

Research

Key developments and hotspots in programmed cell death in liver cancer pain: a bibliometric study

Yanmei Yang¹ · Yongjin He¹ · Ping Zhang¹ · Chunyan Wang²

Received: 31 January 2025 / Accepted: 20 May 2025

Published online: 01 June 2025

© The Author(s) 2025 **OPEN**

Abstract

Objectives This bibliometric study aimed to elucidate key developments, influential publications, and emerging research hotspots on programmed cell death (PCD) in liver cancer-associated pain, thereby providing guidance for future mechanism-based, patient-centered therapies.

Methods A comprehensive search was performed in the Web of Science using terms encompassing liver cancer, pain, and various PCD modalities. After multi-stage screening for relevance and quality, a dataset of 324 articles (2000–2024) was analyzed. Tools such as VOSviewer and Bibliometrix facilitated performance analysis, co-citation mapping, keyword clustering, and trend topic identification.

Results The annual publication output increased notably after 2015, reflecting intensified interest in molecular pathways (apoptosis, ferroptosis, autophagy) and their clinical implications. China led in publication volume, while the USA and several European countries demonstrated high impact and extensive international collaborations. Keyword analysis revealed five thematic clusters, highlighting the prominence of inflammation, NF-κB signaling, oxidative stress-mediated apoptosis, combined therapeutic approaches, and metastasis-driven pain. Highly cited articles focused on flavonoids in apoptosis, immunogenic cell death, and cyclooxygenase-2 regulation, underscoring a shift toward integrative regimens that target both tumor progression and pain mechanisms.

Conclusion Programmed cell death research in liver cancer pain has evolved into a rapidly expanding, multidisciplinary field. Findings point to a paradigm shift from purely cytotoxic strategies to more holistic approaches that merge immunotherapy, biomarker-driven diagnosis, and targeted interventions aimed at alleviating pain while controlling tumor growth. These insights lay the groundwork for precision-oriented, mechanism-based treatments that address the multifaceted challenges faced by patients with advanced liver cancer.

Keywords Programmed cell death · Liver cancer pain · Apoptosis · Autophagy · Immunotherapy

1 Introduction

Programmed cell death (PCD) has gained increasing prominence as an essential molecular process influencing both tumor progression and pain dynamics in liver cancer, prompting a wave of integrative investigations that merge advanced oncology with palliative care insights [1–3]. Researchers have highlighted that the interplay between various PCD pathways—such as apoptosis, autophagy, necroptosis, and ferroptosis—and tumor-induced inflammation is far more intricate than initially assumed, driving the development of novel therapeutic strategies aimed at

✉ Chunyan Wang, wcy1066125720@163.com | ¹Tianjin First Central Hospital, Tianjin, China. ²Yunyang County People's Hospital, Chongqing, China.



mitigating hepatic tumor burdens while simultaneously alleviating cancer-related pain [4–6]. In this rapidly evolving landscape, multifactorial approaches have become inevitable, with immunotherapies, targeted drugs, and supportive care converging to address the needs of diverse patient populations [7–10].

Moreover, the globalization of scholarly output underscores the heightened importance of cross-continental collaboration: large-scale clinical trials in Asia, mechanistic studies in Europe, and translational research efforts in North America collectively highlight the universal relevance of exploring PCD as it pertains to pain modulation [11–15]. Recognizing that future palliative paradigms must integrate molecular underpinnings with patient-centered care, scholars increasingly rely on bibliometric methodologies to chart emerging trends, identify gaps in knowledge, and propose new avenues for intervention [16–19].

Against this backdrop, the present bibliometric study endeavors to distill key developments in PCD-related liver cancer pain research, shed light on the most influential publications and authors, elucidate patterns of international collaboration, and ultimately guide upcoming inquiries into mechanism-based, precision-oriented pain management for individuals affected by this challenging disease.

2 Method

2.1 Data source and search strategy

Web of Science served as the primary data source for this investigation, reflecting an emphasis on comprehensive, high-quality bibliographic records. The platform's interdisciplinary nature (covering scientific, social, and health domains) makes it a strong foundation for discovering relevant studies. In addition to offering robust citation metrics, Web of Science provides consistent data extraction formats, facilitating reproducible bibliometric analyses.

A targeted search was conducted using the following formula:

TS = ("liver cancer" OR "hepatic cancer" OR "hepatic carcinoma" OR "liver carcinoma" OR "hepatocellular carcinoma" OR HCC OR "fibrolamellar carcinoma" OR hepatoma OR "hepatocarcinoma" OR "liver tumor" OR "liver tumour" OR "liver neoplasm" OR "primary liver cancer" OR "primary liver tumor" OR "primary liver tumour" OR "secondary liver cancer" OR "metastatic liver cancer" OR cholangiocarcinoma OR "cholangiocellular carcinoma" OR "intrahepatic cholangiocarcinoma" OR ICC OR "biliary cancer" OR "biliary carcinoma" OR "biliary malignant neoplasm" OR "hepatobiliary cancer" OR "hepatobiliary carcinoma" OR "hepatobiliary malignancy" OR "hepatobiliary neoplasm" OR "hepatobiliary tumor" OR "hepatobiliary tumour")

AND

(pain OR ache OR "acute pain" OR "chronic pain" OR "painful" OR "pain syndrome" OR "cancer pain" OR "tumor pain" OR "tumour pain" OR "cancer-related pain" OR "pain condition" OR "painful condition" OR "pain mechanism" OR "pain crisis" OR "incident pain" OR "breakthrough pain" OR "end-of-dose pain" OR "pain assessment" OR "pain measurement" OR "pain score" OR "pain rating" OR "pain scale" OR "pain evaluation" OR "pain tolerance" OR "pain threshold" OR "pain intensity" OR "pain relief" OR "pain control" OR "pain management" OR "pain therapy" OR "pain treatment" OR "pain palliation" OR "palliative care" OR palliative OR "palliative medicine" OR "supportive care" OR analgesic OR analgesics OR analgesia OR "analgesic regimen" OR anodyne OR opioid OR opioids OR "opioid analgesic" OR "narcotic analgesics" OR "non-opioid analgesics" OR NSAIDs OR nociception OR hyperalgesia OR allodynia OR sedation)

AND

("programmed cell death" OR "regulated cell death" OR PCD OR RCD OR apoptosis OR "apoptotic cell death" OR pyroptosis OR "pyroptotic cell death" OR necroptosis OR "necroptotic cell death" OR ferroptosis OR "ferroptotic cell death" OR cuproptosis OR autophagy OR "autophagic cell death" OR anoikis OR entosis OR netosis OR lysoptosis OR parthanatos OR paraptosis OR mitophagy OR autosis OR eryptosis OR phagoptosis OR "immunogenic cell death" OR ICD OR "programmed necrosis" OR "programmed cell demise" OR "cell suicide" OR "caspase-dependent cell death" OR "caspase-independent cell death")

Synonyms such as 'painful condition' or 'pain syndrome' were selected based on preliminary scoping searches and consultation with clinical experts in palliative care, ensuring that varied terminology used in the literature for liver-cancer-related pain would be captured comprehensively. While the inclusion of other databases (e.g., PubMed, Scopus) could potentially retrieve additional records, Web of Science was chosen for its robust citation metrics, consistent data formats, and established track record in bibliometric analyses; this approach may slightly underestimate the global

publication volume but ensures reproducibility in data handling. This formula captures three overarching concepts—(1) liver cancer–related terms, (2) pain-related terms, and (3) programmed cell death–related terms—combined with the Boolean operator AND for precision. The search targeted titles, abstracts, and keywords, ensuring that both core and emerging topics were included. The final database query was performed on February 1, 2025. All retrieved records were subsequently exported in compatible formats for further processing. No date or language filters were applied in the initial search, and all document types were considered except for editorial comments, letters, and meeting abstracts that did not present substantive research data.

2.2 Literature screening and selection

Following data retrieval, an initial pool of publications was compiled from the Web of Science query. YY and YH then conducted a preliminary screening by reviewing abstracts and titles to exclude articles unrelated to liver cancer pain and programmed cell death. The preliminary exclusion focused on non-research materials such as editorial comments, letters, and proceedings without substantive data. This step ensured that only scholarly contributions with relevant content remained for deeper evaluation.

Subsequently, PZ and CW undertook a more in-depth inspection of each record. Their objective was to verify whether the full text aligned with the study's inclusion criteria: a direct examination of programmed (or regulated) cell death mechanisms in the context of liver cancer–associated pain. Articles only tangentially mentioning pain or programmed cell death without substantial discussion were removed. Additional exclusions following full-text review included cases where the primary emphasis was on liver disease without explicit discussion of pain mechanisms or on cell-death pathways that did not directly intersect with pain-related outcomes. Conversely, no restriction on publication date or region was imposed, enabling a comprehensive and global perspective.

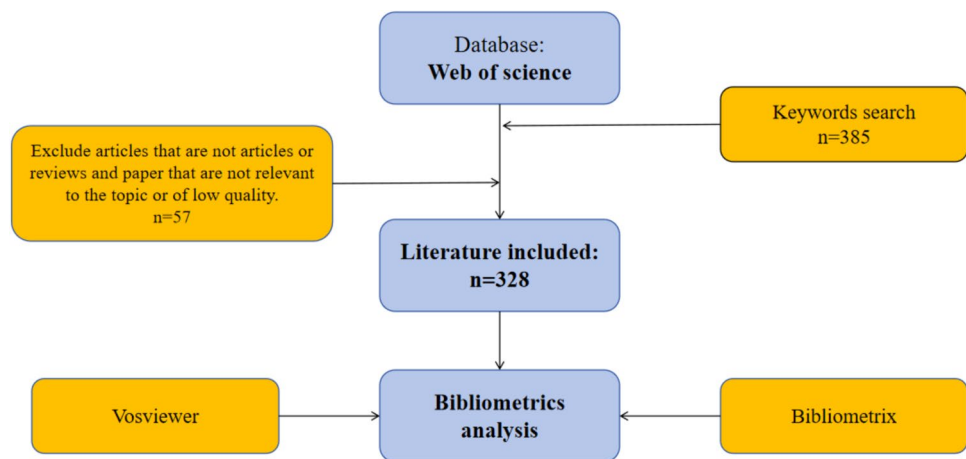
As a final quality check, YY and CW reviewed the refined set of publications to ensure consistency. Any discrepancies were resolved by thorough discussion and consensus. This multi-stage, team-based screening approach supported both rigor and reliability, as multiple investigators examined each publication independently. Disagreements at any stage triggered further evaluation until unanimous decisions were achieved. The result is a curated corpus of studies that reflects a nuanced view of the intersection of liver cancer, pain management, and various forms of cell death, positioning the dataset for robust bibliometric and content analyses in the subsequent sections.

2.3 Bibliometric methodology

As shown in Fig. 1, the bibliometric methodology deployed in this investigation combined performance analysis and scientific mapping to generate a multifaceted overview of scholarly activity related to liver cancer pain and programmed cell death. First, the Web of Science–derived records were downloaded in the “txt” formats. These files were then pre-processed in R studio (4.41) to remove duplicate entries, standardize author names, and ensure consistency in journal abbreviations. Duplicate records were identified by cross-matching DOIs, titles, and author lists; any discrepancies were manually resolved, ensuring that each article in the final corpus was unique.

To visualize co-citation, co-occurrence, and collaboration patterns, two primary tools were employed: VOSviewer (version 1.6.20) and Bibliometrix (version 4.3.1). VOSviewer excels at creating network visualizations, where nodes (e.g., authors, keywords, or journals) and links (e.g., co-authorship, co-occurrence, or citation relationships) offer an integrative depiction of the research landscape. The relative importance of each node is reflected by circle size, and total link strength (TLS) quantifies the connection intensity. Bibliometrix, a comprehensive R-based package, provides advanced statistical analysis, enabling identification of high-impact articles, emergent research clusters, and collaboration networks. In this context, TLS represents the cumulative weight of connections (co-authorship, co-citation, or co-occurrence) that a given node maintains with all other nodes in the network, providing a quantitative measure of its overall integrative influence within the map. This tool also generates diverse graphical representations—such as thematic maps—illuminating how scholarly interests evolve over time. The dual application of VOSviewer and Bibliometrix enhances both breadth and depth in bibliometric interpretation. This integrated strategy ensures that the findings are not only statistically sound but also visually interpretable, laying the groundwork for a structured synthesis of the discovered themes in relation to programmed cell death and liver cancer pain.

Fig. 1 Research methodology in this bibliometric study



2.4 Content analysis

To supplement the quantitative perspective gained from bibliometric analyses, a content analysis was performed using a synthetic knowledge synthesis method. This approach merges textual examination techniques with bibliometric findings to present a more holistic depiction of scientific discourse surrounding programmed cell death in liver cancer pain. The first step involved collating the full-text articles identified through the rigorous screening process. These publications formed the raw dataset for thematic exploration. Text mining procedures were applied to extract keywords, common phrases, and conceptual threads within the literature. These data points were then clustered and represented through the co-occurrence maps generated by bibliometric software. Themes and codes emerged from these clusters, signifying convergences in topics such as autophagy-linked pain regulation or apoptotic pathways in oncologic palliative care. Each cluster's internal components were examined for interrelated factors, revealing how researchers have approached specific mechanistic or clinical aspects of cell death in liver tumors.

Within each distinct cluster, concepts were refined and categorized, leading to the assignment of thematic designations capturing the essence of the literature. Emerging themes were systematically documented in a consolidated reference framework. This framework contributes robust qualitative insights that complement the quantitative metrics gleaned from the preceding analyses.

3 Results

3.1 Publication characteristics

As shown in Fig. 2, a total of 324 publications on programmed cell death in liver cancer pain were identified, spanning the years 2000–2024. Although initial studies appeared as early as 2000 ($n=4$), the field maintained relatively modest growth until around 2011, when more systematic inquiries into the molecular intricacies of pain and cell death in hepatocellular malignancies began to surface. A notable upswing occurred from 2015 onward, coinciding with growing clinical interest in immunotherapies and targeted treatments for advanced liver cancer. This pattern was reflected globally, as research hubs in Asia, North America, and Europe began to converge on the importance of regulated cell death pathways—such as apoptosis, autophagy, and ferroptosis—for innovative pain-management strategies. By 2019, the annual publication count had surged to 32, followed by sustained high output in subsequent years, peaking at 41 publications in 2022. Examination of regional foci reveals that Western institutions often contributed foundational work on immunogenic cell death mechanisms, while research teams in East Asia advanced clinical trials integrating emerging analgesic protocols. These cross-continental efforts have shaped new frontiers in both palliative practice and molecular oncology, exemplified by the adaptation of immune checkpoint inhibitors alongside novel pain-modulation techniques. Even as the total count dipped slightly in 2023, the continued trajectory into 2024 ($n=26$) signals that the interplay between programmed cell death pathways and pain therapeutics remains a rapidly evolving domain. Although our search strategy also covered cholangiocarcinoma and metastatic liver tumors, the final dataset contained fewer articles explicitly centered on these

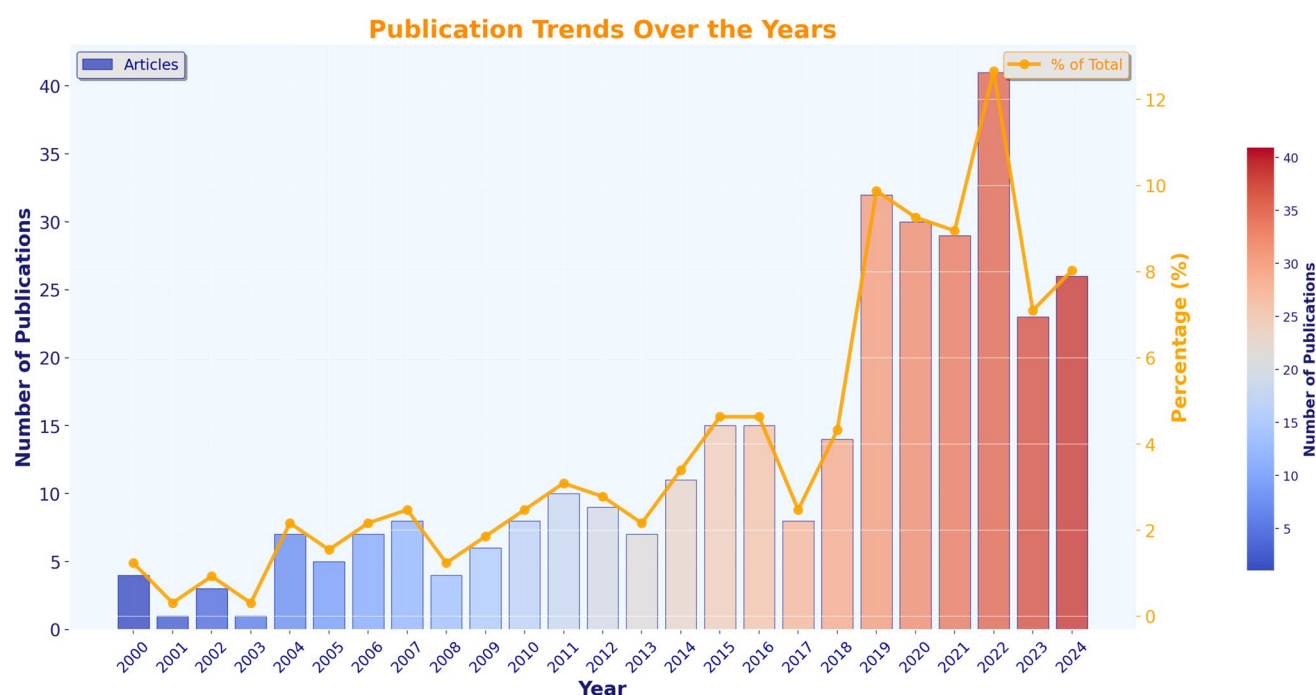


Fig. 2 Annual Publication Output in programmed cell death in liver cancer pain (2000–2024)

malignancies, likely reflecting their comparatively lower publication volume in this niche; as a result, the majority of included studies and thematic clusters naturally emphasized HCC-specific pain and cell-death mechanisms. The overall trend underscores how the refinement of targeted therapies and supportive care practices has fueled steady global expansion of scholarship, driving the discipline toward more integrated, mechanism-based pain management solutions for patients with liver cancer.

3.2 Top 10 most cited publications and authors

As shown in Table 1 [20–29], all the most highly cited works in this field demonstrate a strong focus on uncovering molecular mechanisms at the interface of pain regulation and tumor cell death in hepatocellular carcinoma. The publication with the highest citation impact [20] offers an extensive review on flavonoids in cancer and apoptosis, underscoring how these compounds can modulate multiple pathways central to programmed cell death. The second most cited article [21] explores α -fetoprotein as a pivotal diagnostic and prognostic marker, an insight that has significantly shaped the clinical approach to both early detection and ongoing surveillance in advanced liver cancer. Other top-cited studies reflect pivotal advances in translational research, ranging from mechanistic toxicogenomics in human hepatoma cells [22] to the dynamics of hyperprogressive disease during PD-1 blockade [23], highlighting the growing emphasis on immunotherapeutic strategies. Multiple investigations [24, 26, 28, 29] delve into cellular stress responses, mitochondrial function, and key signaling pathways, illustrating how targeted pharmacological interventions can modulate apoptosis, necroptosis, and other regulated cell death pathways to alleviate tumor-driven pain. Complementary reviews [25] on cyclooxygenase-2 biology further reveal how the refinement of tumor-related inflammatory processes intersects with therapeutic applications. Collectively, these publications exemplify a growing consensus that innovative, mechanism-based treatments—whether focusing on natural product-derived molecules, advanced immunotherapies, or precise biomarker-driven interventions—offer promising directions for improving both the survival and quality of life of patients suffering from liver cancer pain.

3.3 Most productive journals

As shown in Table 2, the studies were disseminated across numerous journals, with at least four publications appearing in ten distinct sources. Journal of Ethnopharmacology emerged as the most prolific venue, with 11 articles (247 total

Table 1 Most cited publications and authors

No	Title	Authors	Journal	Web of Science citation	Total citation	Publication type
1	Flavonoids in Cancer and Apoptosis [20]	Abotaleb M etal	CANCERS	488	509	Review
2	Diagnostic and prognostic role of α -fetoprotein in hepatocellular carcinoma:: Both or neither [21]?	Farinati F etal	AMERICAN JOURNAL OF GASTROENTEROLOGY	341	367	Article
3	Toxicogenomics-based discrimination of toxic mechanism in HepG2 human hepatoma cells [22]	Burczynski ME etal	TOXICOLOGICAL SCIENCES	198	232	Article
4	Hyperprogressive disease during PD-1 blockade in patients with advanced hepatocellular carcinoma [23]	Kim CG etal	JOURNAL OF HEPATOLOGY	128	134	Article
5	Pterostilbene inhibited tumor invasion via suppressing multiple signal transduction pathways in human hepatocellular carcinoma cells [24]	Pan MH etal	CARCINOGENESIS	128	142	Article
6	Biology of Cox-2: An Application in Cancer Therapeutics [25]	Khan Z etal	CURRENT DRUG TARGETS	126	144	Review
7	Acetylsalicylic acid-induced oxidative stress, cell cycle arrest, apoptosis and mitochondrial dysfunction in human hepatoma HepG2 cells [26]	Raza H etal	EUROPEAN JOURNAL OF PHARMACOLOGY	118	126	Article
8	Arsenic trioxide in patients with hepatocellular carcinoma: a phase II trial [27]	Lin CC etal	INVESTIGATIONAL NEW DRUGS	110	119	Article
9	Alpha-fetoprotein: a new member of intracellular signal molecules in regulation of the PI3K/AKT signaling in human hepatoma cell lines [28]	Li MS etal	INTERNATIONAL JOURNAL OF CANCER	103	119	Article
10	Suppressing DRP1-mediated mitochondrial fission and mitophagy increases mitochondrial apoptosis of hepatocellular carcinoma cells in the setting of hypoxia [29]	Lin XH etal	ONCOGENESIS	55	63	Article

citations), reflecting strong interest in natural-product research intersecting with oncological pain management and programmed cell death. *Frontiers in Oncology* and *Frontiers in Pharmacology* both contributed eight articles, indicating an expanding focus on integrative and translational perspectives, while *Oncology Reports* (n=6) and *Journal of Hepatology* (n=5) demonstrated substantial impact—particularly the latter, which exhibited a remarkably high average citation count (133.40). *Molecular Medicine Reports*, *World Journal of Gastroenterology*, *International Journal of Molecular Sciences*, and *Molecules* (each with five articles) further underscore an interdisciplinary shift toward molecular pathways governing tumor progression and pain regulation, often coupling traditional pharmacological insights with evolving cellular and immunologic findings. *International Journal of Cancer*, publishing four articles with a robust average citation (68.00), epitomizes the mainstream engagement of cancer-focused periodicals with the intersection of hepatic oncology and regulated cell death. This collective body of high-citation journals signals the broadening of inquiry into mechanistic underpinnings and clinical applications, guiding future submissions and reinforcing the pivotal role that interdisciplinary journals play in shaping our understanding of pain-related apoptosis, necroptosis, and other programmed cell death pathways in liver cancer.

4 Keyword analysis

A comprehensive strategy combining synthetic information synthesis, text mining, and bibliometric mapping was adopted to explore key terms related to liver cancer pain. Drawing on text mining results from 324 publications, a total of 345 keywords were identified. VOSviewer-assisted cluster analysis further organized these terms into five distinct groups, each requiring a minimum co-occurrence of two (Fig. 3 and Table 3). We opted for this minimum co-occurrence threshold of two to capture less frequent but potentially relevant terms, while excluding keywords that appeared only once and lacked any meaningful network connections. Node size within the clusters reflected the frequency with which certain keywords emerged, highlighting “hepatocellular carcinoma,” “apoptosis,” “cancer,” “inflammation,” and “pain” as the most prominent. These findings underscore the community’s emphasis on deciphering molecular mechanisms and therapeutic pathways, along with the role of inflammatory processes in hepatic malignancies. “apoptosis,” “inflammation,” and related terms repeatedly appeared, indicating that investigations into inflammatory mediators and cell-death pathways remain central to oncological research. The VOSviewer co-occurrence map (Fig. 4, Table 3) provides a visual representation of these interactions. In the Blue cluster, “inflammation” and “NSAIDs” emerged as pivotal concepts, underscoring anti-inflammatory strategies in oncology. The Red cluster underscored the relevance of “NF-kappa-B” and “hepatocellular carcinoma cells,” suggesting the importance of transcriptional regulation in HCC progression. Within the Green cluster, “apoptosis,” “oxidative stress,” and “bcl-2” predominated, indicating the significance of programmed cell death in disease management. The Yellow cluster highlighted broader therapeutic directions through “therapy,” “chemotherapy,” and “immunotherapy,” while the Purple cluster drew attention to “metastasis,” “pain,” and “angiogenesis,” illuminating challenges posed by advanced disease and tumor-induced pain. Collectively, these clusters reveal how the interplay between inflammation, cell

Table 2 Most productive sources of publications

No	Source	Number of articles	Total citation	Average citation	Total link strengths	JCR 2023
1	Journal of Ethnopharmacology	11	247	22.45	15	4.8
2	Frontiers in Oncology	8	65	8.13	13	3.5
3	Frontiers in Pharmacology	8	205	25.63	29	4.4
4	Oncology Reports	6	217	36.17	18	3.8
5	Journal of Hepatology	5	667	133.40	30	26.8
6	Molecular Medicine Reports	5	74	14.80	10	3.4
7	World Journal of Gastroenterology	5	202	40.40	15	4.3
8	International Journal of Molecular Sciences	5	102	20.40	9	4.9
9	Molecules	5	204	40.80	18	4.2
10	International Journal of Cancer	4	272	68.00	24	5.7



death mechanisms, and evolving treatment modalities drives the current research agenda on liver cancer pain (Fig. 5).

4.1.1 Theme 1: inflammation and anticancer strategies (Cluster 1)

4.1.2 Theme 2: NF- κ B signaling and regulation in HCC (Cluster 2)

Table 3 Content analysis

Cluster color & no	Cluster theme	Codes (keywords)	Subcategories
Blue (Cluster 1)	Inflammation and anticancer strategies	inflammation, COX-2, celecoxib, NSAIDs, aspirin, anticancer, gene expression, breast cancer, lung cancer, nonsteroidal anti-inflammatory, etc	1. Anti-inflammatory pathways in cancer 2. Role of NSAIDs/COX-2 inhibitors 3. Multi-cancer context
Red (Cluster 2)	NF-κB signaling and regulation in HCC	NF-kappa-B, human hepatocellular carcinoma, hepatocellular carcinoma cells, up-regulation, down-regulation, growth, in vitro, etc	1. NF-κB-related transcriptional regulation 2. Impact on hepatocellular carcinoma cell proliferation and growth
Green (Cluster 3)	Apoptosis and oxidative stress in liver cancer	apoptosis, oxidative stress, induction, glutathione, cell death, bcl-2, activation, inhibition, HepG2 cells, cytotoxicity, death, etc	1. Key pathways of programmed cell death 2. Oxidative stress-induced cytotoxicity 3. Bcl-2 and related genes
Yellow (Cluster 4)	Therapeutic approaches for HCC	hepatocellular carcinoma, therapy, chemotherapy, immunotherapy, radiofrequency ablation, transarterial chemoembolization, sorafenib, diagnosis, etc	1. Systemic therapy (chemotherapy, immunotherapy) 2. Local/regional therapies (RFA, TACE) 3. Diagnostic tools
Purple (Cluster 5)	Cancer progression, metastasis, and pain	cancer, metastasis, invasion, migration, angiogenesis, pain, neuropathic pain, resistance, etc	1. Tumor microenvironment and angiogenesis 2. Metastatic processes 3. Pain management and drug resistance

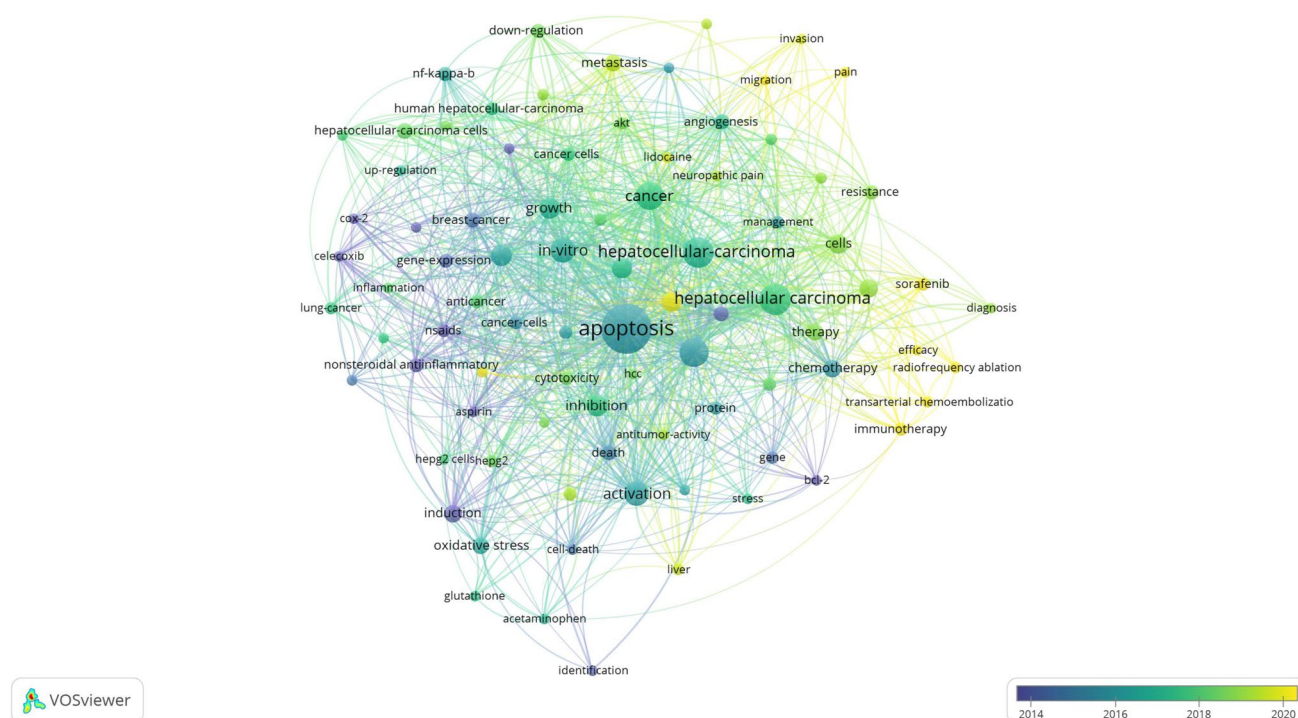


Fig. 4 Keyword clustering with timeline

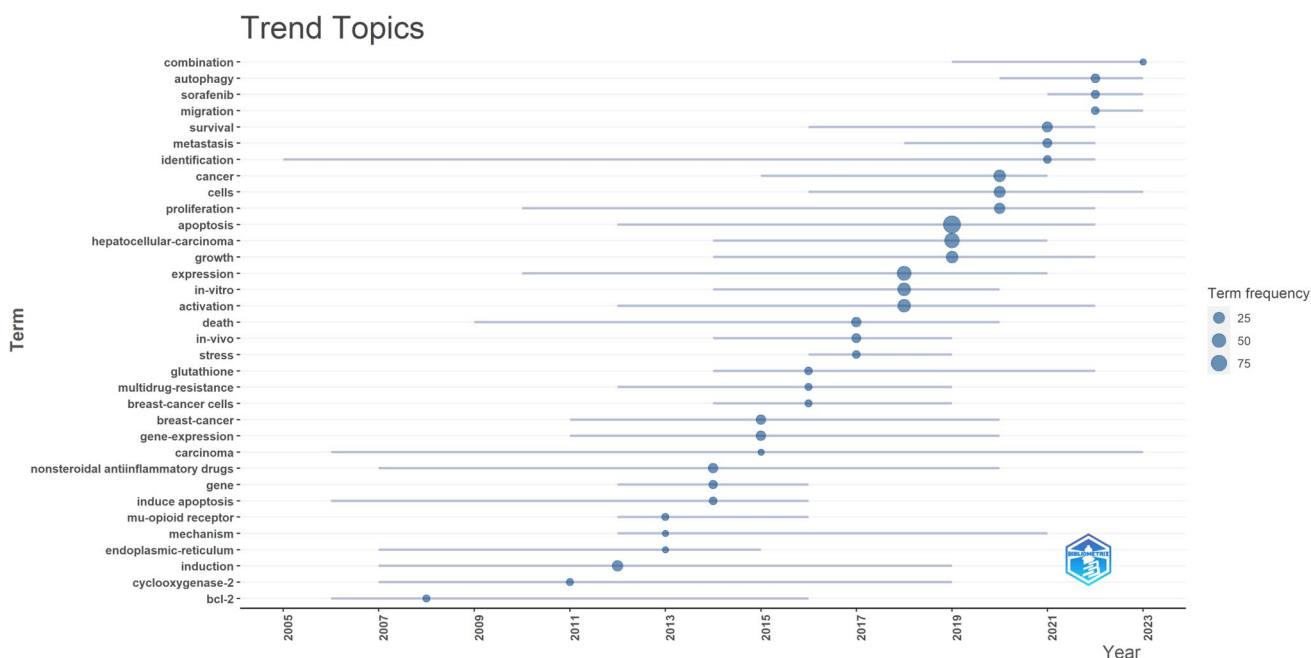


Fig. 5 Trend topics analysis

4.1.3 Theme 3: apoptosis and oxidative stress in liver cancer (Cluster 3)

This theme involves the interplay between oxidative stress, apoptosis, and molecular signaling cascades critical for cell death regulation in HepG2 and other liver cancer cell models. Keywords including “bcl-2,” “glutathione,” and “cytotoxicity” point to the core processes governing programmed cell death. The cluster underscores the significance of both pro- and

anti-apoptotic factors in dictating cell fate, reflecting a growing interest in therapeutic agents that tip the balance toward tumor cell demise via oxidative stress induction.

4.1.4 Theme 4: therapeutic approaches for HCC (Cluster 4)

Capturing a wide spectrum of treatment modalities, this theme highlights systemic therapies such as chemotherapy and immunotherapy, as well as local and regional interventions including radiofrequency ablation (RFA) and transarterial chemoembolization (TACE). The emphasis on diagnostic tools underscores the necessity for early detection, while references to agents like sorafenib reflect the continually evolving pharmaceutical landscape. The cluster thus conveys how multiple approaches are converging to form a more personalized and integrative paradigm for managing hepatocellular carcinoma.

4.1.5 Theme 5: cancer progression, metastasis, and pain (Cluster 5)

The final theme explores the multifaceted challenges posed by advanced disease, emphasizing metastatic mechanisms, resistance to therapy, and the emergence of neuropathic pain. Terms such as “angiogenesis” and “migration” highlight tumor microenvironment dynamics, while “pain” emerges as a pivotal clinical concern requiring both pharmacological and nonpharmacological management strategies. Collectively, these insights into metastasis, invasion, and pain reflect the continued drive to design interventions that not only extend survival but also improve quality of life for patients with advanced liver cancer. Metastatic lesions to bone can provoke extensive osteoclast-driven resorption and local inflammatory responses, amplifying nociceptive signals, whereas peritoneal or neural-involving metastases may compress or irritate regional nerves, directly escalating pain severity.

4.2 Most productive countries and collaboration

As shown in Table 4, publications in this domain originated from multiple countries, with the People’s Republic of China leading in sheer volume (146 documents) and total link strength (TLS = 20), indicating both a robust output and extensive international collaborations. The USA, Germany, and South Korea also showed high productivity and notable TLS values (16, 14, and 11, respectively), reflecting their importance in shaping global research directions on programmed cell death in liver cancer pain. Although nations such as Italy, France, and Spain contributed fewer publications (16, 6, and 8, respectively), they exhibited higher citations per article—particularly France (64.33) and Italy (62.50)—suggesting that their work exerts a disproportionately strong impact on the field. Japan and England further illustrate this dynamic, featuring lower document counts (15 and 7) but elevated citation averages (45.33 and 43.14), underscoring concentrated pockets of research excellence. Meanwhile, India’s growing scholarly output (9 publications, 25.89 citations per article) underscores an emerging contribution to an increasingly globalized research landscape. These indicators collectively highlight the discipline’s expanding geographical reach and the heightened scientific dialogue around mechanisms

Table 4 Number of publications and citations by country

Country	Documents	Citations	Total link strength	Number of citations per article
People's Republic of China	146	3817	20	26.14
USA	49	2309	16	47.12
Germany	25	905	14	36.20
South Korea	23	633	11	27.52
Italy	16	1000	10	62.50
Japan	15	680	10	45.33
India	9	233	8	25.89
Spain	8	451	6	56.38
England	7	302	6	43.14
France	6	386	7	64.33

of cell death and pain control in hepatic malignancies, with leading countries forging cross-border collaborations that accelerate the translation of basic findings into clinical applications.

4.3 Trend topics

By employing VOSviewer for layer visualization and Bibliometrix for trend topic analysis (Figs. 4 and 5), we identified thematic shifts in the literature on programmed cell death in liver cancer–associated pain. In the VOSviewer display, larger circles correspond to a higher frequency of keyword usage, while colors depict the chronological progression from earlier research (blue) to more recent investigations (yellow). Early studies predominantly featured the keywords “apoptosis,” “hepatocellular carcinoma,” “cancer,” and “inflammation,” underscoring initial interests in fundamental tumor biology and inflammatory pain processes. In contrast, newer studies increasingly emphasize “autophagy,” “metastasis,” “sorafenib,” “immunotherapy,” and “combination therapy,” illustrating the emerging scope of experimental and clinical pursuits. To further substantiate these findings and clarify the field’s ongoing evolution, we performed an additional trend topic analysis with Bibliometrix. In that approach, the circle size and placement within the table reflect both the frequency of keyword usage and its predominant time period, demonstrating a surge in attention toward “multidrug-resistance,” “oxidative stress,” “migration,” and “mechanism.” This progression indicates a shift from research centered primarily on apoptosis to investigations encompassing autophagic pathways, targeted therapies, and immunomodulatory strategies that address both tumor growth and pain control. Parallel advancements in intervention strategies—ranging from anti-inflammatory agents (e.g., NSAIDs, COX-2 inhibitors) to immunotherapeutic and autophagy-focused treatments—highlight an increasingly integrated, mechanism-driven approach aimed at simultaneously managing cancer progression and enhancing patient quality of life.

5 Discussion

5.1 Field development analysis

The development of scholarship on programmed cell death in liver cancer pain, as evidenced by our bibliometric findings, reflects a progressive shift from exploratory, mechanistic inquiries into how cells die in hepatic malignancies toward increasingly integrated, translational strategies that bridge molecular research, clinical management, and palliative care. While the results demonstrate a relatively modest early trajectory marked by focused inquiries into apoptosis and inflammatory pain pathways, a closer reading reveals that the convergence of immunological insights, targeted therapies, and advanced diagnostic protocols spurred a marked acceleration from approximately 2015 onward. This is not merely a rise in output but, more significantly, a methodological broadening: alongside traditional reductionist approaches that isolate single pathways (e.g., NF- κ B, Bcl-2, or COX-2 signaling), contemporary investigations emphasize interlocking regulatory networks, including autophagic and ferroptotic processes, whose clinical implications extend well beyond tumor control per se. The domain has been particularly invigorated by the interplay of targeted immunotherapies—e.g., immune checkpoint inhibitors—and combination regimens that place pain alleviation on par with tumoricidal efficacy, underscoring a newfound focus on patient-centric outcomes.

Noteworthy, too, is the global distribution of these scholarly efforts. Although Western nations contributed foundational research on immunogenic cell death, East Asian institutions have often provided large-scale clinical trials and mechanistic studies, thereby catalyzing new cross-continental collaborations that integrate fundamental science with real-world patient cohorts. This dynamic collaboration landscape enriches the field by infusing it with a plurality of perspectives: Western laboratories might prioritize the discovery of novel regulators of programmed cell death and their synergy with immunotherapy, while Asian clinical centers refine these mechanistic insights through high-volume patient registries, bridging bench with bedside. Such synergy is reinforced by the increasingly interdisciplinary nature of the top publication venues—ranging from journals dedicated to ethnopharmacology and natural product research to those focusing on gastroenterology, oncology, and molecular medicine—which collectively accelerate the cross-pollination of ideas. In parallel, the refined understanding of how tumor biology interfaces with neuropathic or inflammatory pain mechanisms paves the way for mechanistically informed analgesic interventions. The identification of trending topics such as oxidative stress, autophagy, and multidrug resistance underscores the field’s evolution away from a monolithic view of apoptosis as the sole gatekeeper of cell death. Researchers are instead mapping a complex web of regulated cell demise, implicating pyroptosis, ferroptosis, and necroptosis in the pathogenesis of pain in advanced liver disease.

This conceptual expansion resonates with the emergence of combination therapies involving agents like sorafenib or other multikinase inhibitors: while these drugs were initially championed for their tumoricidal properties, a secondary impetus involves their ability to modulate peripheral and central pain signaling through the same molecular pathways that govern cell survival. Such an integrative perspective, in which oncogenic pathways and nociceptive circuits are viewed as co-regulated processes, is fueling novel therapeutic paradigms aimed at both halting tumor spread and mitigating pain. The co-occurrence analyses, which cluster inflammation, metastasis, and pain within overlapping thematic structures, affirm that the clinical complexity of hepatocellular carcinoma (HCC) demands a similarly multifaceted research response. Indeed, investigators are increasingly adopting advanced models—ranging from 3D organoids to patient-derived xenografts—to capture the full spectrum of tumor–host interactions, including the immunological crosstalk that exacerbates pain states. This level of complexity is also mirrored in the prominence of “combination therapy” and “immunotherapy” as emerging keywords: where once the field emphasized either tumoricidal or analgesic endpoints in isolation, there is now a recognition that efficacious palliation, especially in advanced HCC, requires a synchronized approach targeting both tumor progression and its underlying molecular drivers of pain [30–35]. Further underlining the sophistication of contemporary research are the high-impact publications that bridge fundamental mechanisms (e.g., stress response, mitochondrial dysfunction, or inflammatory signaling) with potential biomarkers (e.g., α -fetoprotein or immune markers) to guide both prognosis and therapeutic customization. Such biomarker-driven strategies resonate with the broader move toward precision medicine, suggesting that future developments may prioritize real-time monitoring of cell death pathways, possibly via circulating tumor DNA or exosomal signals, to tailor analgesic and oncologic interventions alike. Complementary research into natural products and phytochemicals also indicates an appetite for exploring less conventional, potentially synergistic agents that may simultaneously modulate multiple cellular targets—apoptotic, autophagic, or immunologic—while yielding fewer side effects. Ultimately, the field’s trajectory points to a decisive transition: from piecemeal explorations of pain pathophysiology and cell death in liver cancer to a harmonized framework in which the molecular intricacies of tumor biology, immune regulation, and neuroinflammation are not only elucidated but also harnessed for therapeutic gain.

The bibliometric patterns attest to a rapid intensification of international collaborations and thematic diversification, implying that future breakthroughs will likely emerge from consortia that blend molecular oncology, pharmacology, immunology, and pain science. By situating these advancements within a broader clinical narrative—one that foregrounds patient quality of life—the discipline is poised to refine our collective understanding of how to disrupt malignant processes while simultaneously mitigating the burden of chronic or refractory pain. Thus, what began as a specialized focus on cell death pathways in hepatic tumors has matured into a richly interdisciplinary domain, driving innovation that promises not only improved survival but also a better quality of life for those battling liver cancer pain.

5.2 Field hotspot analysis

The current hotspots within this rapidly evolving domain spring from an intricate confluence of molecular discovery, translational application, and clinical imperatives, forming multiple investigative trajectories that collectively redefine our understanding of programmed cell death in the context of liver cancer pain. As gleaned from the results, researchers are not only refining classical concepts of apoptosis but also foregrounding a spectrum of cell-death modalities—encompassing ferroptosis, pyroptosis, necroptosis, and emerging subtypes of autophagic dysfunction—thereby expanding the repertoire of mechanistic targets for mitigating oncogenesis and alleviating pain. For example, ferroptosis involves iron-dependent lipid peroxidation leading to cell death, which may synergize with certain chemotherapy agents and modulate pain through oxidative-stress pathways, whereas pyroptosis, driven by gasdermin pore formation and robust pro-inflammatory cytokine release, can either exacerbate or potentially redirect inflammatory pain responses depending on the tumor microenvironment. Necroptosis, as a receptor-interacting protein kinase-driven process, often causes the release of damage-associated molecular patterns (DAMPs) that can intensify inflammatory pain, while pyroptosis commonly elevates IL-1 β levels contributing to nociceptive hypersensitivity, and ferroptosis may influence pain through oxidative stress mediators that affect peripheral nerve endings.

One discernible hotspot involves the nuanced role of inflammatory mediators and their downstream signaling pathways: instead of merely cataloging inflammation as a byproduct of cancer progression, recent studies delve into how cytokine regulation and immune microenvironment remodeling may be leveraged to induce more precise and tolerable analgesic outcomes, pointing toward an imminent paradigm in which modulators of inflammation serve dual oncologic and palliative functions. Another prominent theme, reflected in the shift toward sophisticated pharmacological and genetic interventions, situates combination therapy at the forefront of innovation: while single-agent regimens

once dominated clinical trials, the literature now illuminates the synergistic potential of coupling immune checkpoint inhibitors with agents that specifically manipulate regulated cell death pathways—a phenomenon especially relevant for advanced hepatocellular carcinoma, where standard therapies often falter. This synergy is further reinforced by the growing attention to the tumor microenvironment and metastatic cascades, highlighting that local control of hepatic lesions alone is insufficient in the face of systemic tumor spread and pain amplification. Indeed, investigations that merge molecular imaging, high-throughput screening, and multi-omics analyses reveal that the interplay between malignant cells and infiltrating immune subsets can drive both neuropathic and inflammatory pain signatures, thus spurring efforts to tailor novel analgesic modalities alongside cytotoxic regimens [36–40]. For instance, a recent Phase II trial (NCT04556669) is investigating the addition of ferroptosis-inducing agents to standard care in advanced HCC, measuring not only tumor response but also patient-reported pain scores as co-primary endpoints, while an ongoing multicenter study (NCT04698915) explores pyroptosis-targeted combination therapy to enhance analgesic efficacy in progressive hepatobiliary tumors. Moreover, neuropathic pain, often triggered by nerve infiltration or compression, may not respond to immunomodulatory regimens in the same way that inflammatory pain—driven primarily by cytokines and cellular debris—does, reinforcing the need to customize PCD-based treatments based on the underlying pain mechanism. On the technological front, the incorporation of next-generation sequencing, single-cell transcriptomics, and CRISPR-based gene editing into the field has propelled mechanistic clarity: by dissecting heterogeneous tumor cell populations and identifying which sub-clones rely on specific cell death pathways, researchers can customize interventions that selectively trigger tumoricidal processes while minimizing off-target pain exacerbation [41–45]. Furthermore, the interest in biomarkers—ranging from circulating tumor DNA to exosomal cargo—heralds an emerging hotspot focused on precision monitoring [46–50]. Rather than relying solely on histological and symptomatic endpoints, new frameworks increasingly position biomarker panels as real-time indicators of how effectively a therapy prompts programmed cell death and modulates pain [51–56]. Additionally, the trend toward integrative palliative strategies cannot be overlooked: multi-disciplinary teams are beginning to incorporate complementary medicine perspectives, such as herbal extracts or nutraceuticals with putative pro-apoptotic or anti-inflammatory properties, into mainstream oncology protocols.

Though once at the periphery, these alternative approaches have garnered newfound legitimacy as researchers characterize the molecular underpinnings of naturally derived compounds—particularly in modulating reactive oxygen species, mitochondrial pathways, and pro-inflammatory mediators central to both tumor progression and pain perception [57–63]. At the same time, a corollary hotspot has emerged around managing the balance between effective tumoricidal interventions and potential adverse events, including paradoxical pain amplification through certain necrotic or pyroptotic pathways. This consideration has led to conceptual refinements: no longer are forms of regulated cell death viewed strictly as beneficial or detrimental, but instead as processes whose clinical impact may hinge on the kinetic interplay between tumor clearance and the release of algesic factors. As a result, an entire subfield now explores the concept of immunogenic cell death, wherein tumor apoptosis or necrosis fosters an anti-tumor immune response while minimizing local pain. Concomitantly, the global distribution of research hints at another pivotal hotspot: cross-continental collaborations that integrate molecular data from high-prevalence regions with technological resources from established research hubs, thus fueling a more nuanced examination of epidemiological patterns, genetic predispositions, and culturally adapted palliative measures. Investigators appear increasingly inclined to form consortia that harness large-scale patient registries and advanced data analytics to correlate genotype–phenotype relationships with pain phenotypes, thereby expanding the evidence base for personalized therapeutic regimens.

Moreover, the intensifying momentum around novel analgesic targets—particularly those tied to neuroinflammatory processes—underscores a growing recognition that pain in liver cancer is multifactorial, shaped by peripheral and central nervous system mechanisms, tumor microenvironment factors, and patient-specific immunological landscapes. This integrative viewpoint aligns with the appearance of innovative terms in keyword trend analyses, such as “combination immunotherapy,” “autophagic flux,” and “neuroinflammation,” underscoring the community’s pivot toward comprehensive modalities that converge on both cancer biology and pain pathophysiology. Collectively, these evolving focal points signal a critical transformation in the field’s priorities: where traditional research once demarcated pain management as a largely symptomatic adjunct to oncology care, the current intellectual surge treats pain as an integral element of the therapeutic landscape—one that can be meaningfully influenced by modulating cell death pathways. By merging methodological rigor (e.g., advanced imaging, transcriptomics) with translational savvy (e.g., biomarker-driven trials, combination regimens), the field positions itself to unravel longstanding clinical dilemmas such as recurrent disease, metastasis-related pain flares, and drug resistance. In doing so, it clears a path toward robust, mechanism-based interventions that illuminate not only how best to destroy hepatic tumor cells but also how to reconcile that cytotoxic imperative with the urgent need for effective palliation. Taken together, these converging streams of inquiry—from immunomodulation and

biomarker development to synergy in combination therapies—constitute the principal hotspots now invigorating the study of programmed cell death in liver cancer pain. They reflect the community's collective shift toward a more holistic, integrated model that addresses the molecular underpinnings of tumor progression and pain simultaneously, setting the stage for breakthroughs with genuine clinical impact and improved quality of life for affected patients.

6 Conclusion

This bibliometric analysis reveals a rapidly expanding field at the intersection of programmed cell death mechanisms and the management of liver cancer-related pain. The corpus illustrates how initial explorations into apoptosis and inflammatory pathways have evolved into an integrated, multidisciplinary endeavor that bridges basic molecular discoveries—such as ferroptosis and autophagy—with clinical innovations, including targeted immunotherapies and combination regimens. Geographic diffusion of scholarship further underscores the global resonance of this topic, with collaborative studies spanning Asia, Europe, and North America. High-impact publications consistently emphasize the reciprocal link between tumor progression and pain, highlighting the promise of mechanistic interventions that address both oncogenesis and analgesia. Indeed, evolving research clusters demonstrate a pivot from purely cytotoxic objectives toward more nuanced aims that incorporate patient-centered outcomes, especially for advanced hepatocellular carcinoma. In addition to spotlighting established interventions like COX-2 inhibition and sorafenib, newer investigations embrace cutting-edge genomic tools and biomarker-driven strategies, moving the field closer to personalized approaches. Collectively, these trends underscore the growing consensus that optimal care in liver cancer transcends tumor eradication alone, encompassing the modulation of regulated cell death pathways to achieve meaningful pain relief.

Author contributions YY and YH conceived and designed the study. PZ and CW analyzed data. YY and YH collected data. PZ and CW wrote. YY and YH helped with the final revision of this manuscript. All authors reviewed and approved the final manuscript.

Funding This study was not funded.

Data availability The data used to support the findings of this study are included within the article.

Declarations

Declaration of generative AI and AI-assisted technologies in the writing process During the preparation of this work the used ChatGPT in order to improve authors language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Competing interests The authors declare no competing interests.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

1. Xie Z, Zhao M, Yan C, et al. Cathepsin B in programmed cell death machinery: mechanisms of execution and regulatory pathways. *Cell Death Dis.* 2023;14(4):255.
2. Zhao J, Roberts A, Wang Z, et al. Emerging role of PD-1 in the central nervous system and brain diseases. *Neurosci Bull.* 2021;37(8):1188–202.
3. Duan H, Wang T, Luo Z, et al. Neoadjuvant programmed cell death protein 1 inhibitors combined with chemotherapy in resectable non-small cell lung cancer: an open-label, multicenter, single-arm study. *Transl Lung Cancer Res.* 2021;10(2):1020.
4. Yang Y, Yang W, Zhang R, et al. Peripheral mechanism of cancer-induced bone pain. *Neurosci Bull.* 2024;40(6):815–30.

5. Wang C, Sandhu J, Ouyang C, et al. Clinical response to immunotherapy targeting programmed cell death receptor 1/programmed cell death ligand 1 in patients with treatment-resistant microsatellite stable colorectal cancer with and without liver metastases. *JAMA Netw Open*. 2021;4(8):e2118416–e2118416.
6. Tang K, Seo J, Tiu BC, et al. Association of cutaneous immune-related adverse events with increased survival in patients treated with anti-programmed cell death 1 and anti-programmed cell death ligand 1 therapy. *JAMA Dermatol*. 2022;158(2):189–93.
7. Rischin D, Khushalani NI, Schmultz CD, et al. Integrated analysis of a phase 2 study of cemiplimab in advanced cutaneous squamous cell carcinoma: extended follow-up of outcomes and quality of life analysis. *J Immunother Cancer*. 2021;9(8):e002757.
8. Cao Q, Wu X, Zhang Q, et al. Mechanisms of action of the BCL-2 inhibitor venetoclax in multiple myeloma: a literature review. *Front Pharmacol*. 2023;14:1291920.
9. Kong F, Sun K, Zhu J, et al. PD-L1 improves motor function and alleviates neuropathic pain in male mice after spinal cord injury by inhibiting MAPK pathway. *Front Immunol*. 2021;12: 670646.
10. Li C, Wang W, Xie S, et al. The programmed cell death of macrophages, endothelial cells, and tubular epithelial cells in sepsis-AKI. *Front Med*. 2021;8: 796724.
11. Chen RY, Zhu Y, Shen YY, et al. The role of PD-1 signaling in health and immune-related diseases. *Front Immunol*. 2023;14:1163633.
12. Cao Q, Zhang Q, Chen YQ, et al. Risk factors for the development of hepatocellular carcinoma in Chengdu: a prospective cohort study. *Eur Rev Med Pharmacol Sci*. 2022;26(24):9447.
13. Yu C, Yang B, Najafi M. Targeting of cancer cell death mechanisms by curcumin: implications to cancer therapy. *Basic Clin Pharmacol Toxicol*. 2021;129(6):397–415.
14. Cao Q, Wu X, Chen Y, et al. The impact of concurrent bacterial lung infection on immunotherapy in patients with non-small cell lung cancer: a retrospective cohort study. *Front Cell Infect Microbiol*. 2023;13:1257638.
15. Mettu NB, Ou FS, Zemla TJ, et al. Assessment of capecitabine and bevacizumab with or without atezolizumab for the treatment of refractory metastatic colorectal cancer: a randomized clinical trial. *JAMA Netw Open*. 2022;5(2):e2149040–e2149040.
16. Mokhnacheva YV, Tsvetkova VA. Development of bibliometrics as a scientific field. *Sci Tech Inf Process*. 2020;47:158–63.
17. Pessin VZ, Yamane LH, Siman RR. Smart bibliometrics: an integrated method of science mapping and bibliometric analysis. *Scientometrics*. 2022;127(6):3695–718.
18. Gan Y, Li D, Robinson N, et al. Practical guidance on bibliometric analysis and mapping knowledge domains methodology—a summary. *Eur J Integr Med*. 2022;56: 102203.
19. Bukar UA, Sayeed MS, Razak SFA, et al. A method for analyzing text using VOSviewer. *MethodsX*. 2023;11: 102339.
20. Abotaleb M, Samuel SM, Varghese E, et al. Flavonoids in cancer and apoptosis. *Cancers*. 2018;11(1):28.
21. Farinati F, Marino D, De Giorgio M, et al. Diagnostic and prognostic role of α -fetoprotein in hepatocellular carcinoma: both or neither? *Off J Am College Gastroenterol*. 2006;101(3):524–32.
22. Burczynski ME, McMillian M, Ciervo J, et al. Toxicogenomics-based discrimination of toxic mechanism in HepG2 human hepatoma cells. *Toxicol Sci*. 2000;58(2):399–415.
23. Kim CG, Kim C, Yoon SE, et al. Hyperprogressive disease during PD-1 blockade in patients with advanced hepatocellular carcinoma. *J Hepatol*. 2021;74(2):350–9.
24. Pan MH, Chiou YS, Chen WJ, et al. Pterostilbene inhibited tumor invasion via suppressing multiple signal transduction pathways in human hepatocellular carcinoma cells. *Carcinogenesis*. 2009;30(7):1234–42.
25. Khan Z, Khan N, Tiwari R, et al. Biology of Cox-2: an application in cancer therapeutics. *Curr Drug Targets*. 2011;12(7):1082–93.
26. Raza H, John A, Benedict S. Acetylsalicylic acid-induced oxidative stress, cell cycle arrest, apoptosis and mitochondrial dysfunction in human hepatoma HepG2 cells. *Eur J Pharmacol*. 2011;668(1–2):15–24.
27. Lin CC, Hsu C, Hsu CH, et al. Arsenic trioxide in patients with hepatocellular carcinoma: a phase II trial. *Invest New Drugs*. 2007;25:77–84.
28. Li M, Li H, Li C, et al. Alpha-fetoprotein: a new member of intracellular signal molecules in regulation of the PI3K/AKT signaling in human hepatoma cell lines. *Int J Cancer*. 2011;128(3):524–32.
29. Lin XH, Qiu BQ, Ma M, et al. Suppressing DRP1-mediated mitochondrial fission and mitophagy increases mitochondrial apoptosis of hepatocellular carcinoma cells in the setting of hypoxia. *Oncogenesis*. 2020;9(7):67.
30. Onoyama T, Takeda Y, Yamashita T, et al. Programmed cell death-1 inhibitor-related sclerosing cholangitis: a systematic review. *World J Gastroenterol*. 2020;26(3):353.
31. Ribeiro H, Sarmiento-Ribeiro AB, Andrade JP, et al. Apoptosis and (in) pain—potential clinical implications. *Biomedicines*. 2022;10(6):1255.
32. Waghela BN, Vaidya FU, Ranjan K, et al. AGE-RAGE synergy influences programmed cell death signaling to promote cancer. *Mol Cell Biochem*. 2021;476:585–98.
33. Cao Q, Wang Q, Wu X, et al. A literature review: mechanisms of antitumor pharmacological action of leonurine alkaloid. *Front Pharmacol*. 2023;14:1272546.
34. Hilliard A, Hilliard B, Zheng SJ, et al. Translational regulation of autoimmune inflammation and lymphoma genesis by programmed cell death 4. *J Immunol*. 2006;177(11):8095–102.
35. O’Kane GM, Labbé C, Doherty MK, et al. Monitoring and management of immune-related adverse events associated with programmed cell death protein-1 axis inhibitors in lung cancer. *Oncologist*. 2017;22(1):70–80.
36. Gaule P, Smithy JW, Toki M, et al. A quantitative comparison of antibodies to programmed cell death 1 ligand 1. *JAMA Oncol*. 2017;3(2):256–9.
37. Wang Z, Ying J, Xu J, et al. Safety, antitumor activity, and pharmacokinetics of toripalimab, a programmed cell death 1 inhibitor, in patients with advanced non-small cell lung cancer: a phase 1 trial. *JAMA Netw Open*. 2020;3(10):e2013770–e2013770.
38. Wang LL, Patel G, Chiesa-Fuxench ZC, et al. Timing of onset of adverse cutaneous reactions associated with programmed cell death protein 1 inhibitor therapy. *JAMA Dermatol*. 2018;154(9):1057–61.
39. Zhao J, Jiang P, Guo S, et al. Apoptosis, autophagy, NETosis, necroptosis, and pyroptosis mediated programmed cell death as targets for innovative therapy in rheumatoid arthritis. *Front Immunol*. 2021;12: 809806.

40. Scheiner B, Kirstein MM, Hücke F, et al. Programmed cell death protein-1 (PD-1)-targeted immunotherapy in advanced hepatocellular carcinoma: efficacy and safety data from an international multicentre real-world cohort. *Aliment Pharmacol Ther.* 2019;49(10):1323–33.
41. Laycock H, Ramdin C, Grayer J, et al. Causes and management of acute oncological pain: a narrative review. *Anaesthesia*, 2025.
42. Zhang X, Zhang P, Cong A, et al. Unraveling molecular networks in thymic epithelial tumors: deciphering the unique signatures. *Front Immunol.* 2023;14:1264325.
43. Chehelgerdi M, Chehelgerdi M, Khorramian-Ghahfarokhi M, et al. Comprehensive review of CRISPR-based gene editing: mechanisms, challenges, and applications in cancer therapy. *Mol Cancer.* 2024;23(1):9.
44. Wu X, Zhou Z, Cao Q, et al. Reprogramming of Treg cells in the inflammatory microenvironment during immunotherapy: a literature review. *Front Immunol.* 2023;14:1268188.
45. Khurram I, Khan MU, Ibrahim S, et al. Thapsigargin and its prodrug derivatives: exploring novel approaches for targeted cancer therapy through calcium signaling disruption. *Med Oncol.* 2025;42(1):1–21.
46. Xiang Z, Xie Q, Yu Z. Exosomal DNA: role in reflecting tumor genetic heterogeneity, diagnosis, and disease monitoring. *Cancers.* 2023;16(1):57.
47. Mishra M, Ahmed R, Das DK, et al. Recent advancements in the application of circulating tumor DNA as biomarkers for early detection of cancers. *ACS Biomater Sci Eng.* 2024;10(8):4740–56.
48. Song G, Peng G, Zhang J, et al. Uncovering the potential role of oxidative stress in the development of periodontitis and establishing a stable diagnostic model via combining single-cell and machine learning analysis. *Front Immunol.* 2023;14:1181467.
49. Souza VGP, Forder A, Brockley LJ, et al. Liquid biopsy in lung cancer: biomarkers for the management of recurrence and metastasis. *Int J Mol Sci.* 2023;24(10):8894.
50. Luo H, Zhang H, Mao J, et al. Exosome-based nanoimmunotherapy targeting TAMs, a promising strategy for glioma. *Cell Death Dis.* 2023;14(4):235.
51. Das S, Dey MK, Devireddy R, et al. Biomarkers in cancer detection, diagnosis, and prognosis. *Sensors.* 2023;24(1):37.
52. Sarhadi VK, Armengol G. Molecular biomarkers in cancer. *Biomolecules.* 2022;12(8):1021.
53. You Y, Chen Y, Wang X, et al. Accelerometer-measured physical activity patterns are associated with phenotypic age: Isotemporal substitution effects. *Heliyon.* 2023;9(9):e19158.
54. van Rensburg HJJ, Spiliopoulou P, Siu LL. Circulating biomarkers for therapeutic monitoring of anti-cancer agents. *The Oncologist.* 2022;27(5):352–62.
55. Qiang C, Qi Z, Yi Q. Mechanisms of p2x7 receptor involvement in pain regulation: a literature review. *Acta Med Mediterr.* 2022;38(2):1187–94.
56. Jiang H. Latest research progress of liquid biopsy in tumor—a narrative review. *Cancer Manag Res.* 2024;16:1031–42.
57. Dakal T C, Dhakar R, Beura A, et al. Emerging methods and techniques for cancer biomarker discovery. *Pathology-Research and Practice*, 2024: 155567.
58. Singh R, Manna PP. Reactive oxygen species in cancer progression and its role in therapeutics. *Explor Med.* 2022;3(1):43–57.
59. Cao Q, Zhang Q, Li XC, et al. Impact of sleep status on lung adenocarcinoma risk: a prospective cohort study. *Eur Rev Med Pharmacol Sci.* 2022;26(20):7641–8.
60. Cheng PF, Ge MM, Ye DW, et al. Targeting the main sources of reactive oxygen species production: possible therapeutic implications in chronic pain. *Curr Neuropharmacol.* 2024;22(12):1960–85.
61. Cao Q, Zhang Q, Zhou KX, et al. Lung cancer screening study from a smoking population in Kunming. *Eur Rev Med Pharmacol Sci.* 2022;26(19):7091–8.
62. Duitama M, Moreno Y, Santander SP, et al. TRP channels as molecular targets to relieve cancer pain. *Biomolecules.* 2021;12(1):1.
63. Lan Q, Ouyang A, Chen Y, et al. Pain, lactate, and anesthetics: intertwined regulators of tumor metabolism and immunity. *Front Oncol.* 2025;15:153.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.