DOI: 10.15825/1995-1191-2025-3-134-145

BIBLIOMETRIC ANALYSIS OF RESEARCH ON THE USE OF MESENCHYMAL STEM CELLS IN ACUTE AND CHRONIC LIVER DISEASES

M.Yu. Shagidulin[1, 2], N.A. Onishchenko[1], A.I. Kostysheva[2], I.A. Lychagin[2], A.O. Nikolskaya[1], S.V. Gautier[1, 2]

[1] Shumakov National Medical Research Center of Transplantology and Artificial Organs, Moscow, Russian Federation

[2] Sechenov University, Moscow, Russian Federation

Objective: to conduct a comprehensive bibliometric analysis of publications from 2008 to 2024 on the problem of cell therapy for liver diseases using mesenchymal stem cells (MSCs) with stem-like properties, with the goal of identifying new ways to tackle this problem. **Materials and methods.** A bibliometric analysis was carried out using the Scopus electronic database. The search included article titles, abstracts, and keywords. The dataset was exported in BibTeX and CSV formats for compatibility with VOSviewer and R software. Data were analyzed using R (version 4.4.2) and visualized through the Bibliometrix online analytical platform and VOSviewer (version 1.6.20). **Results.** The analysis identified four distinct periods of publication activity reflecting the evolution of research into the use of MSCs for liver regeneration in cases of liver injury. Period 1 (2008–2012) – This phase was marked by exploratory studies investigating the therapeutic potential of MSCs derived from various sources, including bone marrow, adipose tissue, and umbilical cord cells. Early findings highlighted the promise of MSC-based therapy and underscored the need for more rigorous and targeted research. Period 2 (2013–2016) – During this period, research focused on elucidating the mechanisms underlying the regulatory and regenerative effects of MSCs on damaged organs. Significant progress was made in the field of tissue engineering, aimed at enhancing the survival and functional integration of apoptotic MSCs post-transplantation. Period 3 (2017–2020), and more notably period 4 (2021–2024), were marked by the expansion, deepening, and intensification of research into the properties of apoptotic MSCs. Particular emphasis was placed on the regulatory functions and therapeutic potential of their secreted paracrine and trophic factors – specifically exosomes, extracellular vesicles, and apoptotic bodies. **Conclusion.** This bibliometric analysis has outlined key directions for further research in the development and application of cell technologies, particularly the use of MSCs in regenerative medicine. Future studies will likely focus on identifying the most active paracrine and trophic factors, elucidating their chemical structures and biological functions, and subsequently manufacturing chemical and pharmaceutical agents with bioactive regenerative properties. Such advancements would help standardize the production of MSC-based therapeutics and increase their availability for clinical use. Moreover, the bibliometric approach applied in this study can serve as a valuable tool for tracking and forecasting trends in related biomedical research fields.

Keywords: mesenchymal stromal cells, transplantation, stem cells, chronic liver disease, liver failure, fibrosis, cirrhosis, regenerative medicine, bibliometric analysis.

INTRODUCTION

The problem of treating chronic liver failure remains unresolved worldwide. Mortality reaches approximately 2 million people annually (about 4% of all deaths), with severe liver failure due to fibrosis or cirrhosis accounting for nearly 50% of these cases [1]. Liver cirrhosis is currently the 11th leading cause of death globally, while liver cancer ranks 16th; together, they represent 3.5% of all deaths worldwide. Cirrhosis also ranks among the top 20 causes of disability and accounts for 2.1% of disability worldwide [2].

At the current stage of medical therapeutic options, this problem can be definitively addressed only by donor liver transplantation [2–5]. Meanwhile, the persistent shortage of donor organs and the steadily increasing number of patients requiring liver transplantation severely limit access to this method. Given the limited efficacy of available medications and antifibrotic therapies, there is ongoing interest in developing more accessible, physiological, and effective approaches – particularly those that can stimulate the patient's own regenerative capacity of the liver.

Corresponding author: Murat Shagidulin. Address: 1, Shchukinskaya str., Moscow, 123182, Russian Federation. Phone: (499) 196-87-90. E-mail: dr.shagidulin@mail.ru

The use of mesenchymal stromal cells (MSCs) with stem cell properties isolated from autologous or allogeneic human tissues has become a promising new therapeutic strategy that has been developed worldwide since the last third of the 20th century.

Research into the therapeutic potential of MSCs in liver diseases is still ongoing. However, we were unable to find any studies that highlight and evaluate the trends and patterns of further development of biomedical research in this field in the 21st century, which could bring us closer to solving the problem of cell therapy and make MSCs and MSC-derived products widely available in clinical practice.

The objective of this work is to conduct an comprehensive bibliometric analysis of published studies conducted over the past 16 years (2008–2024) on the problem of cell therapy for liver diseases using MSCs in order to identify possible new ways to tackle this problem.

MATERIALS AND METHODS

In this study, a bibliometric (quantitative) analysis was performed using a comprehensive set of methods aimed at describing the current state, identifying research trends, and projecting future directions in global scientific work on the use of MSCs in the treatment of liver diseases over the past 16 years (2008–2024). The analysis was conducted using the Scopus electronic database, which offers extensive metadata (authors, keywords, countries, citations, etc.) and enables dynamic and detailed bibliometric evaluation over time (years).

The search was performed by abstract, article title, and keywords using the following query: (“hepatic*” OR “liver*”) AND (“mesenchymal stem cell*” OR “mesenchymal stromal cell*”). To assess the proportion of clinical studies within the initial dataset, an additional query was applied using the terms: treatment or case report or treat or clinical trial.

The search was carried out on December 24, 2024, and all files were downloaded on the same day to avoid discrepancies related to daily database updates. Complete publication records and cited references were exported in both BibTeX and CSV formats (the Scopus interface allows export in several formats: text, CSV, and BibTeX). The BibTeX file was imported into R software (version 4.4.2) and then into the online analytical platform Bibliometrix (https://www.bibliometrix.org), as described in [6]. To visually construct tag clouds (keywords), the CSV file was imported into VOSviewer (version 1.6.20, https://www.vosviewer.com) [7].

The dataset was filtered using the following criteria: document type (article), publication period (2008–2024), with no restrictions on language or country of publication.

While working on the Bibliometrix platform, a bibliometric analysis was carried out, beginning with general descriptive statistics. The analysis initially focused on the core bibliometric indicators reported by the original authors and then expanded to include country-specific metrics. Each of the major categories was examined in detail, including: annual scientific output; publication sources; number of articles per author; frequency distributions of scientific contributions; author keywords; thematic dendrograms; article citation metrics; national publication activity; national citation impact; and national collaboration networks.

For keyword analysis, the most frequently occurring author keywords were used. A list of synonyms was compiled and grouped under a single keyword or phrase. In each case, the first word in the list was selected as the representative keyword.

1. Mesenchymal stem cell, mesenchymal stem cells, mesenchymal stromal cell, mesenchymal stromal cells, stem cells, stem cell, mscs, mesenchymal stem cells (mscs), msc, mesenchymal stromal cell.
2. Stem cell transplantation, mesenchymal stem cell transplantation, stem cell therapy, stem cell transplantation, cell transplantation, cellular therapy.
3. Rat, rats, rats sprague-dawley.
4. Animals, animal, animal experiment, animal model, disease models.
5. Mouse, mice, mice inbred C57BL, C57BL mouse.
6. Exosome, exosomes.
7. Cell culture, cells cultured.
8. Bone marrow cell, bone marrow, bone marrow cells, bone marrow mesenchymal stem cell, bone marrow-derived mesenchymal stem cells, bone marrow mesenchymal stem cells, bmscs.
9. Human, humans.
10. Umbilical cord, human umbilical.
11. Liver fibrosis, fibrosis, hepatic fibrosis.
12. Regenerative medicine, regeneration.
13. Liver cirrhosis, cirrhosis.
14. Differentiation, cell differentiation.
15. Hepatocyte, hepatocytes.
16. Acute liver failure, acute liver injury.
17. Chronic liver failure, Chronic liver injury.
18. Immunotherapy, immunomodulation, immunosuppression.

A number of stop words were identified and excluded from the analysis:

1. Article.
2. Priority Journal.
3. Review.

Excel (version 2411) was used to create tables and graphs.

RESULTS

A total of 6,527 articles were initially identified, after which a selection algorithm was applied to isolate topic-relevant publications. The overall dataset consisted of: original articles (4,181), reviews (1,844), editorials

(123), book chapters (113), conference papers (75), notes (57), short surveys (47), letters (41), errata (33), retracted publications (8), conference reviews (2), books (2), and data papers (1). Only original articles (4,181) were retained for further analysis; therefore, 2,346 publications were excluded.

Next, filtering based on the publication timeframe (2008–2024) was applied without restrictions on language or country of origin. This resulted in 244 additional exclusions, and a refined total of 3,937 articles. However, only 3,892 articles were successfully imported and analyzed using the Bibliometrix platform (https://bibliometric.com/), as 45 articles were unavailable or incompatible with the analytics software.

The initial set of 6,527 publications was composed of articles written in multiple languages, including English (5,925), Chinese (486), Russian (63), Japanese (9), French (9), German (7), Ukrainian (5), Polish (4), Persian (4), Korean (4), Hungarian (4), Portuguese (3), Spanish (2), Czech (1), and Arabic (1).

An additional search query targeting clinical research terms revealed that a big chunk of the analyzed publications were clinical studies – 2,304 articles, representing 58.6% of the 3,892 publications analyzed during the study period.

We analyzed the dynamics of publication activity over the entire study period (2008–2024) using the previously defined search query (by abstract, title, and keywords). The results showed that 655 articles were published during 2008–2012, 914 articles during 2013–2016, 1,027 articles during 2017–2020, and 1,296 articles during 2021–2024. Thus, a consistent and steady increase in thematic publications was observed across the four time intervals.

Similarly, year-by-year analysis indicated an increase from 89 publications in 2008 to 353 publications in 2021. In particular, two notable peaks of heightened publication activity were observed in 2015 and 2021 (Fig. 1).

The number of articles reporting the results of clinical studies has also shown a steady upward trend. In 2008, clinical studies accounted for 33.7% of total publications (30 out of 89 articles); in 2016, this figure rose to 54.9% (134 out of 244); and by 2024, it had reached 71.25% (228 out of 320 articles). These data indicate growing interest among clinicians in the potential of cell therapy, with most publications representing pilot studies or early-phase clinical trials.

In the next phase of our study, we proceeded to consolidate and summarize the bibliometric data for the selected articles based on key parameters for the period 2008–2024.

The analysis revealed that the total number of sources (journals and books) amounted to 1,148, and the total number of articles analyzed was 3,892. The annual growth rate in publications was calculated at 8.33%. The average age of the documents reviewed was 6.46 years, and the average number of citations per article was 29.65. A total of 6,481 author keywords (DE) were identified across the dataset. The articles were authored by 16,245 persons, with an average of 7.9 co-authors per publication, and the proportion of international co-authorship was 17.78%.

Thus, bibliometric evaluation according to our selected parameters confirmed a steady annual increase in publication output (8.33%) and demonstrated that the published work in this field is characterized by extensive multi-authorship and a relatively high level of international collaboration (17.78%).

Fig. 2 presents the dynamics of publication activity in the 10 most prolific journals on this topic and lists the titles of the journals that most frequently published relevant articles during the study period (2008–2024).

Analysis of the data shown in Fig. 2 confirms that the number of publications appearing in the leading thematic journals on this topic has been steadily increasing from year to year.

Next, our study focused on identifying the most influential and highly cited articles in the field, as well as the most active authors contributing to the subject area. Table 1 provides a list of the 25 most cited publications,

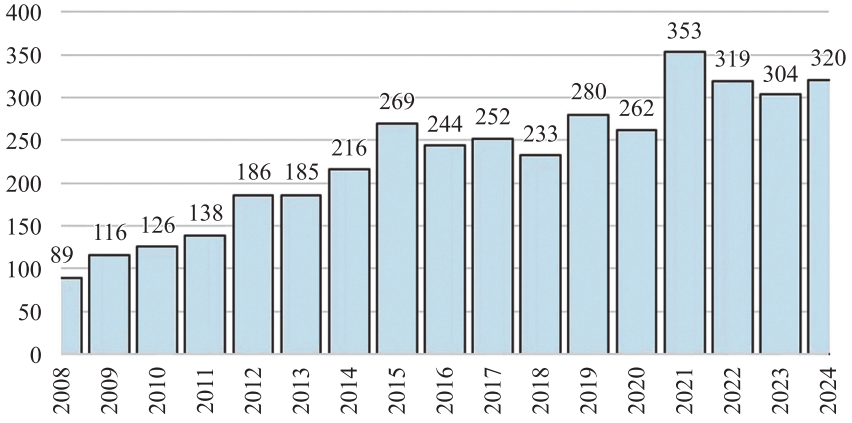

Fig. 1. Trends in the annual number of global publications on the use of mesenchymal stem cells in liver diseases, 2008–2024

including their title, first author, journal, year of publication, and DOI.

A comparative analysis of the publication activity of the 25 most productive authors showed that they maintained a consistently high publication output across all periods beginning in 2008. However, these highly active authors rarely appeared among the first authors of the 25 most cited articles (Table 1). This finding suggests that the most frequently publishing authors likely lead large research teams, and the most highly cited works may reflect the collective output of these groups.

The next stage of our study involved analysis of overall scientific activity across different countries with respect to the topic under investigation. The evaluation was conducted according to five key criteria: Articles (total number of theme-specific publications from a country), Articles % (percentage of thematic articles relative to the country's total scientific output), SCP (single country publications, number of articles authored solely by researchers from one country), MCP (multiple country publications, number of articles co-authored by researchers from different countries), MCP % (proportion of internationally co-authored articles relative to the country's total thematic publications). The results of this country-level analysis are presented in Fig. 3.

Analysis of the results presented in Fig. 3 shows that the most active countries in this field are China, the United States, South Korea, Japan, Iran, Egypt, and Germany. Among them, China exhibits the highest absolute number of publications on this topic, with most of its articles authored exclusively by Chinese researchers. By contrast, countries with lower absolute publication output demonstrate a markedly higher proportion of international collaboration.

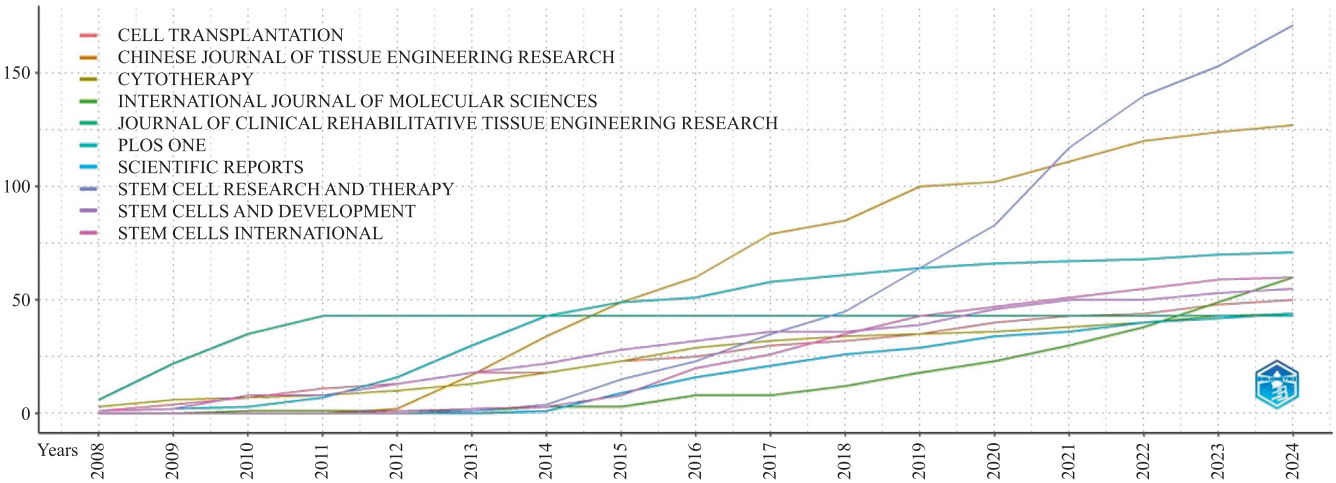

Fig. 2. Trends in the number of publications from 2008 to 2024 in the 10 most prominent thematic journals in the world (journal names indicated in the figure)

Table 1

Most cited articles on the use of MSCs in liver disease: a bibliometric overview

Article	DOI	Citation count
A randomized, double-blind, placebo-controlled, dose-escalation study of intravenous adult human mesenchymal stem cells (prochymal) after acute myocardial infarction. HARE JM, 2009, J AM COLL CARDIOL	10.1016/j.jacc.2009.06.055	1161
Extracellular vesicle *in vivo* biodistribution is determined by cell source, route of administration and targeting. WIKLANDER OPB, 2015, J EXTRACELL VESICLES	10.3402/jev.v4.26316	1103
Multivascular networks and functional intravascular topologies within biocompatible hydrogels. GRIGORYAN B, 2019, SCI	10.1126/science.aav9750	1007
Pulmonary passage is a major obstacle for intravenous stem cell delivery: the pulmonary first-pass effect. FISCHER UM, 2009, STEM CELLS DEV	10.1089/scd.2008.0253	993
Adipose tissue dysfunction as determinant of obesity-associated metabolic complications. LONGO M, 2019, INT J MOL SCI	10.3390/ijms20092358	975
Coronavirus disease 2019 (COVID-19): current status and future perspectives. LI H, 2020, INT J ANTIMICROB AGENTS	10.1016/j.ijantimicag.2020.105951	822

End of Table 1

Article	DOI	Citation count
Aggregation of human mesenchymal stromal cells (MSCs) into 3D spheroids enhances their antiinflammatory properties. BARTOSH TJ, 2010, PROC NATL ACAD SCI USA	10.1073/pnas.1008117107	783
Exosomes derived from human umbilical cord mesenchymal stem cells alleviate liver fibrosis. LI T, 2013, STEM CELLS DEV	10.1089/scd.2012.0395	733
Perivascular Gli1+ progenitors are key contributors to injury-induced organ fibrosis. KRAMANN R, 2015, CELL STEM CELL	10.1016/j.stem.2014.11.004	725
Mesenchymal stem cells: mechanisms of inflammation. SINGER NG, 2011, ANNU REV PATHOL MECH DIS	10.1146/annurev-pathol-011110-130230	713
Allogeneic human mesenchymal stem cells for treatment of *E. coli* endotoxin-induced acute lung injury in the *ex vivo* perfused human lung. LEE JW, 2009, PROC NATL ACAD SCI USA	10.1073/pnas.0907996106	621
Mesenchymal stem cells are short-lived and do not migrate beyond the lungs after intravenous infusion. EGGENHOFER E, 2012, FRONT IMMUNOL	10.3389/fimmu.2012.00297	614
Direct evidence of mesenchymal stem cell tropism for tumor and wounding microenvironments using *in vivo* bioluminescent imaging. KIDD S, 2009, STEM CELLS	10.1002/stem.187	594
Exosomes derived from miR-122-modified adipose tissue-derived MSCs increase chemosensitivity of hepatocellular carcinoma. LOU G, 2015, J HEMATOL ONCOL	10.1186/s13045-015-0220-7	587
Immunosuppressive properties of mesenchymal stem cells: advances and applications. DE MIGUEL MP, 2012, CURR MOL MED	10.2174/156652412800619950	568
Multipotent mesenchymal stromal cells obtained from diverse human tissues share functional properties and gene-expression profile with CD146+ perivascular cells and fibroblasts. COVAS DT, 2008, EXP HEMATOL	10.1016/j.exphem.2007.12.015	523
Microvesicles derived from adult human bone marrow and tissue specific mesenchymal stem cells shuttle selected pattern of miRNAs. COLLINO F, 2010, PLOS ONE	10.1371/journal.pone.0011803	521
Mesenchymal stem cell–derived molecules directly modulate hepatocellular death and regeneration *in vitro* and *in vivo*. VAN POLL D, 2008, HEPATOLOGY	10.1002/hep.22236	473
Mesenchymal stem cell-derived exosomes promote hepatic regeneration in drug-induced liver injury models. TAN CY, 2014, STEM CELL RES THER	10.1186/scrt465	459
Stem cell therapy for liver disease: parameters governing the success of using bone marrow mesenchymal stem cells. KUO TK, 2008, GASTROENTEROLOGY	10.1053/j.gastro.2008.03.015	428
Unique multipotent cells in adult human mesenchymal cell populations. KURODA Y, 2010, PROC NATL ACAD SCI USA	10.1073/pnas.0911647107	416
Airway delivery of mesenchymal stem cells prevents arrested alveolar growth in neonatal lung injury in rats. VAN HAAFTEN T, 2009, AM J RESPIR CRIT CARE MED	10.1164/rccm.200902-0179OC	395
Improvement of liver function in liver cirrhosis patients after autologous mesenchymal stem cell injection: a phase I–II clinical trial. KHARAZIHA P, 2009, EUR J GASTROENTEROL HEPATOL	10.1097/MEG.0b013e32832a1f6c	395
Immunomodulation by therapeutic mesenchymal stromal cells (MSC) is triggered through phagocytosis of MSC by monocytic cells. DE WITTE SFH, 2018, STEM CELLS	10.1002/stem.2779	391
Bone marrow stromal/stem cell-derived extracellular vesicles regulate osteoblast activity and differentiation *in vitro* and promote bone regeneration *in vivo*. QIN Y, 2016, SCI REP	10.1038/srep21961	380

For example, Switzerland shows 71.4% of its publications as collaborative (MCP), while Saudi Arabia and Sweden show 61.5% and 58.5%, respectively.

To identify further trends in the development of MSC-based therapies for acute and chronic liver diseases, and to reveal potential new research directions, we next analyzed the changing frequency of major author keywords across different time intervals.

After reviewing 3,892 articles published between 2008 and 2024 (655 articles in 2008–2012; 914 in 2013–2016; 1,027 in 2017–2020; and 1,296 in 2021–2024), we identified a total of 52 recurring author keywords, from which we selected what we consider to be the 32 most thematically significant keywords used in articles related to MSC-based treatment of liver diseases.

Based on the annual frequency of use of these keywords within each time period, trend trajectories were constructed for each of the selected keywords. The results are summarized in Table 2, where each keyword appears with the identifier assigned to it by the analytical software used in the study.

To obtain the absolute number of keyword occurrences across the study periods, the frequency indicated for the period 2008–2012 should be multiplied by 5 (representing 5 years), and those for subsequent periods (2013–2016, 2017–2020, 2021–2024) should each be multiplied by 4 years. The combined total across all periods gives the absolute frequency of a given keyword. For example, for the term mesenchymal stem cell: $50.2 \times 5 + 88 \times 4 + 93.75 \times 4 + 116.75 \times 4 = 1445$ total occurrences.

Analysis of the keyword usage trends presented in Table 2 shows that the problem of treating acute and chronic liver failure using cellular technologies remains highly relevant and unresolved. This is evidenced by the steadily increasing total number of publications and the rising proportion of clinical studies – most of which are still pilot trials.

A growing number of studies now focus on the effects of MSCs in promoting regeneration of hepatocytes and hepatic stellate cells, as well as their role in modulating immune-mediated inflammation in the liver and restoring systemic immune homeostasis – conditions necessary for effective regenerative repair. While bone marrow-derived MSCs remain a major source, interest in adipose-derived MSCs is increasing, likely due to their easier accessibility.

There is also a notable rise in studies exploring the involvement of apoptosis and oxidative stress mechanisms in MSC activity. Importantly, a surge of new keywords appeared in Period 3 (2017–2020) and especially in Period 4 (2021–2024), such as exosomes and extracellular

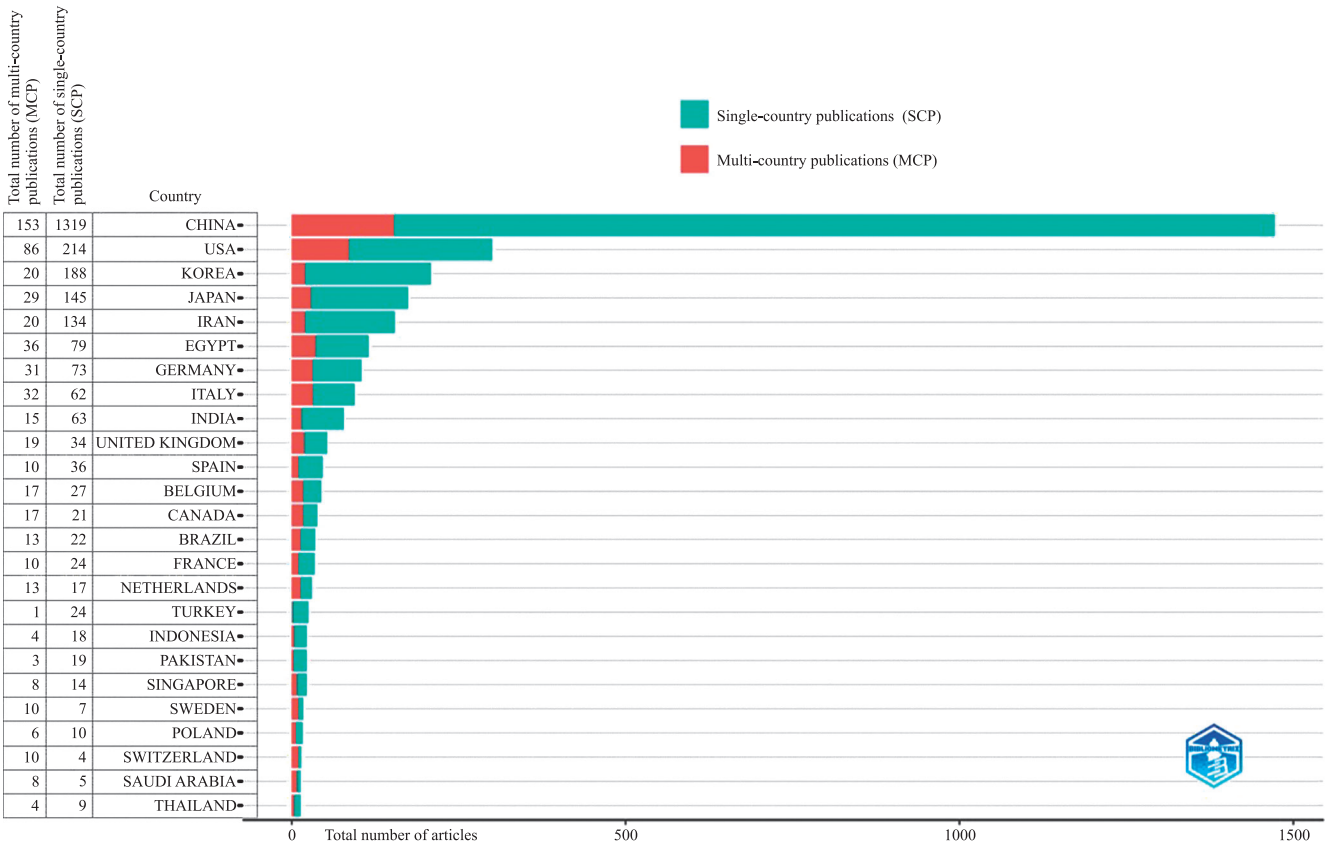

Fig. 3. Total number of thematic publications on MSCs in liver disease, categorized by country. The bars represent the number of publications produced solely by authors from the same country (SCP, single-country publications) and those resulting from international collaborations (MCP, multiple country publications)

vesicles, indicating a shift toward cell-free MSC-based therapies, focusing on paracrine and trophic mechanisms.

To visualize the dynamics of research focus across the observation periods, we constructed a Sankey diagram presented in Fig. 4. This diagram illustrates the evolving interaction between the most prominent keywords in different periods.

In the first stage (2008–2012), several keywords were only loosely connected to the topic of MSCs; however, many of these terms later converged into a clearly defined mesenchymal cell cluster in the second stage. During the second period (2013–2016), a separate set of keywords emerged that had not appeared in the earlier stage. In the third stage (2017–2020) these terms merged into thematic clusters such as liver regeneration and hepatocyte, reflecting a growing focus on the cellular sources and specific liver pathologies being addressed.

In the third stage, new branches also appeared from the earlier mesenchymal cell cluster of the second stage and are involved in the implementation of the mechanisms of their therapeutic potential in the models used. The fourth stage (2021–2024) is characterized by a more detailed exploration of the role of MSCs in associated conditions and complications of liver disease, as well as their influence on specific mechanisms that determine therapeutic efficacy.

Thus, Fig. 4 clearly visualizes both the direction and intensity of evolution in research priorities across different time intervals, based on the dynamics and clustering of the most commonly used keywords.

Table 2

Trends in keyword usage over time: annual frequency of key terms in publications across distinct time periods

S/N	Keywords	Research periods					
		2008–2024	2008–2012	2013–2016	2017–2020	2021–2024	2008–2024 trend
		Total	Per year	Per year	Per year	Per year	
1	Mesenchymal stem cell	1445	50,2	88	93,75	116,75	
2	Bone marrow cell	275	10,6	21	17,25	17,25	
3	Liver fibrosis	254	3,8	8,75	17	47	
4	Stem cell transplantation	172	5,6	14	14	8	
5	Cell therapy	164	4,4	5	15,5	15	
6	Hepatocyte	155	8	12,25	9	7,5	
7	Liver cirrhosis	149	3	11,25	10,75	11,5	
8	Liver	139	5,4	5	10,75	12,25	
9	Differentiation	132	10	9,75	5	5,75	
10	Exosomes	110	0,2	2	12,25	28,75	
12	Acute liver failure	97	2	8,25	6	7,5	
13	Transplantation	96	4,8	10	5	3	
14	Extracellular vesicles	95	0	1	6,25	16,5	
15	Tissue engineering	91	0,8	6,75	11,25	3,75	
16	Inflammation	90	1	2,5	6,75	12	
18	Liver regeneration	86	2	6,5	5,5	7	
19	Apoptosis	84	2,2	6,75	5,25	6,25	
20	Hepatic differentiation	65	3,6	4	5,5	2,25	
21	Immunotherapy	58	1,4	1	5,5	6,25	
22	Liver injury	58	1,4	2,25	5	5,5	
23	Adipose tissue	54	2,4	2,75	3,25	4,5	
24	Oxidative stress	54	0,2	1,25	3,5	8,5	
25	Liver transplantation	53	1,2	3	3,5	5,25	
26	Hepatic stellate cells	51	1,4	2,75	3	5,25	
27	Hepatocyte-like cells	47	2,2	4,25	4	0,75	
28	Cirrhosis	44	1	3,5	3	3,25	
30	Liver failure	43	0,8	2,25	4,5	3	
31	Hepatocyte growth factor	41	2	3	2,5	2,25	
32	Regeneration	40	0,4	2	3,75	3,75	
36	Autophagy	33	0	0,75	3	4,5	
44	Acute liver injury	26	0,6	1,5	2,25	2	
50	Liver disease	24	1	1,5	1,5	1,75	

Fig. 4 demonstrates that the evolution of priority research areas follows a wave-like dynamic, with scientific interests converging, diverging, and influencing one another across time, ultimately shaping both current and future investigative directions.

DISCUSSION

Analysis of the results shows that during the first (early) period, 2008–2012, research worldwide was predominantly exploratory, focusing on the therapeutic potential of MSCs. MSCs from various sources, mainly bone marrow (BM), adipose tissue, and umbilical cord, were applied in models of liver injury (acute and chronic liver failure, fibrosis, cirrhosis, hepatocellular carcinoma) in an effort to restore regenerative processes in hepatocytes and hepatic stellate cells.

During this period, research began to investigate proposed mechanisms of MSC action, such as their ability to differentiate into hepatocyte-like cells or to exert effects via homing and secretion of hepatocyte growth factor. However, in subsequent years, the importance of these mechanisms was disputed or not fully confirmed, and publication activity in these specific mechanistic directions gradually declined [8–13].

Notably, in this first period, there was almost a complete absence of keywords such as exosomes, extracellular vesicles, tissue engineering, oxidative stress, immunomodulation, and immunosuppression – terms whose usage increased beginning in the second period, and especially in the third and fourth periods of analysis.

These findings suggest that as early as the second period, a new conceptual framework was emerging regarding the regulatory and regenerative mechanisms of MSCs in damaged organs. The pivotal shift occurred with the landmark hypothesis proposed by Thum et al. in 2005 [12], later confirmed scientifically, which suggested that the therapeutic effect of MSCs and other stem cells is largely mediated through apoptosis of the transplanted cells, developing after isolation, followed by release of paracrine and trophic factors (including exosomes, extracellular vesicles, apoptotic bodies, growth factors, various RNAs, lipids, amino acids, cytokines, chemokines, etc.). These released components act as biologically adequate adaptogenic regulators on cells in the damaged tissue [14, 15].

In the second period, research on tissue engineering intensified, with a focus on developing strategies to maintain MSC viability after transplantation and to prolong their functional presence in the body [16–19]. The positive and encouraging results obtained during the third and fourth periods contributed substantially to the expansion and consolidation of a new research direction centered not only on MSCs themselves, but increasingly on the paracrine factors they secrete.

It became evident that paracrine factors, such as exosomes, extracellular vesicles, and apoptotic bodies, along with trophic factors like hepatocyte growth factor, have a powerful ability to restore structural and functional integrity in the liver and other organs, as well as to modulate systemic immune homeostasis. These factors create a favorable microenvironment for regenerative recovery of damaged tissues [20–26]. This shift is reflected in the sharp rise in the frequency of keywords such as exosomes, extracellular vesicles, conditioned medium, inflammation, immunomodulation, and immunosuppression during the third and especially the fourth periods.

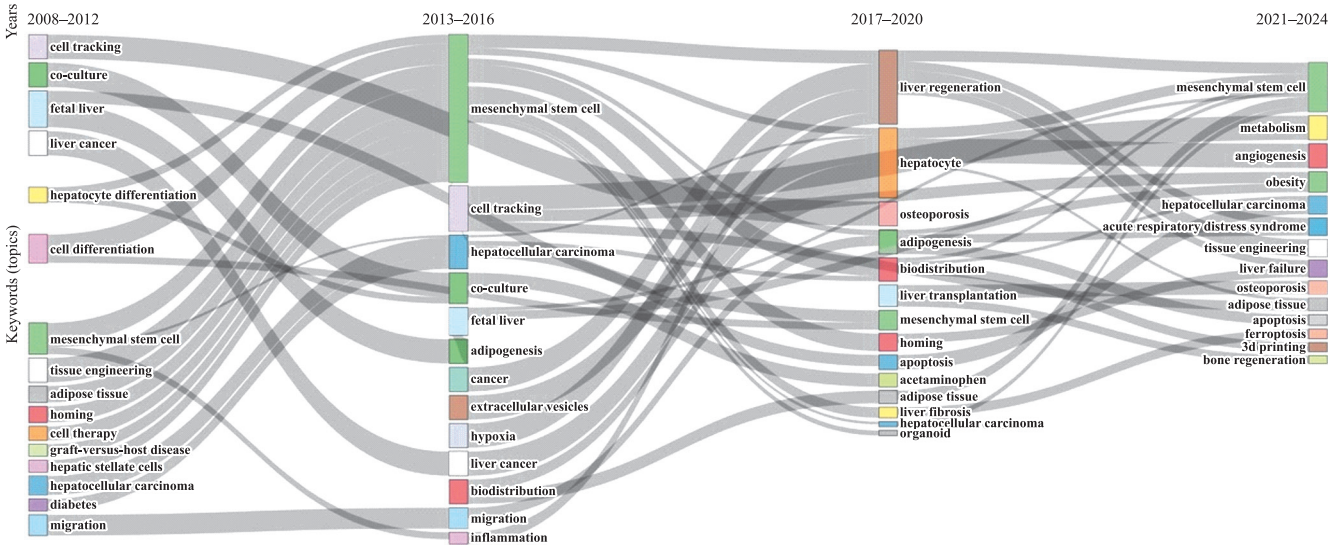

Fig. 4. Wave dynamics illustrating the evolution of keyword frequency and thematic interrelationships in publications from 2008 to 2024 (Sankey diagram). Nodes represent key thematic terms – points where flows begin, end, or intersect. The size of each node reflects the relative frequency and prominence of the keyword in a given period. Flows (connecting lines) indicate the continuity and transition of research themes across time. The width of each flow is proportional to the number of articles in which the linked terms co-occurred, demonstrating how research focus has shifted or evolved over the years

The advantage of using paracrine factors over MSCs is that they have immunosuppressive properties without posing the same oncogenic risk.

Based on the results of the bibliometric analysis, it can be assumed that future research in the field of cell technologies, particularly MSCs for regenerative medicine, will focus on identifying the most bioactive paracrine and trophic factors, determining their chemical structure and functional properties, and subsequently developing pharmaceutical preparations with regenerative bioactivity.

CONCLUSION

For the first time in Russian scientific literature, a bibliometric approach has been applied to quantitatively analyze global patterns and trends in MSC-based research for the treatment of liver diseases.

The findings show that during the period from 2008 to 2024, there was a consistent annual increase in research activity (including clinical studies), with two peaks in publication output observed in 2015 and 2021.

It was also established that research articles on MSCs in the context of liver disease treatment are primarily published in highly rated, specialized journals, and authored by researchers working in countries with strong scientific capacity, mainly China, the United States, South Korea, Japan, Iran, Germany, and others, where a high level of international collaboration is consistently observed.

The analysis of keyword frequency across different time intervals made it possible to identify both scientific patterns and emerging practical trends in the development of MSC isolation and application technologies.

During the early period (2008–2012), studies were largely exploratory and focused on the biological potential and therapeutic benefits of MSCs in treating liver fibrosis and cirrhosis as a form of cell therapy. The rare use of terms such as apoptosis, regenerative medicine, inflammation, and gene therapy – as well as the complete absence of keywords like exosomes, extracellular vesicles, oxidative stress, conditioned medium, immunomodulation, and tissue engineering – reflect a lack of understanding at that time regarding both the paracrine mechanisms of MSC action and the methods required to prolong their viability *in vivo* through tissue engineering strategies.

The 2013–2016 period (second period) is characterized by the rapid development of tissue engineering methods and active research into the mechanisms of MSC therapeutic action. During this time, attention shifted toward MSCs from different sources (bone marrow, adipose tissue, umbilical cord blood, etc.) and their role in apoptosis, with the release of paracrine and trophic factors that exert therapeutic effects.

The 2017–2020 (third period) and 2021–2024 (fourth period) periods are marked by further intensification in the study of MSC mechanisms, particularly the influence of their paracrine and trophic factors – exosomes, extracellular vesicles, growth factors, various RNAs, etc. – on restoring immune homeostasis (inflammation control, immunomodulation, immunosuppression) and structural-functional homeostasis in the liver (regeneration of hepatocytes and hepatic stellate cells, and activation of antifibrotic processes).

The next phase of research will apparently be directed at identifying the most bioactive paracrine and trophic factors, determining their chemical structure and biological properties, and manufacturing chemotherapeutic drugs with bioactive properties.

The bibliometric approach presented in this study can serve as a universal analytical tool for identifying developmental trends in emerging areas of biomedical research and may be effectively used in writing dissertation research.

The authors declare no conflict of interest.

REFERENCES

1. *Yang X, Li Q, Liu W, Zong C, Wei L, Shi Y, Han Z*. Mesenchymal stromal cells in hepatic fibrosis/cirrhosis: from pathogenesis to treatment. *Cell Mol Immunol*. 2023; 20 (6): 583–599. doi: 10.1038/s41423-023-00983-5. Epub 2023 Feb 24.
2. *Halliday N, Wesrtbrook RH*. Liver transplantation: need, indications, patient selection and pre-transplant care. *Br J Hosp Med (Lond)*. 2017; 78 (5): 252–259. doi: 10.12968/hmed.2017.78.5.252.
3. *Olivo R, Guarrera JV, Pyrsopoulos NT*. Liver Transplantation for Acute Liver Failure. *Clin Liver Dis*. 2018; 22 (2): 409–417. doi: 10.1016/j.cld.2018.01.014.
4. Transplantologija i iskusstvennye organy: uchebnik / Pod red. akad. RAN S.V. Gautier. M.: Laboratorija znanij, 2018; 319.
5. *Gautier SV, Konstantinov BA, Cirul'nikova OM*. Transplantacija pecheni. M.: MIA, 2008; 246.
6. https://bibliometric.com/.
7. https://www.vosviewer.com/.
8. *Schwartz RE, Reyes M, Koodie L, Jiang Y, Blackstad M, Lund T et al.* Multipotent adult progenitor cells from bone marrow differentiate into functional hepatocyte-like cells. *J Clin Invest*. 2002; 109 (10): 1291–1302. doi: 10.1172/JCI15182.
9. *Chivu M, Dima SO, Stancu CI, Dobrea C, Uscatescu V, Necula LG et al*. *In vitro* hepatic differentiation of human bone marrow mesenchymal stem cells under differential exposure to liver-specific factors. *Transl Res*. 2009; 154 (3): 122–132. doi: 10.1016/j.trsl.2009.05.007. Epub 2009 Jun 24.
10. *Lange C, Bassler P, Lioznov MV, Bruns H, Kluth D, Zander AR, Fiegel HC*. Liver-specific gene expression in mesenchymal stem cells is induced by liver cells. *World J Gastroenterol*. 2005; 11 (29): 4497–4504. doi: 10.3748/wjg.v11.i29.4497.Chivu.

11. *Ullah M, Liu DD, Thakor AS*. Mesenchymal Stromal Cell Homing: Mechanisms and Strategies for Improvement. *iScience*. 2019; 15: 421–438. doi: 10.1016/j.isci.2019.05.004. Epub 2019 May 9.Liesveld.
12. *Thum T, Bauersachs J, Poole-Wilson PA, Volk HD, Anker SD*. The dying stem cell hypothesis: immune modulation as a novel mechanism for progenitor cell therapy in cardiac muscle. *J Am Coll Cardiol*. 2005; 46 (10): 1799–1802. doi: 10.1016/j.jacc.2005.07.053. Epub 2005 Oct 17.
13. *Liesveld JL, Sharma N, Aljitawi OS*. Stem cell homing: From physiology to therapeutics. *Stem Cells*. 2020; 38 (10): 1241–1253. doi: 10.1002/stem.3242. Epub 2020 Jul 21.
14. *Onishchenko NA, Nikolskaya AO, Gonikova ZZ, Kirsanova LA, Shagidulin MYu, Sevastianov VI*. Apoptotic bone marrow-derived mononuclear cells Accelerate liver regeneration after extended resection. *Russian Journal Of Transplantology And Artificial Organs*. 2022; 24 (4): 85–93. https://doi.org/10.15825/1995-1191-2022-4-85-93.
15. *Kholodenko IV, Kholodenko RV, Majouga AG, Yarygin KN*. Apoptotic MSCs and MSC-Derived Apoptotic Bodies as New Therapeutic Tools. *Curr Issues Mol Biol*. 2022; 44 (11): 5153–5172. doi: 10.3390/cimb44110351.
16. *Gautier SV, Shagidulin MY, Onishchenko NA, Krasheninnikov ME, Il'inskii IM, Mozheiko NP et al*. Correction of cronic liver failure by transplantation of liver cells suspension and cell-engineering designs (experimental investigation). *Annals of the Russian academy of medical sciences*. 2013; 4: 44–51.
17. *Shagidulin MJu, Onishhenko NA, Krasheninnikov ME, Il'inskij IM, Ljundup AV, Mozhejko NP et al*. Transplantacija kletochno-inzhenernyh konstrukcij v pechen' obespechivaet dlitel'nuju podderzhku processov vosstanovitel'noj regeneracii v povrezhdennoj pecheni. *Russian Journal Of Transplantology And Artificial Organs*. 2013; 15 (2): 64–74.
18. *Franquesa M, Hoogduijn MJ, Eggenhofer E, Pinxteren J, Christ B, Shagidulin M et al*. The MiSOT Study Group. Mesenchymal Stem Cells in Solid Organ Transplantation (MiSOT) Fourth Meeting: Lessons Learned from First Clinical Trials. *Transplantation*. 2013; 96 (3): 234–238.
19. *Shagidulin MJu, Onishhenko NA*. Bone marrow stem cells transplantation as a new method of treatment of hepatic failure. The current state of the problem. *Farmateka*. 2013; 18: 130–135.
20. *Zhao T, Sun F, Liu J, Ding T, She J, Mao F et al*. Emerging Role of Mesenchymal Stem Cell-derived Exosomes in Regenerative Medicine. *Curr Stem Cell Res Ther*. 2019; 14 (6): 482–494. doi: 10.2174/1574888X14666190228103230.
21. *Fu Q, Ohnishi S, Sakamoto N*. Conditioned Medium from Human Amnion-Derived Mesenchymal Stem Cells Regulates Activation of Primary Hepatic Stellate Cells. *Stem Cells Int*. 2018; 8: 4898152. doi: 10.1155/2018/4898152. eCollection 2018.
22. *Parekkadan B, van Poll D, Suganuma K, Carter EA, Berthiaume F, Tilles AW, Yarmush ML*. Mesenchymal stem cell-derived molecules reverse fulminant hepatic failure. *PLoS One*. 2007; 2 (9): e941. doi: 10.1371/journal.pone.0000941.
23. *Ohara M, Ohnishi S, Hosono H, Yamamoto K, Yuyama K, Nakamura H et al*. Extracellular Vesicles from Amnion-Derived Mesenchymal Stem Cells Ameliorate Hepatic Inflammation and Fibrosis in Rats. *Stem Cells Int*. 2018; 2018: 3212643. doi: 10.1155/2018/3212643. eCollection 2018.
24. *Nooshabadi VT, Mardpour S, Yousefi-Ahmadipour A, Allahverdi A, Izadpanah M, Daneshimehr F et al*. The extracellular vesicles-derived from mesenchymal stromal cells: A new therapeutic option in regenerative medicine. *J Cell Biochem*. 2018; 119 (10): 8048–8073. doi: 10.1002/jcb.26726. Epub 2018 Jun 22.
25. *Mardpour S, Hassani SN, Mardpour S, Sayahpour F, Vosough M, Ai J et al*. Extracellular vesicles derived from human embryonic stem cell-MSCs ameliorate cirrhosis in thioacetamide-induced chronic liver injury. *J Cell Physiol*. 2018; 233 (12): 9330–9344. doi: 10.1002/jcp.26413. Epub 2018 Jun 19.
26. *Lei Qin, Nian Liu, Chao-le-Meng Bao, Da-Zhi Yang, Gui-Xing Ma, Wei-Hong Yi et al*. Mesenchymal stem cells in fibrotic diseases – the two sides of the same coin. *Acta Pharmacol Sinica*. 2023; 44 (2): 268–287. doi: 10.1038/s41401-022-00952-0.

The article was submitted to the journal on 9.02.2025