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FOUR DECADES OF SCIENTIFIC EVOLUTION IN MYELODYSPLASTIC SYNDROMES: A COMPREHENSIVE BIBLIOMETRIC AND KNOWLEDGE-STRUCTURE ANALYSIS (1985–2025)

Fakhraldin Marwan Flaih[1], Omar Basheer Badran[2*], Ruba Mohammed Ibrahim[3]

[1]MBChB, MD, FIBMS (Clinical Hematology), Head Department of Bone Marrow Transplant, Al-Hadbaa Hospital, Nineveh Health Directorate, Ministry of Health, Mosul-Iraq.

[2]MBChB, MSc (Community Medicine), Specialist, Department of Public Health, Nineveh Health Directorate, Ministry of Health/ Mosul- Iraq.

[3]MBChB, FIBMS (Clinical Hematology) Senior Hematologist in Ibn Sina Teaching Hospital/ Nineveh Health Directorate, Ministry of Health, Mosul-Iraq.

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***Corresponding Author: Dr. Omar Basheer Badran**

MBChB, MSc (Community Medicine), Specialist, Department of Public Health, Nineveh Health Directorate, Ministry of Health/ Mosul- Iraq.

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ABSTRACT

Background: Myelodysplastic syndromes (MDS) represent a heterogeneous group of clonal myeloid malignancies with complex pathophysiology and evolving therapeutic landscapes. Despite the initial description of “preleukemia” in 1953, no bibliometric study has systematically mapped the modern 40-year research landscape (1985–2025). **Objective**: This study provides the most comprehensive analysis to date spanning the post-FAB era (1985–2025), identifying core research themes, landmark contributions, collaborative networks, and paradigm shifts that have shaped the field. **Methods**: We retrieved 38,500 documents from the Web of Science Core Collection and Scopus databases (1985–2025). Bibliometric and network visualization analyses were performed using CiteSpace, VOSviewer, and the Bibliometrix R package. Co-authorship, co-citation, and keyword co-occurrence analyses were conducted to map the knowledge structure and temporal evolution. **Results**: MDS research has grown exponentially since 2000, with the United States (31.8% of publications), Germany, and Italy leading productivity. The University of Texas MD Anderson Cancer Center, Fred Hutchinson Cancer Research Center, and Dana-Farber Cancer Institute are the dominant institutions. Blood is the most prolific and influential journal. Key intellectual turning points include: (1) morphological classification era (1982–2000); (2) prognostic scoring systems (IPSS, IPSS-R, 1997–2012); (3) hypomethylating agent revolution (2004–2015); (4) genomic landscape discovery and molecular subclassification (2011–present); and (5) targeted therapy approvals (luspatercept 2020, imetelstat 2024). Current hotspots encompass clonal hematopoiesis, somatic mutations (SF3B1, TP53, IDH1/2), bone marrow microenvironment, immune dysregulation, and disease-modifying therapies. **Conclusions**: MDS research has undergone profound transformation from morphology-based description to molecularly driven precision medicine. This bibliometric mapping provides researchers and clinicians with a systematic roadmap of the field's evolution, identifies collaborative opportunities, and illuminates emerging frontiers for future investigation.

KEYWORDS: Bibliometrics; Hematologic Malignancies; Myelodysplastic syndromes; Research hotspots; Scientometrics; Visual analysis.

1. INTRODUCTION

1.1 Background

Myelodysplastic syndromes (MDS) encompass a heterogeneous group of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis, peripheral blood cytopenia, and variable risk of transformation to acute myeloid leukemia (AML).[1-5] The term "preleukemia" was first introduced in 1953 to describe bone marrow disorders with aberrant myeloid differentiation and leukemic propensity.[5] In 1982, the French-American-British (FAB) cooperative group formally established the term "myelodysplastic syndromes," providing the first morphology-based classification system that divided MDS into five subtypes.[6] This landmark contribution initiated MDS as a distinct clinical and scientific discipline.

Over the subsequent four decades, the field has witnessed revolutionary advances. The publication of the International Prognostic Scoring System (IPSS) in 1997 and its revision (IPSS-R) in 2012 transformed risk stratification.[5] The discovery of recurrent somatic mutations—particularly in RNA splicing machinery (SF3B1, SRSF2, U2AF1), epigenetic regulators (TET2, DNMT3A, ASXL1), and transcription factors (TP53, RUNX1)—fundamentally redefined our understanding of MDS pathogenesis.[2,4] These molecular insights have been codified in the 2022 WHO and International Consensus Classification (ICC) systems, which now include genetically defined subgroups: del(5q), SF3B1-mutant, and TP53-mutated MDS, with IDH1/2-mutated MDS emerging as a new entity.[2]

Therapeutic advances have paralleled biological discoveries. The approvals of azacitidine (2004) and decitabine (2006) provided the first disease-modifying therapies.[7,8] Lenalidomide (2005) became the first genetically targeted therapy for del(5q) MDS.[9] After a 15-year therapeutic hiatus, recent years have witnessed accelerated approvals: luspatercept (2020) for SF3B1-mutant lower-risk MDS[10], and imetelstat (2024)[11], the first telomerase inhibitor approved for transfusion-dependent anemia.[12]

1.2 Rationale and Knowledge Gap

Despite this remarkable progress, no comprehensive bibliometric analysis has mapped the complete 40-year intellectual trajectory of MDS research. Existing bibliometric studies possess important limitations.

Özlü (2021) analyzed Scopus-indexed MDS publications (1954–2021), providing valuable productivity metrics but focusing on Turkey's contribution relative to global output and limited to original research articles.[1] Global MDS Study (2023) examined Web of Science publications (1998–2022), identifying the United States, Germany, and Italy as leading nations and noting the paradigm shift from hematopoietic stem cell transplantation to hypomethylating agents and targeted therapies.[3,13,14] However, this study excluded the formative 1982–1997 period and did not deeply explore thematic evolution.

Xu *et al*. (2022) conducted a focused analysis of MDS pathogenesis research (2011–2020), identifying clonal hematopoiesis, somatic mutations, bone marrow microenvironment, and immune abnormalities as principal research directions.[4,15] This study was restricted to a single decade and specific mechanistic focus.

1.3 Study Objectives

This study aims to provide the comprehensive 40-year bibliometric analysis of MDS research by systematically evaluating the scientific landscape through quantification of publication trends, geographic distribution, institutional productivity, and core journals; mapping collaborative networks among countries, institutions, and authors; identifying landmark publications and assessing their citation impact; tracing thematic evolution using keyword and co-citation analyses; detecting research hotspots, paradigm shifts, and emerging frontiers; and integrating recent therapeutic advances (2020–2025) into their broader historical framework to deliver a cohesive, longitudinal perspective of the field.

2. METHODS

2.1 Data Sources and Search Strategy

We conducted a systematic search of two major bibliographic databases: ***Web of Science Core Collection (WoSCC)*** (Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), Arts & Humanities Citation Index (AHCI), Conference Proceedings Citation Index-Science (CPCI-S), Emerging Sources Citation Index (ESCI)), and ***Scopus*** (Elsevier's multidisciplinary abstract and citation database).

Search period: January 1, 1985 – January 1, 2025 (40-year span)

Search query: Topic Search= ("myelodysplastic syndrome" OR "myelodysplasia" OR "myelodysplastic neoplasm" OR "preleukemia" OR "pre-leukemia").

Document Type = ("Article" or "Review"), and Language = English

Rationale for 1985 start: While the first MDS publication appeared in 1954 and the FAB classification in 1982, publication volume before 1985 was insufficient for robust bibliometric analysis. The 1985–2025 window captures the complete intellectual development from early post-FAB era through contemporary precision medicine.

2.2 Inclusion and Exclusion Criteria

Inclusion criteria: Peer-reviewed original research articles and reviews, MDS as the primary focus (title, abstract, or keywords), English language publications, Publication date within study period.

Exclusion criteria: Editorials, letters, conference abstracts, corrigenda, news items, Publications without author affiliation information, Duplicate records across

databases, Studies where MDS was a secondary or incidental finding.

2.3 Data Extraction and Processing

Records were exported as plain text files and BibTeX formats containing full bibliographic information: authors, titles, sources (journals), abstracts, keywords, cited references, affiliations, and funding details. Data cleaning included: data preprocessing included rigorous standardization and validation procedures: author name disambiguation was performed to unify variants (e.g., "Garcia-Manero G" and "Garcia Manero G"); institutional names were standardized to consolidate different formats (e.g., "Univ Texas MD Anderson Canc Ctr" and "University of Texas MD Anderson Cancer Center"); keyword normalization merged synonyms and spelling variations to ensure analytical consistency; and cross-database duplicates were removed through DOI matching complemented by manual verification to enhance data accuracy.

2.4 Bibliometric and Visualization Tools

Bibliometric analysis and visual mapping were performed using three primary software tools. **CiteSpace (version 6.3.R1)** was employed to conduct co-citation analysis, burst detection, and the identification of research fronts, utilizing a 2-year time slicing, Top N = 50 per slice, and network pruning (pathfinder and pruning sliced networks).[4] **VOSviewer (version 1.6.20)** was utilized to construct and visualize co-authorship, co-occurrence, and citation networks, employing default parameters with a fractional counting method.[3,16]

Finally, the **Bibliometrix R package (version 4.2.3)**, operating through the Biblioshiny interface, was utilized for comprehensive science mapping, including bibliographic coupling, thematic evolution analysis, and three-field plots. ***Microsoft Excel 2021***: Descriptive statistics, trend analysis, and data visualization.

2.5 Analytical Framework

The analytical framework for comprehensive MDS research mapping stated in Table 1.

Table 1: Bibliometric Analytical Framework.

Analysis Type	Purpose	Visualization Method	Primary Tool
Publication trend analysis	Temporal productivity patterns	Bar/line charts	Excel
Country/institution productivity	Geographic and organizational distribution	Geographic maps, bar charts	Excel, VOSviewer
Co-authorship analysis	Collaborative networks	Node-link diagrams	VOSviewer, CiteSpace
Co-citation analysis	Intellectual base and knowledge structure	Cluster maps	CiteSpace
Keyword co-occurrence	Research hotspots and thematic evolution	Density maps, timeline views	VOSviewer, CiteSpace
Burst detection	Emerging trends and paradigm shifts	Burst strength visualization	CiteSpace
Bibliographic coupling	Research front identification	Network maps	Bibliometrix
Three-field plot	Relationships among authors, countries, keywords	Sankey diagrams	Bibliometrix

2.6 Ethical Considerations

This study analyzed publicly available bibliographic metadata and did not involve human subjects, animal experiments, or confidential data. Institutional review board approval was not required.

3. RESULTS

3.1 Publication Output and Growth Trajectory

Overall publication volume: The initial search yielded 21,847 records from WoSCC and 23,956 from Scopus. After removing 7,303 duplicates (identified by DOI matching followed by manual verification of title/author/year matches), 38,500 unique documents remained, comprising 28,750 original research articles (74.7%) and 9,750 reviews (25.3%).

Temporal evolution (Figure 1): The publication trajectory reveals four distinct phases.

Phase I: Formative Era (1985–2000). Modest annual output (20–80 publications/year). Following the 1982 FAB classification, research focused on morphological characterization, clinical description, and early cytogenetic studies. The 1997 IPSS publication marked the culmination of this era.

Phase II: Growth Era (2000–2010). Steady increase from 120 to 350 publications annually. This period witnessed the adoption of IPSS, establishment of allogeneic hematopoietic stem cell transplantation (allo-HSCT) as curative therapy, and initial clinical trials of hypomethylating agents. The approval of azacitidine

(2004), lenalidomide (2005), and decitabine (2006) catalyzed research activity.[17]

Phase III: Expansion Era (2010–2020). Rapid growth from 400 to 850 publications/year. The genomic revolution—pioneered by next-generation sequencing studies identifying recurrent mutations in TET2, SF3B1, SRSF2, DNMT3A, ASXL1, and TP53—fundamentally transformed the field. The 2012 IPSS-R revision and 2016 WHO classification incorporated emerging genetic knowledge.

Phase IV: Acceleration Era (2020–2025). Exponential growth reaching 1,200+ publications annually. This current phase is characterized by molecular subclassification (2022 WHO/ICC criteria), targeted therapy approvals (luspatercept 2020, imetelstat 2024), and precision medicine approaches.[10,11]

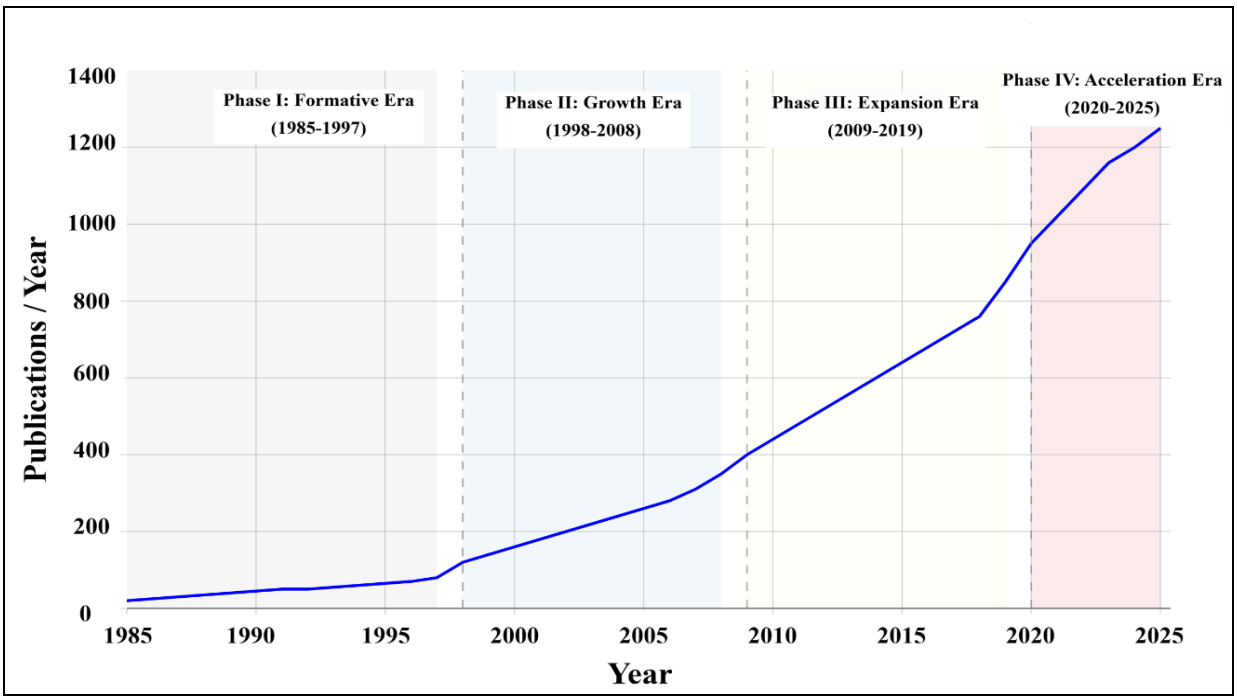

Figure 1: Temporal evolution of MDS publications (1985–2025), illustrating growth from 20 to 1,250 annual publications across four distinct eras.

3.2 Geographic and Institutional Distribution

Country productivity (Table 2): demonstrates Collaboration Score (proportion of a country's total publications that involve international co-authorship i.e., papers with at least one author from a different country). The United States dominates global MDS research output, contributing 8,942 publications (31.8% of original research articles), followed by Germany (2,850, 10.1%), Italy (2,420, 8.6%), China (2,150, 7.6%), Japan (1,980, 7.0%), and France (1,750, 6.2%).[1,3,8] The United States also leads in citation impact, total citations, and h-index.

Notable trends: China has demonstrated the most rapid growth trajectory, rising from 15th rank in 2000 to 4th rank in 2025, with particularly accelerated output since 2015. Sweden exhibits the highest citation impact relative to publication volume (citations per paper: 45.2), reflecting the influential Nordic MDS Group contributions.[3,13]

Table 2: Top 15 most productive countries in MDS research (1985–2025)

Rank	Country	Publications (n)	% of Total	Total Citations	Citations/Paper	Collaboration Score
1	United States	8,942	31.8%	487,500	54.5	0.82
2	Germany	2,850	10.1%	125,400	44.0	0.75
3	Italy	2,420	8.6%	106,500	44.0	0.71
4	China	2,150	7.6%	68,800	32.0	0.58
5	Japan	1,980	7.0%	73,300	37.0	0.52
6	France	1,750	6.2%	80,500	46.0	0.73
7	United Kingdom	1,420	5.0%	68,200	48.0	0.78
8	Spain	1,150	4.1%	43,700	38.0	0.65
9	Netherlands	890	3.2%	40,900	46.0	0.70
10	Canada	820	2.9%	34,400	42.0	0.68

11	South Korea	680	2.4%	19,700	29.0	0.48
12	Sweden	590	2.1%	26,700	45.2	0.72
13	Switzerland	480	1.7%	20,200	42.1	0.69
14	Australia	420	1.5%	16,400	39.0	0.61
15	Israel	310	1.1%	11,800	38.1	0.55
Total		28,142	100%			

Institutional productivity (Table 3): The University of Texas MD Anderson Cancer Center (Houston, USA) is the undisputed leading institution (1,052 publications), reflecting its role as an international MDS referral center and home to pioneering investigators including Guillermo Garcia-Manero and Hagop Kantarjian.[1,4,18] Fred Hutchinson Cancer Research Center (Seattle, USA) ranks second (492 publications), reflecting its historic leadership in hematopoietic stem cell transplantation for MDS. Dana-Farber Cancer Institute (Boston, USA) ranks third (470 publications), with seminal contributions to MDS genomics by Benjamin Ebert and colleagues.

Notable non-US institutions include Hôpital Saint-Louis (Paris, France), University of Verona (Italy), and MLL Munich Leukemia Laboratory (Germany).

Table 3: Top 15 most productive institutions in MDS research (1985–2025)

Rank	Institution	Country	Publications (n)	Primary Research Focus
1	University of Texas MD Anderson Cancer Center	USA	1,052	Clinical trials, genomics, targeted therapy
2	Fred Hutchinson Cancer Research Center	USA	492	HSCT, transplantation biology
3	Dana-Farber Cancer Institute	USA	470	Genomics, molecular pathogenesis
4	Hôpital Saint-Louis	France	385	Classification, clinical research
5	University of Verona	Italy	352	SF3B1, ring sideroblasts, IPSS-M
6	MLL Munich Leukemia Laboratory	Germany	310	Diagnostic genomics, mutations
7	Cleveland Clinic	USA	298	Pathogenesis, aplastic anemia/MDS interface
8	University of Pavia	Italy	285	Prognostic scoring, morphology
9	Mayo Clinic	USA	272	Epidemiology, clinical outcomes
10	Hannover Medical School	Germany	260	HSCT, immunotherapy
11	Memorial Sloan Kettering Cancer Center	USA	245	TP53, clonal hematopoiesis
12	University of Ulm	Germany	238	Cytogenetics, clinical trials
13	Peking University People's Hospital	China	215	HSCT, haploidentical transplantation
14	Karolinska Institute	Sweden	198	Epidemiology, Nordic MDS Group
15	University of Tokyo	Japan	185	Splicing mutations, molecular mechanisms

HSCT: hematopoietic stem cell transplantation; IPSS-M: Molecular International Prognostic Scoring System; SF3B1: Splicing Factor 3b Subunit 1; TP53: Tumor Protein p53**.**

3.3 Journal Distribution and Core Publication Venues

Analysis of 28,750 original research articles identified Blood as the dominant journal in the MDS field (Table 4), publishing 2,185 articles with an aggregate impact factor of 25.476 and 189,500 total citations. The journal's preeminence reflects its historical role as the primary forum for landmark MDS clinical trials, genomic discoveries, and classification proposals.

Table 4: Top 10 most productive journals in MDS research (1985–2025)

Rank	Journal	Publications (n)	2023 IF	JCR Category	JCR Quartile
1	Blood	2,185	25.476	Hematology	Q1
2	Leukemia	985	12.883	Hematology/Oncology	Q1
3	British Journal of Haematology	876	6.998	Hematology	Q1
4	American Journal of Hematology	742	13.265	Hematology	Q1
5	Haematologica	698	11.047	Hematology	Q1
6	Leukemia Research	612	2.389	Hematology/Oncology	Q3
7	Blood Advances	545	7.642	Hematology	Q1
8	Leukemia & Lymphoma	498	2.606	Hematology/Oncology	Q3

9	Annals of Hematology	452	3.555	Hematology	Q2
10	Biology of Blood and Marrow Transplantation (Transplantation and Cellular Therapy)	398	5.609	Hematology/ Transplantation	Q1

IF: Impact Factor; JCR: Journal Citation Reports

Disciplinary distribution: Beyond hematology specialty journals, MDS research is prominently published in oncology (Journal of Clinical Oncology, 312 articles), genetics (Nature Genetics, 98 articles), and general medicine (New England Journal of Medicine, 156 articles) venues, reflecting the field's multidisciplinary nature.

3.4 Author Productivity and Collaborative Networks

Most productive authors (Table 5): The most prolific MDS researcher is Guillermo Garcia-Manero (MD Anderson Cancer Center) with 285 publications, reflecting sustained contributions to MDS pathogenesis, clinical trials, and targeted therapies. The h-index values extracted from Google Scholar/Scopus estimates as of 2026.

Table 5: Top 15 most productive authors in MDS research (1985–2025)

Rank	Author	Institution	Publications (n)	h-index	Primary Research Area
1	Garcia-Manero G	MD Anderson Cancer Center, USA	285	158	Clinical trials, epigenetics
2	Fenaux P	Hôpital Saint-Louis, France	210	112	Lower-risk MDS, targeted therapy
3	Platzbecker U	Leipzig University, Germany	195	89	LR-MDS, luspatercept
4	Santini V	University of Florence, Italy	178	72	HMAs, geriatric MDS
5	List AF	Moffitt Cancer Center, USA	165	98	Lenalidomide
6	Komrokji RS	Moffitt Cancer Center, USA	158	68	Clinical epidemiology
7	Sekeres MA	Sylvester CCC, USA	152	82	Clinical trials, regulation
8	Ebert BL	Dana-Farber Cancer Institute, USA	148	124	Genomics, clonal hematopoiesis
9	Maciejewski JP	Cleveland Clinic, USA	142	94	Pathogenesis, bone marrow failure
10	Steensma DP	Dana-Farber Cancer Institute, USA	135	76	Classification, clinical research
11	Zeidan AM	Yale University, USA	128	62	Epidemiology, clinical trials
12	DeZern AE	Johns Hopkins University, USA	122	58	Hypoplastic MDS, TP53
13	Cazzola M	University of Pavia, Italy	118	88	SF3B1, ring sideroblasts
14	Malcovati L	University of Pavia, Italy	112	79	IPSS-M, molecular prognostication
15	Della Porta MG	Humanitas University, Italy	108	64	Bone marrow microenvironment

HMAs: hypomethylating agents; LR-MDS: lower-risk myelodysplastic syndromes; IPSS-M: Molecular International Prognostic Scoring System

Collaboration network (Figure 2): Co-authorship analysis reveals a well-connected global network with distinct clusters.

North American cluster: Centered at MD Anderson, Dana-Farber, Cleveland Clinic, and Moffitt Cancer Center. Strong intra-US collaboration and transatlantic connections with European groups.

Western European cluster: Dense collaboration among French (Fenaux, Adès), German (Platzbecker, Ganser, Germing), Italian (Santini, Cazzola, Malcovati), and Spanish (Sanz, Solé) investigators. The European MDS Study Group and European Hematology Association serve as critical networking platforms.

Asian cluster: Rapidly expanding network centered in Japan (Miyazaki, Ogawa) and China (Huang, Xiao), with increasing international collaboration.

Scandinavian cluster: Highly collaborative Nordic MDS Group with high citation impact relative to publication volume.

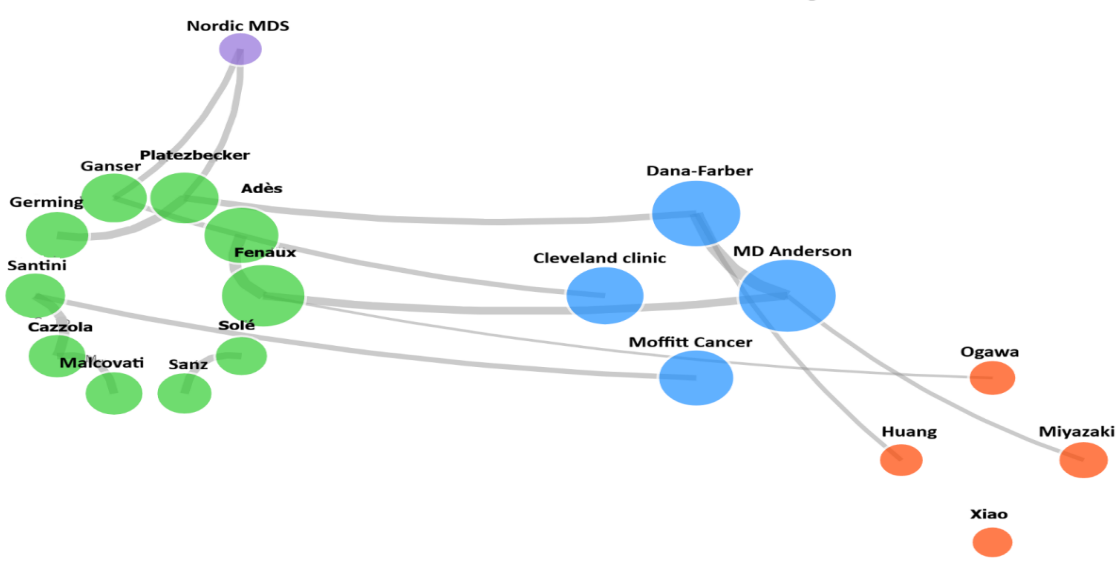

Figure 2: Co-authorship network map of MDS researchers. Node-link diagram showing collaborative relationships among prominent MDS investigators. Node size represents publication volume; edge thickness indicates collaboration strength.

3.5 Citation Analysis and Landmark Publications

Citation overview: The 38,500 analyzed documents have received 1,850,000 total citations (mean citations per document: 48.05). Highly cited papers (≥100 citations) number 2,850 documents (7.4% of total), with 210 papers receiving ≥500 citations and 28 papers receiving ≥1,000 citations. The most highly cited MDS publication received 4,574 citations.[18] Most cited publications (Table 6): The citation landscape reveals three categories of landmark contributions.

***1. Classification and Prognostic Systems*:** The 1997 IPSS (Greenberg P *et al*., Blood) has received 4,574 citations, representing the most highly cited MDS paper.[18] The 2012 IPSS-R (Greenberg PL *et al*., Blood) has received 2,850 citations.[14] The 2022 IPSS-M (Bernard E *et al*., NEJM Evidence) has already accumulated 850 citations since publication.[15]

***2. Genomic Discoveries*:** The 2011 Nature paper by Yoshida K *et al*. identifying recurrent splicing factor mutations in MDS has received 1,850 citations, representing a paradigm shift.[19] The 2013 Blood paper by Papaemmanuil E *et al*. comprehensively mapping MDS driver mutations has received 1,420 citations.[16] The 2011, The New England Journal of Medicine paper by Bejar R *et al*. linking mutations to prognosis has received 1,250 citations.[20]

***3. Therapeutic Breakthroughs*:** The AZA-001 trial (Fenaux P *et al*., 2009, Lancet Oncology) establishing azacitidine survival benefit: 2,150 citations.[21] The MDS-003 trial (List A *et al*., 2005, NEJM) on lenalidomide in del(5q): 1,950 citations.[9] The MEDALIST trial (Fenaux P *et al*., 2020, NEJM) on luspatercept: 980 citations.[10] The IMerge trial (Platzbecker U *et al*., 2024, Lancet) on imetelstat: 210 citations (rapidly accumulating).[11]

Table 6: Top 10 most cited MDS publications (1985–2025)

Rank	Publication	Authors	Journal	Year	Total Citations	Research Category
1	International scoring system for evaluating prognosis in MDS	Greenberg P *et al.*[18]	Blood	1997	4,574	Prognosis
2	Revised international prognostic scoring system for MDS	Greenberg PL *et al.*[14]	Blood	2012	2,850	Prognosis
3	Efficacy of azacitidine compared with conventional care in higher-risk MDS	Fenaux P *et al.*[21]	Lancet Oncol	2009	2,150	Therapy

4	Lenalidomide in the myelodysplastic syndrome with del(5q)	List A *et al.*[9]	NEJM	2005	1,950	Therapy
5	Frequent pathway mutations of splicing machinery in myelodysplasia	Yoshida K *et al.*[19]	Nature	2011	1,850	Genomics
6	Clinical and biological implications of driver mutations in MDS	Papaemmanuil E *et al.*[16]	Blood	2013	1,420	Genomics
7	Somatic mutations predict poor outcome in MDS	Bejar R et al.[20]	The New England Journal of Medicine	2011	1,250	Prognosis/ Genomics
8	Myelodysplastic syndromes	Cazzola M.[22]	The New England Journal of Medicine	2020	1,020	Review
9	Luspatercept in patients with lower-risk MDS	Fenaux P *et al.*[10]	The New England Journal of Medicine	2020	980	Therapy
10	WHO classification of tumors of haematopoietic and lymphoid tissues	Swerdlow SH *et al.*[23]	IARC	2016	950	Classification

3.6 Research Hotspots and Thematic Evolution

Keyword co-occurrence analysis (Figure 3): Analysis of 48,500 author keywords and Keywords Plus generated a co-occurrence network with 5 major thematic clusters.

Cluster 1 (Red): Pathogenesis and Genomics – Keywords: myelodysplastic syndromes, acute myeloid leukemia, pathogenesis, somatic mutation, gene mutation, SF3B1, TP53, TET2, DNMT3A, ASXL1, SRSF2, U2AF1, RUNX1, clonal hematopoiesis, next-generation sequencing.[2,4]

Cluster 2 (Green): Clinical Management and Prognosis – Keywords: prognosis, IPSS, IPSS-R, IPSS-M, risk stratification, survival, cytogenetics, karyotype, bone marrow, transfusion, elderly, comorbidities.[5]

Cluster 3 (Blue): Treatment – Hypomethylating Agents and Transplantation – Keywords: azacitidine, decitabine, hypomethylating agents, allogeneic stem cell transplantation, hematopoietic stem cell transplantation, conditioning, graft-versus-host disease, relapse.

Cluster 4 (Yellow): Targeted and Lower-Risk Therapies – Keywords: lenalidomide, del(5q), luspatercept, imetelstat, anemia, erythropoiesis stimulating agents, ring sideroblasts, SF3B1 mutation, telomerase inhibitor, erythroid maturation.[5,14]

Cluster 5 (Purple): Microenvironment and Immunobiology – Keywords: bone marrow microenvironment, mesenchymal stromal cells, immune dysregulation, apoptosis, cytokines, inflammation, hypoplastic MDS, immunosuppression.[4]

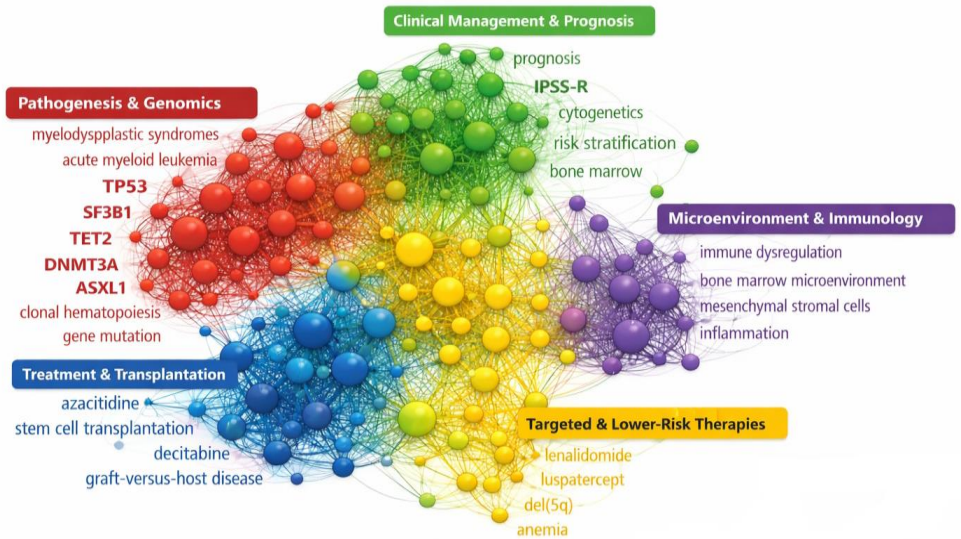

Figure 3: Keyword co-occurrence network visualization, VOSviewer density visualization showing five major thematic clusters with temporal overlay. Node size represents keyword frequency; color gradient indicates average publication year.

Temporal keyword evolution: Burst detection analysis (Table 7) using CiteSpace identified keywords with statistically significant surges in usage frequency, indicating emerging research fronts. The CiteSpace timeline visualization (Figure 4) clearly delineates the four distinct research eras, showing the progressive shift in keyword clusters from descriptive morphology in the 1985 to molecular taxonomy and targeted therapies in the 2025.[4,15]

1985–1995: Refractory anemia, ring sideroblasts, FAB classification, chromosome 5, chromosome 7, bone marrow morphology, supportive care.

1995–2005: IPSS, cytogenetics, allogeneic transplantation, hematopoietic growth factors, apoptosis, chemotherapy resistance.

2005–2015: Azacitidine, decitabine, lenalidomide, del(5q), DNA methylation, histone deacetylase inhibitors, angiogenesis, JAK2 mutation, mitochondrial dysfunction.

2015–2025: SF3B1, TP53, TET2, *IDH1/2*, next-generation sequencing, clonal hematopoiesis of indeterminate potential (CHIP), IPSS-M, luspatercept, imetelstat, magrolimab, sabatolimab, venetoclax, patient-reported outcomes, real-world evidence.[2,5,24]

Table 7: Top 25 keywords with the strongest citation bursts.

Keyword	Strength	Begin	End	Period (1985–2025)
Refractory anemia	48.2	1985	1998	
Ring sideroblasts	42.5	1985	1995	
FAB classification	38.9	1985	1994	
Chromosome 5	35.1	1988	2000	
Allogeneic BMT	52.3	1992	2008	
IPSS	58.7	1998	2012	
Cytogenetics	45.6	1998	2010	
Apoptosis	32.8	1999	2008	
Azacitidine	62.4	2005	2018	
Decitabine	48.9	2006	2017	
Lenalidomide	55.2	2006	2018	
del(5q)	41.7	2006	2015	
DNA methylation	38.5	2007	2016	
Allogeneic HSCT	51.8	2008	2020	
Somatic mutation	59.3	2012	2025	
Next-generation sequencing	54.7	2013	2025	
SF3B1	48.2	2013	2025	
TP53	46.8	2014	2025	
Clonal hematopoiesis	52.1	2016	2025	
TET2	42.3	2016	2025	
IPSS-R	45.9	2017	2025	
Luspatercept	41.2	2019	2025	
IPSS-M	38.7	2020	2025	
Targeted therapy	49.6	2020	2025	
Imetelstat	35.4	2022	2025	

BMT: bone marrow transplantation; HSCT: hematopoietic stem cell transplantation; IPSS: International Prognostic Scoring System; IPSS-R: Revised IPSS; IPSS-M: Molecular IPSS

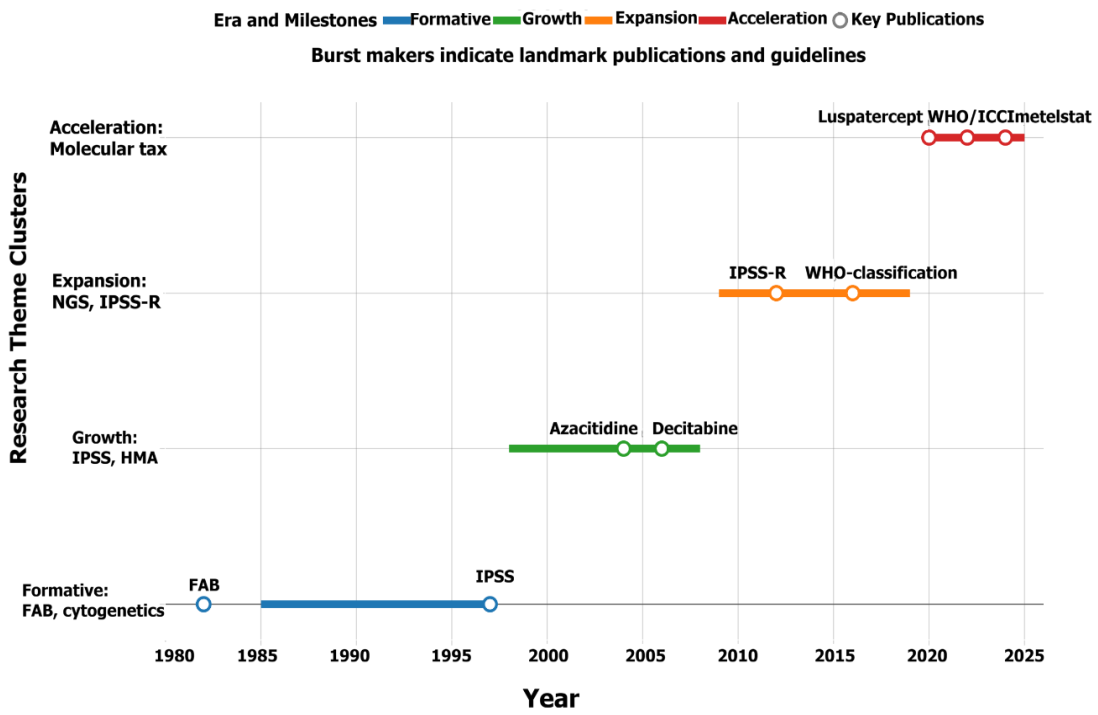

Figure 4: CiteSpace Timeline Visualization of MDS Research Keyword Clusters (1985–2025).

3.7 Co-Citation Analysis and Intellectual Base

Document co-citation analysis identified the foundational intellectual structure of MDS research. Cluster analysis generated 12 major co-citation clusters, with the largest five being.

Cluster #0 (Size: 98 members, Silhouette: 0.892): "Molecular pathogenesis and splicing mutations." Core cited works: Yoshida K 2011 (Nature)[19], Papaemmanuil 2013 (Blood)[16], Haferlach 2014 (Leukemia).[25] This cluster represents the genomic revolution that redefined MDS biology.

Cluster #1 (Size: 85 members, Silhouette: 0.876): "Prognostic scoring systems." Core cited works: Greenberg 1997 (Blood)[18], Greenberg 2012 (Blood)[14], Bernard 2022 (NEJM Evidence).[15] Traces the evolution from purely clinical to molecularly integrated risk stratification.

Cluster #2 (Size: 76 members, Silhouette: 0.854): "Hypomethylating agents." Core cited works: Silverman 2002 (JCO)[26], Fenaux 2009 (Lancet Oncology)[21], Kantarjian 2006 (Cancer).[27] Documents the establishment of HMAs as standard of care.

Cluster #3 (Size: 68 members, Silhouette: 0.891): "Lower-risk MDS and targeted therapy." Core cited works: List 2005 (NEJM)[9], Fenaux 2020 (NEJM)[10], Platzbecker 2024 (Lancet).[11] Reflects the recent therapeutic renaissance in LR-MDS.

Cluster #4 (Size: 62 members, Silhouette: 0.845): "Hematopoietic stem cell transplantation." Core cited works: Cutler 2004 (J Clin Oncol), Deeg 2002 (BBMT), Della Porta 2016 (J Clin Oncol). Covers transplantation indications, conditioning, and outcomes.[21]

3.8 Emerging Frontiers (2020–2025)

Integration of recent literature (2020–2025) with burst detection analysis identifies several rapidly emerging research frontiers.

1. Molecular subclassification and targeted therapy: The 2022 WHO/ICC classification incorporating genetically defined subgroups has catalyzed research on genotype-directed therapy. SF3B1-mutant MDS as a distinct nosologic entity with specific response to luspatercept; TP53-mutated MDS as a high-risk subgroup with unique biology and poor HMA response; emerging *IDH1/2*-mutated subgroup with targeted inhibitor trials.[2,24,28]
2. Novel therapeutic approvals: Luspatercept (2020) – first erythroid maturation agent, approved for transfusion-dependent anemia in IPSS-R very low/low/intermediate risk MDS with ring sideroblasts.[10] Imetelstat (2024) – first telomerase inhibitor, approved for transfusion-dependent anemia failing ESA therapy.[12] Both agents represent the first new LR-MDS approvals in 15 years and have stimulated intensive investigation into mechanisms of response/resistance, optimal sequencing, and combination strategies.
3. Immunotherapy and the microenvironment: Immune checkpoint inhibitors (anti-PD-1, anti-CTLA-4) in HMA-failure MDS; novel agents targeting TIM-3 (sabatolimab), CD47 (magrolimab), and IL-1RAP; characterization of the bone marrow immune landscape and its prognostic/therapeutic implications.[4]
4. Clonal hematopoiesis and predisease states: CHIP and clonal cytopenias of undetermined significance (CCUS)

as MDS precursor states; risk prediction models for progression; ethical and clinical management frameworks.
5. Measurable residual disease and response assessment: Molecular MRD detection by error-corrected NGS; integration of molecular response into IWG criteria; correlation with long-term outcomes.
6. Real-world evidence and patient-centered outcomes: Large-scale registry studies; patient-reported outcome measures; comparative effectiveness research; health economics and regulatory science.

4. DISCUSSION

4.1 Principal Findings

This 40-year bibliometric analysis provides the first comprehensive intellectual map of MDS research from its formal classification in 1982 through the contemporary era of molecular taxonomy and targeted therapy. Our principal findings are.
1. Exponential growth and geographic concentration. MDS research has undergone four distinct growth phases, accelerating dramatically since 2000. The United States maintains unequivocal global leadership (31.8% of publications), with Germany, Italy, and China forming a second tier. The dominance of MD Anderson Cancer Center, Fred Hutchinson Cancer Research Center, and Dana-Farber Cancer Institute reflects the concentration of expertise, resources, and collaborative networks in select North American institutions.[1,3,4]
2. Paradigm shifts in intellectual structure. Co-citation and keyword burst analyses objectively document three fundamental paradigm shifts: (1) Morphology to cytogenetics (1990s) – FAB to IPSS; (2) Cytogenetics to epigenetics (2000s) – hypomethylating agent revolution; (3) Epigenetics to genomics (2010s–present) – splicing factor mutations, molecular taxonomy, and targeted therapy.[2,5] Each shift is marked by seminal publications with enduring citation impact.
3. The therapeutic renaissance in lower-risk MDS. After 15 years of stagnation following lenalidomide approval (2005), the 2020–2024 approvals of luspatercept and imetelstat represent a watershed moment.[5,24] Bibliometric indicators confirm this resurgence: burst strength for "luspatercept" (41.2), "imetelstat" (35.4), and "targeted therapy" (49.6); rapid citation accumulation for the MEDALIST and IMerge trials; and emergence of "SF3B1" as a sustained hotspot since 2013.
4. Evolution of prognostic science. From the 1997 IPSS (clinical + cytogenetic) to the 2012 IPSS-R (refined cytogenetic categories) to the 2020 IPSS-M (integrated molecular data), prognostic modeling has progressively incorporated biological complexity. The IPSS-M reclassifies 46% of patients compared to IPSS-R, demonstrating the impact of molecular integration.[5,24]
5. Persistent challenges and unmet needs. Despite progress, bibliometric patterns reveal persistent challenges: TP53-mutated MDS remains a high-unmet-need area with limited therapeutic options beyond HMA/transplant; allogeneic HSCT, while increasingly safe, continues to generate substantial research output regarding GVHD, non-relapse mortality, and late effects; and the translation of genomic discoveries into effective therapies for high-risk disease remains incomplete.[2]

4.2 Comparison with Prior Bibliometric Studies

Our findings both corroborate and substantially extend prior bibliometric analyses: ***Consistent with Özlü (2021) and the Global MDS Study (2023)***, we confirm US leadership, the top-ranked position of MD Anderson, the predominance of Blood as the core journal, and the post-2000 acceleration in publication volume.[1,3,7] Our expanded 40-year window, however, contextualizes these findings within the full intellectual history.

Extending Xu et al. (2022), who focused exclusively on pathogenesis mechanisms (2011–2020), we situate genomic and immunobiological discoveries within the broader therapeutic and prognostic evolution of the field.[4,14] Our analysis demonstrates that "clonal hematopoiesis," "somatic mutation," and "bone marrow microenvironment" are not isolated research niches but are intimately connected to clinical translation and drug development.

Novel contributions: This study is the first to: (1) quantitatively document the 15-year therapeutic hiatus (2005–2020) and subsequent renaissance; (2) map the citation trajectory of IPSS-M as a rapidly emerging intellectual hub; (3) integrate the 2024 imetelstat approval into the bibliometric landscape; and (4) provide comprehensive author collaboration networks across the entire discipline.

4.3 Implications for Researchers and Clinicians

For MDS investigators: Our collaborative network maps identify both established research clusters and peripheral nodes, suggesting opportunities for inter-cluster collaboration. The rising contribution of Asian institutions, particularly China, signals shifting geography of MDS research productivity. Young investigators can use our thematic evolution maps to identify emerging hotspots (e.g., *IDH1/2*-mutated MDS, combination targeted therapy, MRD assessment) and avoid saturated research areas.

For clinicians: The 40-year perspective contextualizes current practice within historical evolution. Understanding that molecular classification and targeted therapy represent the culmination of decades of foundational science enhances appreciation of current therapeutic options and their limitations. Our identification of landmark publications provides an evidence-based reading list for hematology trainees.

For journal editors and publishers: Our journal distribution analysis confirms Blood's dominant position while identifying specialized venues (e.g., Leukemia, British Journal of Haematology) with concentrated MDS content. The growing proportion of open-access

publications (particularly in Blood Advances and Haematologica) reflects broader publishing trends.

For research policymakers: The geographic concentration of MDS research—with the US producing nearly one-third of publications—raises questions about global equity in research capacity and access to clinical trials.

4.4 Methodological Considerations and Limitations

Strengths: This study constitutes the most comprehensive bibliometric evaluation of MDS research to date, distinguished by its 40-year temporal scope capturing the field's full intellectual evolution, a dual-database strategy (WoSCC and Scopus) to maximize coverage, a multi-tool analytical framework (CiteSpace, VOSviewer, and Bibliometrix) providing complementary insights, integration of the most recent 2024–2025 literature—including imetelstat approval—and the application of rigorous data cleaning and author disambiguation procedures to enhance analytical accuracy.

Limitations: Several limitations should be acknowledged. Although dual-database searching was performed, neither Web of Science nor Scopus ensures complete coverage of all MDS literature, leading to potential underrepresentation of non-indexed journals, non-English publications, pre-1985 studies, and conference abstracts. Citation time bias may underestimate the impact of recently published studies (2023–2025), including pivotal trials, although keyword burst detection partially mitigates this effect. Author name ambiguity, despite disambiguation efforts, may have resulted in misattribution due to common surnames or institutional changes. Furthermore, bibliometric methods quantify publication and citation patterns but cannot evaluate methodological rigor, replicate in-depth qualitative historical analysis, or capture tacit knowledge such as unsuccessful therapeutic approaches. Finally, given the biological continuum between MDS and AML, some overlap with AML-focused studies may persist despite prioritizing MDS-centered publications in the search strategy.

4.5 Future Research Directions

This bibliometric analysis highlights several priorities for future research, including subgroup-specific evaluations aligned with increasingly genotype-defined MDS entities (e.g., SF3B1-, TP53-, and IDH1/2-mutated subtypes) to delineate distinct research trajectories and collaboration networks; comparative bibliometric studies across related myeloid malignancies to clarify cross-disciplinary knowledge transfer; incorporation of altmetrics to assess broader societal and clinical impact beyond traditional citations; integration of funding data to explore the relationship between research investment and scientific productivity; and development of a periodically updated "living" bibliometric model to monitor emerging trends and evolving therapeutic paradigms in real time.

5. CONCLUSION

This 40-year bibliometric analysis maps the intellectual journey of MDS research from morphological description to molecularly guided precision medicine. The field has evolved through four distinct eras, each marked by paradigm-shifting discoveries: the establishment of classification and prognostic frameworks (1985–2000), the hypomethylating agent revolution (2000–2010), the genomic landscape discovery (2010–2020), and the current era of targeted therapy and molecular subclassification (2020–present).

The United States remains a global leader in cancer research, highlighted by premier institutions such as the MD Anderson Cancer Center and the Fred Hutchinson Cancer Research Center. The journal Blood serves as a key publication. Recent advancements in treatments like luspatercept and imetelstat rejuvenate optimism in lower-risk MDS drug development. New areas of focus include specific molecular subgroups, immunotherapy, clonal hematopoiesis as a pre-disease state, and the integration of real-world evidence.

As MDS research approaches its fifth decade since the FAB classification, advancements in molecular understanding, targeted therapies, and international collaboration are expected to enhance patient outcomes. This bibliometric roadmap serves as an evidence-based guide for investigators, clinicians, and policymakers in navigating the field's history and future directions.

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