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ORIGINAL ARTICLE

Stem cells and secretome in aplastic anaemia: a bibliometric analysis of global research trends (2018–2023) and future directions for regenerative therapies

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ABSTRACT

Aim This study analysed research trends related to stem cells and secretome in aplastic anemia between 2018 and 2023 using a bibliometric approach to understand developments and research distribution in this field.

Methods The Scopus database was used to search for relevant articles on aplastic anaemia and its relationship to stem cells or secretome, collecting publication and citation data found in article titles, abstracts, and keywords. VOSviewer and Biblioshiny bibliometric software were used to visualize author, country, journal, and keyword networks. Visualization maps aimed to highlight the emergence of words and phrases in titles and abstracts.

Results Based on information from 1,405 articles identified from 2018 to 2023, publication numbers experienced significant fluctuations. Research showed that publications on aplastic anaemia, stem cells, or secretome increased by an average of 2.52% annually over the past five years. The most productive country was China with 321 documents, while the most productive institution was the Chinese Academy of Medical Sciences & Peking Union Medical College with 53 documents. We identified four cluster groups: "severe aplastic anaemia", "allogeneic stem cell transplantation", "bone marrow failure", and "hematopoietic stem cell transplantation".

Conclusion This study provides a comprehensive overview of research trends in aplastic anaemia related to stem cells and secretome from 2018 to 2023, highlighting steady growth and key contributors like China. Future research will likely focus on secretome applications and international collaborations to advance regenerative therapies for aplastic anaemia.

Keywords: aplastic anaemia, bibliometrics, secretome, stem cells, mesenchymal stem cells

INTRODUCTION

Aplastic anaemia is a medical condition characterized by chronic primary hematopoietic failure caused by injury, resulting in reduced or absent hematopoietic precursors in the bone marrow, accompanied by pancytopenia (1). Multiple factors can influence this condition, including genetic predisposition, environmental exposures, infections, autoimmune mechanisms, and idiopathic causes. Understanding these factors affecting aplastic anaemia is crucial for developing more effective treatment strategies (2). Over the past several decades, using stem cells and secretome as regenerative therapeutic approaches has garnered significant attention in medicine. Hematopoietic stem cell transplantation represents one of the primary therapeutic options for patients with severe aplastic anaemia, especially for those without matched donors (2). Mesenchymal stem cells (MSCs) and their secretome are potential therapies for aplastic anaemia, where the bone marrow fails to produce sufficient blood cells. The secretome from MSCs contains various growth factors and cytokines that can support blood cell regeneration and repair the bone marrow microenvironment (3). Bioinformatic analyses have revealed several key molecular pathways through which the MSC secretome influences haematopoiesis in aplastic anaemia (4). Transcriptomic profiling has identified differential expression of genes involved in cell cycle regulation, apoptosis, and immune modulation in CD34+

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progenitor cells exposed to MSC-derived extracellular vesicles (EVs) (5). Specifically, MSC secretome upregulates C-X-C motif chemokine ligand 12 (CXCL12), stem cell factor (SCF), thrombopoietin (TPO), and FMS-like tyrosine kinase 3 ligand (FLT3L) expression in bone marrow stromal cells, which are crucial for hematopoietic stem cell (HSC) maintenance and proliferation (6,7). Proteomic analyses of MSC-derived EVs have identified over 200 proteins involved in cell adhesion, migration, proliferation, and immune regulation, with particular enrichment in factors like interleukin-6 (IL-6), leukaemia inhibitory factor (LIF), stromal cell-derived factor 1 (SDF-1), and hepatocyte growth factor (HGF) that directly support haematopoiesis (8,9). Single-cell RNA sequencing studies have demonstrated that MSC secretome modulates the expression of key transcription factors like GATA binding protein 1 (GATA1), GATA binding protein 2 (GATA2), and purine-rich box-1 (SPI1) in HSCs, redirecting differentiation toward erythroid and myeloid lineages (10, 11). Furthermore, pathway analysis through gene ontology and KEGG has revealed significant enrichment of phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), janus kinase/signal transducer and activator of transcription (JAK/STAT), and mitogen-activated protein kinase (MAPK) signalling pathways in HSCs treated with MSC secretome, all of which are critical for hematopoietic cell survival and proliferation (12–14).

In aplastic anaemia patients, genetic variants in human leukocyte antigen-DR15 (HLA-DR15), anti-thymocyte globulin (ATG), runt-related transcription factor 1 (RUNX1), and additional sex combs-like 1 (ASXL1) have been identified as predisposing factors that interact with MSC secretome response pathways (15,16). Polymorphisms in cytokine receptor genes like interleukin-17 receptor (IL-17R), interleukin-2 receptor (IL-2R), and interferon gamma receptor (IFN-γR) affect the response to immunomodulatory factors in MSC secretome, potentially explaining variable therapeutic outcomes (17). Epigenetic profiling has also revealed that MSC secretome induces hypomethylation of promoter regions controlling genes involved in haematopoiesis, such as homebox B4 (HOXB4) and GATA2, potentially restoring normal HSC function (18). Recent studies have highlighted the role of secretome in reducing cytotoxic effects and enhancing hematopoietic cell regeneration without significant immunosuppression risks (19). Bioinformatics network analyses have identified miRNA-mRNA interaction networks, with miR-146a, miR-155, and miR-223 from MSC-EVs targeting genes involved in T-cell activation and pro-inflammatory cytokine production, thereby mitigating immune-mediated destruction of HSCs (20). The pathophysiology of aplastic anaemia involves complex interactions between genetic susceptibilities and environmental factors. The disease typically manifests through three primary mechanisms: intrinsic stem cell defects, immune-mediated destruction of hematopoietic stem cells, and alterations in the bone marrow microenvironment (1). Approximately 70-80% of aplastic anaemia cases are attributed to autoimmune mechanisms, where T-cell-mediated attacks target CD34+ hematopoietic progenitor cells, leading to their destruction and impaired proliferation (21).

Spatial transcriptomics and multi-omics integration approaches have recently mapped the bone marrow niche alterations in aplastic anaemia, revealing dysregulation of the CXCL12-CXCR4 axis and N-cadherin-mediated cell adhesion pathways that are directly modulated by MSC secretome components (6,22). Machine learning algorithms applied to multi-omics data have identified biomarker signatures predicting response to MSC secretome therapy, with elevated expression of CD55, CD59, and reduced NLRP3 inflammasome activation correlating with favourable outcomes (22,23). This understanding of the underlying pathophysiology has led to the development of various therapeutic approaches, including stem cell transplantation and immunosuppressive therapies.

There is growing interest in using stem cells and their secretomes to treat aplastic anaemia. As a result, conducting a bibliometric analysis of the relevant scientific literature from the past five years has become essential. Bibliometric analysis allows us to understand research trends, geographical distribution, researcher collaborations, and the influence of this topic in the scientific community.

This study has focused on publications discussing stem cell or secretome applications in aplastic anaemia between 2018 and 2023 to map scientific developments, challenges, and future opportunities.

MATERIALS AND METHODS

Materials and study design

Data for this bibliometric analysis were extracted from the Scopus database in September 2024. The initial search targeted article titles, abstracts, and keywords using the following formula: (“anemia” OR “anaemia”) AND aplastic AND (“stem cell” OR “secretome”). The complete search strategy was TITLE-ABS-KEY (“anemia” OR “anaemia”) AND aplastic AND (“stem cell” OR “secretome”) AND PUBYEAR > 2018 AND PUBYEAR < 2024 AND (LIMIT-TO(EXACTKEYWORD, “Human”) AND (LIMIT-TO(LANGUAGE, “English”). The analysis was limited to articles published from 2018 to 2023 and written in English. In total, 1,405 articles were identified and exported as CSV files for further analysis (Figure 1).

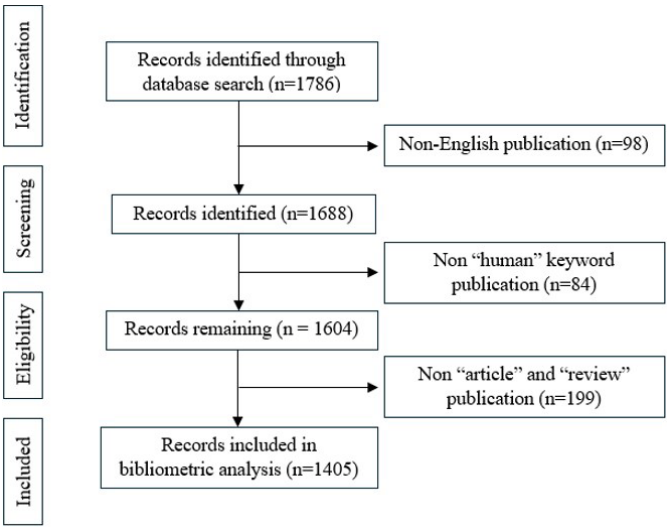

Figure 1. Literature search process flow diagram

Methods

To ensure a comprehensive and unbiased bibliometric analysis, a multi-step methodology was employed. Scopus was selected as the database due to its extensive coverage of biomedical literature and robust citation tracking capabilities. The search strategy was carefully refined through pilot searches to

maximize the retrieval of relevant articles while minimizing irrelevant results. Following data extraction, the exported comma-separated values (CSV) files were systematically cleaned to remove duplicates and correct inconsistencies in author names, affiliations, and keywords. The bibliometric analysis encompassed various parameters, including publication output by year and document type, source metrics such as journals and impact factors, author productivity, collaboration networks, contributions from institutions and countries, citation metrics highlighting the most cited papers and citation patterns, as well as keyword and thematic analyses involving co-occurrence networks and thematic evolution. For visualization, VOSviewer 1.6.19 was utilized to create network visualizations covering co-authorship, co-citation, and keyword co-occurrence, while Biblioshiny supplemented these with additional analyses and visualizations of research themes and trends.

Statistical analysis

Descriptive statistics were used to summarize publication growth rates. Bradford's law was applied to identify core journals in the research field, supporting the bibliometric findings and enhancing the robustness of the analysis.

RESULTS

A total of 1,405 documents were identified consisting of 226 reviews (16.1%) and 1,179 articles (83.9%). Results showed that publications about stem cells or secretome in aplastic anaemia increased by an average of 2.52% annually, indicating considerable interest in researching this topic. Publication trends on stem cells or secretome in aplastic anaemia experienced significant fluctuations from 2018 to 2023. Two thousand nineteen research trends experienced a surge, reaching their peak in 2021, followed by a gradual decline in 2022 and 2023. Various factors, including the COVID-19 pandemic and increased research funding opportunities in this field, may have influenced the increase from 2019 to 2021. The decline from 2022 to 2023 could be attributed to several factors, including uneven technological development across countries, limited research funding, and various other factors (Figure 2A). Leading journals included Biology of Blood and Marrow Transplantation (73 documents), Transplantation and Cellular Therapy (69), and Frontiers in Immunology (40), reflecting the multidisciplinary nature encompassing haematology, immunology, and transplantation (Figure 2B). The United States (341 documents), China (326), and Japan (118) dominated research output, influenced by strong infrastructure and investments, while Southeast Asian countries lagged behind, pointing to regional research gaps and opportunities for collaboration (Figure 2C). International collaborations remain limited (15.02% co-authorship), highlighting potential for enhancing global research networks (Figure 2D).

Highly cited works included Young NS et al.'s 2018 comprehensive review (447 citations) and D'Souza et al.'s 2020 study on hematopoietic cell transplantation trends (347 citations), underscoring pivotal insights into aplastic anaemia pathophysiology and treatments (Table 1). Thematic clustering identified four major areas: clinical management of severe aplastic anaemia; allogeneic stem cell transplantation and its adaptation during COVID-19; bone marrow failure with mesenchymal stem cell therapies; and pharmaceutical approaches including eltrombopag and immunosuppressive therapy (Figure 3A, B, Table 2).

Cluster analysis identified four main research areas: Cluster 1 focuses on severe aplastic anaemia, including clinical management, conditioning regimens, complications, and survival; Cluster 2 covers allogeneic stem cell transplantation, emphasizing special populations like children and the impact of COVID-19; Cluster 3 centres on bone marrow failure, linking aplastic anaemia with related disorders and mesenchymal stem cell therapies; Cluster 4 highlights hematopoietic stem cell transplantation alongside pharmaceutical treatments such as eltrombopag and immunosuppressive therapy. This reflects an evolving, interconnected research landscape that recognizes disease heterogeneity and the need for personalized therapies.

Keyword analysis showed "aplastic anaemia", "hematopoietic stem cell transplantation", and "male" as the most frequent, while "mortality", "chronic myeloid leukaemia", and "human cell" were less studied, indicating research gaps (Figure 3C-D). Temporal trends reveal a shift from foundational treatment

Table 1. Ten most valuable publications based on citation count

No	Title	Year	Source	Citations
1	Aplastic Anemia	2018	N England J Med	447
2	Current Use of and Trends in Hematopoietic Cell Transplantation in the United States	2020	Biol Blood Marrow Transplant	347
3	Clonal Hematopoiesis and Evolution to Hematopoietic Malignancies	2018	Cell Stem Cell	325
4	Indications for haematopoietic stem cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2019	2019	Bone Marrow Transplant	257
5	Cancer in the National Cancer Institute inherited bone marrow failure syndrome cohort after fifteen years of follow-up	2018	Haematologica	230
6	The consensus on indications, conditioning regimen, and donor selection of allogeneic hematopoietic cell transplantation for hematological diseases in China—recommendations from the Chinese Society of Hematology	2018	J Hematol Oncol	219
7	Diagnostic utility of telomere length testing in a hospital-based setting	2018	Proc Natl Acad Sci USA	153
8	The consensus from The Chinese Society of Hematology on indications, conditioning regimens and donor selection for allogeneic hematopoietic stem cell transplantation: 2021 update	2021	J Hematol Oncol	150
9	The EBMT activity survey on hematopoietic-cell transplantation and cellular therapy 2018: CAR-T's come into focus	2020	Bone Marrow Transplant	150
10	Ribosomal proteins and human diseases: molecular mechanisms and targeted therapy	2021	Signal Transduct Target Ther	149

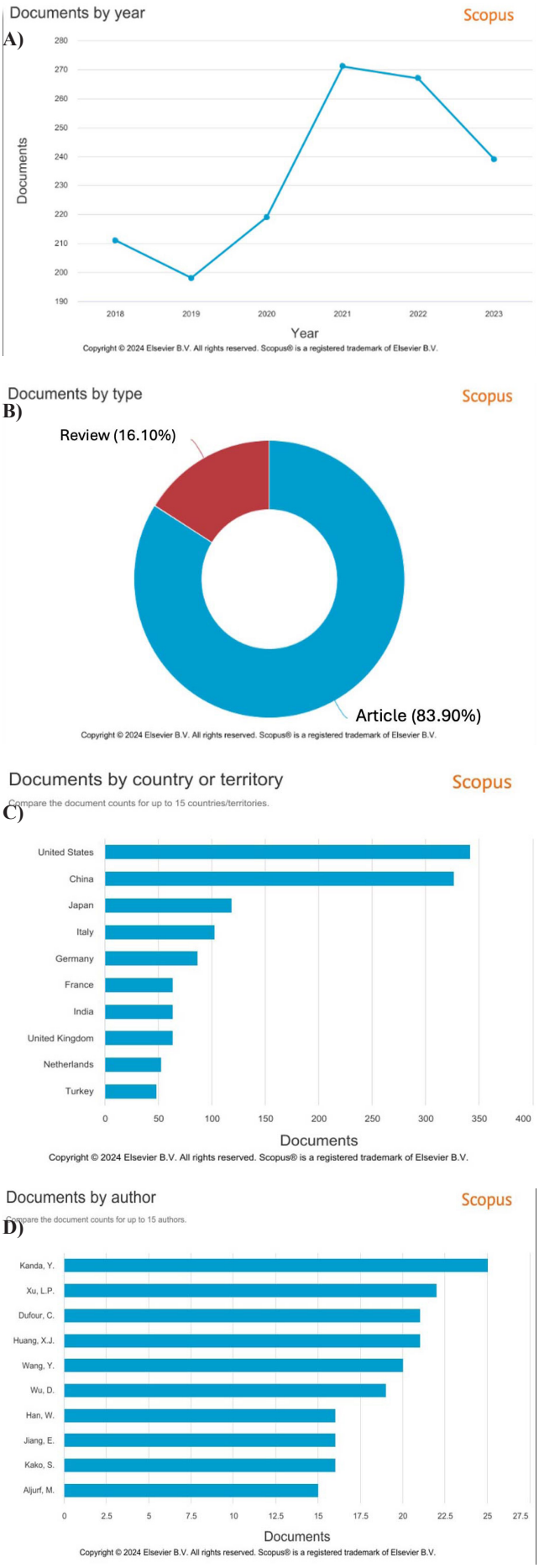

Figure 2. Publication types and publication development. A) Document by year; B) Document by type. Countries and authors with the most publications on stem cells or secretome in aplastic anaemia: C) Document by country or territory; D) Document by author

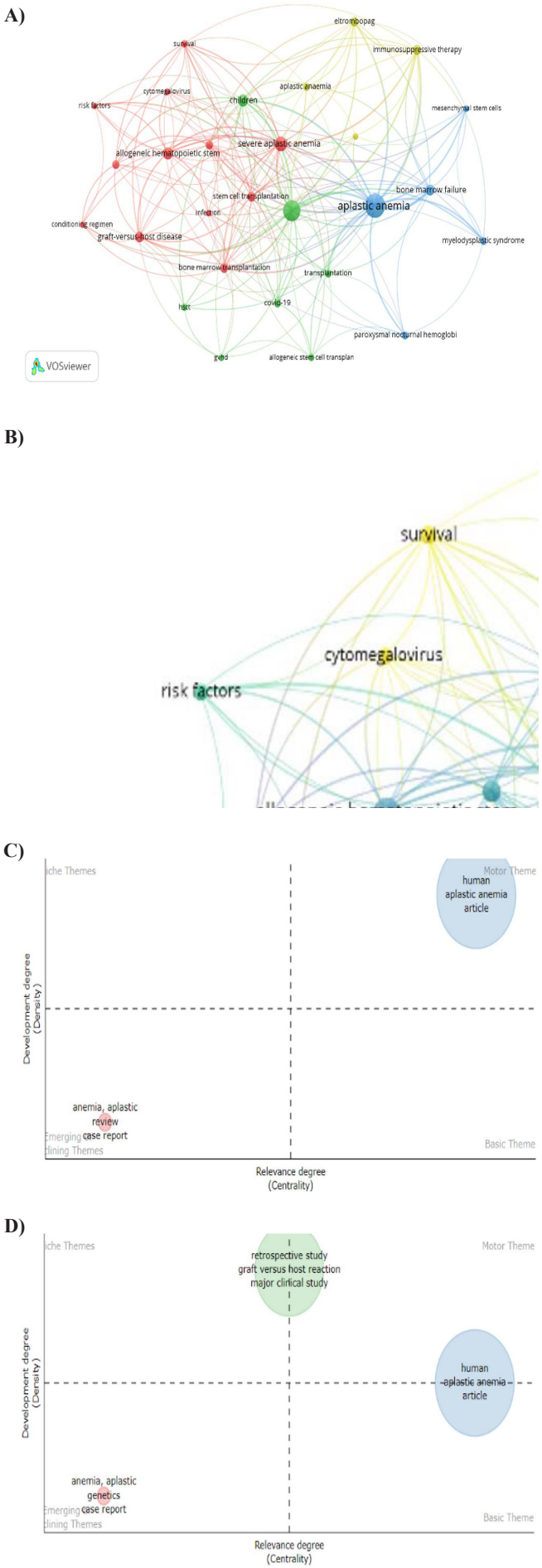

Figure 3. Network Visualization. A) Overlay Visualization; B) using VOSviewer; C) themes in 2018-2021; D) themes in 2022-2023

Table 2. Co-occurrence clusters of keywords based on authors

No	Cluster 1 (12 items)	Cluster 2 (7 items)	Cluster 3 (5 items)	Cluster 4 (4 items)
1	Allogenic hematopoietic stem cell transplantation	Allogeneic stem cell transplantation	Aplastic anaemia	Aplastic anaemia
2	Bone marrow transplantation	Children	Bone marrow failure	Eltrombopag
3	Conditioning regimen	Covid-19	Mesenchymal stem cells	Hematopoietic stem cell transplantation
4	Cytomegalovirus	Graft-versus-host-disease (GVHD)	Myelodysplastic syndrome	Immunosuppressive therapy
5	Graft-versus-host disease	Hematopoietic stem cell transplantation		
6	Hematopoietic cell transplantation	Hematopoietic stem cell transplantation		
7	Infection	Transplantation		
8	Paediatric			
9	Risk factors			
10	Severe aplastic anemia			
11	Stem cell transplantation			
12	Survival			

and disease mechanism focus (2018–2021) to specialized approaches including novel drugs, genetics, and outcome optimization (2022–2023). Emerging interests include secretome therapies, COVID-19's influence, and thrombopoietin receptor agonists like eltrombopag, suggesting promising directions for future aplastic anaemia management.

DISCUSSION

Aplastic anaemia is a chronic failure of the bone marrow to produce blood cells, often resulting in pancytopenia (1). Multiple factors, including genetics, environment, infections, and autoimmunity, contribute to its onset, highlighting the need for improved treatments. Our bibliometric analysis of 1,405 articles from 2018 to 2023 showed continued research interest, especially in countries with advanced healthcare infrastructure like the United States, China, and Japan.

Molecular studies reveal that the mesenchymal stem cell (MSC) secretome plays a significant role in supporting haematopoiesis and bone marrow function (24–26). Thematic clustering in our analysis puts "hematopoietic stem cell transplantation" and "bone marrow failure" at the forefront, underscoring the importance of stem cell therapies. MSC secretome components help restore the bone marrow niche and influence key signalling molecules (6), while pharmaceutical strategies such as eltrombopag target specific molecular pathways like JAK/STAT and MAPK to boost stem cell activity (13,19). In addition, stem cell therapy, particularly hematopoietic stem cell transplantation (HSCT), has emerged as a cornerstone in managing severe aplastic anaemia. This therapy offers the potential for a cure by replacing the dysfunctional or depleted hematopoietic system with healthy progenitor cells from a compatible donor, restoring normal blood cell production. HSCT is widely recognized as the treatment of choice for younger patients with severe disease who have a suitable donor. This molecular convergence explains the synergistic effects of combination therapies and supports the evolving research trends identified in our temporal analysis.

Research interest has also grown in immunosuppressive therapies, paralleling new findings that MSC secretomes carry miRNAs able to modulate T-cell activity and inflammatory cytokines, potentially protecting hematopoietic stem cells from immune-mediated damage (27,28). The intersection with COVID-19 research emphasizes shared inflammatory mechanisms and highlights opportunities for cross-applications in bone marrow failure treatment (29).

Genetic and multi-omics studies remain underrepresented but show immense promise for future research. Advances in CRISPR screening and proteomics have identified new molecular targets, paving the way for more personalized therapies (30–32). Highly cited works in the field, such as Young's "Aplastic Anemia," reflect the ongoing evolution of molecular understanding and the emergence of proteomic biomarkers that could refine treatment selection (15,21). Specifically, proteomic analyses have identified over 200 proteins in MSC-derived extracellular vesicles involved in cell adhesion (33,34), migration, proliferation, and immune regulation, with particular enrichment in factors like IL-6, LIF, SDF-1, and HGF that directly support haematopoiesis (35-37).

Top journals in the field demonstrated its multidisciplinary nature, while spatial transcriptomics revealed how MSC secretomes modulate critical cellular interactions within the bone marrow niche (6). The field's progression from basic research to targeted therapies indicates maturing scientific strategies. Increased international collaboration and the integration of genetic and secretome-based approaches will be essential for advancing precision medicine in aplastic anaemia.

In conclusion, current research trends, molecular insights, and evolving therapies for aplastic anaemia illustrate a dynamic landscape with exciting prospects for effective and personalized treatment strategies.

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TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

AUTHOR CONTRIBUTIONS STATEMENT

Conceptualization, supervision, and validation: CPM, HS, YLRD; Methodology, formal analysis, and data curation: CPM; Writing original draft, analysis, and visualization: CPM and AP; Review draft and project administration: BS and AGM.

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