrating multi-omics data, such as genomics and proteomics, key biomarkers related to apoptosis can be identified to guide individualized treatment.[127] These biomarkers can help predict patient response to immunotherapy and optimize treatment plans, thereby increasing efficacy and reducing resistance. Building on this, personalized approaches guided by multi-omics data (e.g., genomics and proteomics) can further refine the identification of apoptosis-related biomarkers for tailoring treatment regimens. Such strategies would improve patient selection for ICIs and other immunotherapies, addressing challenges such as resistance and heterogeneous responses.

In summary, while multiple challenges exist in inducing apoptosis for LC immunotherapy, emerging technologies present important opportunities to overcome these barriers.

Through gene editing, nanodrug delivery, and personalized medicine, future approaches may effectively enhance apoptosis induction, ultimately improving the prognosis for LC patients.

Technical bottlenecks and future research directions

Despite identifying multiple promising research directions, several key technical bottlenecks must be overcome to realize their potential. Current apoptosis-inducing agents for LC cells lack sufficient tumor specificity, necessitating the development of multi-target nanocarriers responsive to TME characteristics (pH, hypoxia, redox state).[56,128,129] The inability to monitor apoptotic responses in real-time during immunotherapy limits precise treatment adjustments, making the development of specific tracers and improved imaging resolution essential.[130,131] The lack of standardized apoptosis assessment methods leads to inconsistent results, requiring validated liquid biopsy approaches implementable across different clinical settings.[132] Additional technical barriers include the rapid activation of compensatory survival pathways following apoptosis induction,[133] insufficient analytical tools for integrating multi-omics data with apoptotic responses,[134] and challenges in scaling production of complex combination therapies.[135] Current approaches also often lack LC tissue specificity, necessitating the development of lung-specific delivery systems or exploitation of unique vulnerabilities in LC cell apoptotic machinery.[136,137] Addressing these technical bottlenecks requires multidisciplinary collaboration between immunologists, oncologists, bioengineers, computational biologists, and pharmaceutical scientists – essential for translating promising research directions into clinically effective therapies that meaningfully improve outcomes for LC patients.

Limitations and future directions

Despite its valuable insights, this study has certain limitations: (i) The literature search was limited to the WoSCC due to difficulties in standardizing raw data formats from other databases like Scopus and PubMed, which hindered a unified analysis. (ii) Only publications in English were included, potentially introducing significant publication bias. This limitation is particularly relevant for research on TCM in LC immunotherapy, as substantial work in this field is published in Chinese-language journals not indexed in WoSCC. Given that our analysis identified TCM as one of the seven major research clusters and an emerging research frontier, this exclusion may have led to an underrepresentation of the full scope, depth, and historical context of TCM research in cancer immunotherapy. Important clinical trials, mechanistic studies, and historical developments regarding apoptosis regulation by TCM compounds might have been overlooked, potentially affecting our understanding of this research cluster's development and influence. This limitation highlights the need for future bibliometric studies to develop methods for including multilingual research outputs, especially when analyzing research areas where significant contributions are made in non-English publications. (iii) Although manual efforts were made to standardize terminology variations, achieving full consistency was challenging, which may have led to minor discrepancies.

Future research should aim to integrate data from multiple sources, such as Scopus and PubMed, once a standardized method for harmonizing file formats is established. Such integration would facilitate a more comprehensive analysis. Expanding the inclusion criteria to consider non-English publications could also provide a more global perspective on the topic. Additionally, employing advanced natural language processing tools for data standardization could improve the accuracy and uniformity of bibliometric studies. Further research should also explore the interactions between apoptosis and emerging therapies, with the goal of identifying innovative treatment strategies and addressing the evolving challenges in LC therapy.

Conclusion

This bibliometric analysis provides the first comprehensive exploration of apoptosis in LC immunotherapy, highlighting significant research growth since 2015. Our findings have important clinical implications for improving the limited response rates currently seen in LC immunotherapy. The emerging focus on combination strategies targeting both immune checkpoints and apoptotic pathways could overcome the dual-pathway resistance frequently observed in LC patients. Key biomarkers identified in our citation analysis (PD-L1 expression, ctDNA dynamics, *NOX4* levels) may enhance patient selection, potentially increasing treatment efficacy while reducing unnecessary interventions. Emerging technologies highlighted in our research clusters—*CRISPR*-based gene editing, targeted nanodelivery systems, and metabolic interventions like ferroptosis inducers – represent promising approaches for clinical translation with improved precision and reduced toxicity. Future treatment regimens will likely integrate multiple cell death mechanisms while leveraging personalized approaches based on patient-specific apoptotic pathway alterations. Enhanced global collaboration and precision targeting of apoptotic mechanisms, as revealed by our analysis, are essential for translating these research trends into improved survival outcomes for LC patients.

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Author contributions

CRediT: **Chun-Jian Zuo:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing; **Jie Tian:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Data availability statement

The datasets used during the present study are available from the corresponding authors upon reasonable request.

Ethics approval and consent to participate

As this study does not involve animal and patient experiments, the ethical approval and consent to participate are not necessary.

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