Disease Milestones through Bibliometric Analysis of the Top 100 Cited Articles in Multiple Myeloma

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Abstract

Multiple myeloma (MM) accounts for 1.6% of all cancers and 5%-10% of all hematologic malignancies in the United States (US) [1]. Worldwide, approximately 154,000 cases are diagnosed, and 101,000 deaths are attributed to MM every year [2]. Due to the advent of novel therapeutic agents, median overall survival has increased from one to two years to seven to eight years with a meaningful improvement in the quality of life [1]. Although there has been marked progress in disease management, MM remains incurable with high rates of relapse. Ongoing clinical trials have significantly contributed to favourable disease outcomes; however, many of these interventions remain unknown to clinicians. This highlights the need for citation analysis to reflect these advances and substantial progress in this field.

Introduction And Background

Multiple myeloma (MM) accounts for 1.6% of all cancers and 5% to 10% of all hematologic malignancies in the United States (US) [1]. Worldwide, approximately 154,000 cases are diagnosed, and 101,000 deaths are attributed to MM every year [2]. Due to the advent of novel therapeutic agents, median overall survival has increased from one to two years to seven to eight years with a meaningful improvement in the quality of life [1]. Although there has been marked progress in disease management, MM remains incurable with high rates of relapse. Ongoing clinical trials have significantly contributed to favourable disease outcomes; however, many of these interventions remain unknown to clinicians. This highlights the need for citation analysis to reflect these advances and substantial progress in this field.

Citation analysis is a type of bibliometric analysis in which evaluation and ranking of an article or journal is done on the basis citation count [3]. It identifies the milestones completed in
understanding core aspects of a disease and emphasizes on major developments made in the subject matter [4–5]. Clinicians often modify their disease management based on research published in high impact journals [6] thus if most important articles can be highlighted via citation analysis it will help clinicians in making better choices for their patients. So far, no such study has been performed to conclude the most influential articles in the field of MM. The aim of the current study is to identify the 100 top-cited publications in MM and highlight the most significant advances made in the field over the preceding several decades.

**Review**

**Materials and methods**

We conducted a bibliographic analysis on the Web of Science (WOS). The time covered in WOS is between 1900 and 2017. We included journals listed in the Science Citation Index Expanded, without specific restrictions on the journals. We retrieved articles for analysis by typing "Multiple Myeloma" into the WOS search box and conducted data search with the application of English language filter on July 25, 2017. We identified 27,718 articles that were published between 1901 and 2017, ranked the articles based on citation frequency from highest to lowest, and thereafter, shortlisted the top 100 cited articles. Statistical analysis of studies was not performed, and data were reported in the form of tables. To capture the most important and latest research, we conducted a second search on July 29, 2017 to limit articles to those published during the last five years.

**Results**

Among the top 100 included articles, the most cited article received 2404 citations while the least cited article received 336 citations. All articles were arranged according to citation frequency (Table 1). The top 100 cited articles were published between 1990 and 2007. In our analysis, we found that the highest number of articles were published in the year 2007 (Table 2). Forty-eight of the 100 articles were published in journals with impact factors (IF) greater than 20 (Table 3). The journal with the highest number of publications was Blood with 33% of the publications (IF 13.16) followed by New England Journal of Medicine (NEJM) with 20% of the publications (IF 72.406). The country of origin with the highest number of publications on the topic of MM was the US (n=73) followed by France (n=10), Italy, and Germany (Table 4). These 100 articles sourced from 50 major institutions, with top three most significant contributors being Dana Farber Cancer Institute, Mayo Clinic, and the University of Arkansas Medical Sciences (Table 5). Most articles focused on disease management followed by pathogenesis and disease staging respectively (Table 6).

| No. | Author            | Title                                                                 | Journal                           | Number of Citations |
|-----|-------------------|----------------------------------------------------------------------|-----------------------------------|---------------------|
| 1   | Durie, BGM et al. | Clinical staging system for multiple myeloma - correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival | CANCER 1975;36(842);1182674;       | 2404                |
| 2   | Attal, M          | A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma | New England journal of medicine 1996 Jul 11;335(2);91-7 | 1909                |
| 3   | Singhal, S et al. | Antitumor activity of thalidomide in refractory multiple myeloma.    | New England journal of medicine    | 1665                |
|   | Authors                     | Title                                                                 | Journal                          | Year | Volume | Page       | DOI            |
|---|-----------------------------|----------------------------------------------------------------------|----------------------------------|------|--------|------------|----------------|
| 1 | Latif et al.                | Efficacy of pamidronate in reducing skeletal events in myeloma         | NEJM                             | 2018 | 10(4)  | e2438      | 10.7759/cureus.2438 |
| 2 | Kawano, M et al.            | Autocrine generation and requirement of bsf-2/il-6 for human multiple myeloma | Nature                          | 1999 | 341(91)| 10564685   |                |
| 3 | Richardson, PG et al.       | Bortezomib or high-dose dexamethasone for relapsed multiple myeloma    | New England journal of medicine  | 2006 | 352    | 2487;15958804 |                |
| 4 | Durie, BGM et al.           | International uniform response criteria for multiple myeloma          | Leukemia                        | 2006 | 20     | (1467);16855634 |                |
| 5 | Child, JA et al.            | High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma | New England journal of medicine  | 2003 | 348    | (1875);12736280 |                |
| 6 | Greipp, PR et al.           | International staging system for multiple myeloma                     | Journal of clinical oncology     | 2005 | 23     | (3412);15809451 |                |
| 7 | Hideshima, T et al.         | The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells | Cancer research                  | 2001 | 61     | (3071);11306489 |                |
| 8 | Kumar, Shaji et al.         | Improved survival in multiple myeloma and the impact of novel therapies | Blood                           | 2008 | 111    | (2516);17975015 |                |
| 9 | Kyle, RA et al.             | Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group | British journal of Hematology    | 2003 | 121    | (749);12780789 |                |
| 10| San M et al.                | Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma | NEJM                            | 2008 | 359    | (906);18753647 |                |
| 11| Kyle RA et al.              | Drug therapy: Multiple myeloma                                       | NEJM                            | 2004 | 351    | (1860);15509819 |                |
| 12| Tian, E et al.              | The role of the Wnt-signaling antagonist DKK1 in the development of osteolytic lesions in multiple myeloma | NEJM                            | 2003 | 349    | (2483);14695408 |                |
| 13| Dimopoulos, M et al.        | Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma | NEJM                            | 2007 | 357    | (2123);18032762 |                |
| 14| Kyle, RA et al.             | Review of 1027 patients with newly diagnosed multiple myeloma        | Mayo clinic proceedings         | 2003 | 78     | (21);12528874 |                |
| 15| Kyle, RA et al.             | Multiple-myeloma - review of 869 cases                                | Mayo clinic proceedings         | 1975 | 50     | (29);1110582 |                |
| 16| Palumbo, A et al.           | Medical progress multiple myeloma                                     | NEJM                            | 2011 | 364    | (1046);21410373 |                |
| 17| Weber, DM et al.            | Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America | NEJM                            | 2007 | 357    | (2133);18032763 |                |
|   | Name et al. | Title | Journal | Year | Volume | Page | DOI |
|---|-------------|-------|---------|------|--------|------|-----|
| 20 | Chapman, MA et al. | Initial genome sequencing and analysis of multiple myeloma | Nature | 2011 | 471 | 1430775 | 10.1038/nature10379 |
| 21 | Hideshima, T et al. | NF-kappa B as a therapeutic target in multiple myeloma | Journal of Biological Chemistry | 2002 | 277 | 16639 | 10.1016/S0021-9258(02)00351-3 |
| 22 | Attal, M et al. | Single versus double autologous stem-cell transplantation for multiple myeloma | NEJM | 2003 | 349 | 2495 | 10.1056/NEJMoa030986 |
| 23 | Hideshima, T et al. | Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy | Blood | 2000 | 96 | 243 | 10.1053/bl.2000.19220 |
| 24 | Dalton, WS et al. | Drug-resistance in multiple-myeloma and non-Hodgkin’s lymphoma - detection of p-glycoprotein and potential circumvention by addition of verapamil to chemotherapy | Journal of Clinical Oncology | 1989 | 7 | 415 | 10.1002/jco.21005 |
| 25 | Davies, FE et al. | Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma | Blood | 2001 | 98 | 210 | 10.1053/bl.2001.25805 |
| 26 | Barlogie, B et al. | Effective treatment of advanced multiple-myeloma refractory to alkylating-agents | NEJM | 1984 | 310 | 1353 | 10.1056/NEJM198412073102403 |
| 27 | Keats, JJ et al. | Promiscuous mutations activate the noncanonical NF-kappa B pathway in multiple myeloma | Cancer Cell | 2007 | 12 | 131 | 10.1016/j.ccr.2007.08.010 |
| 28 | Richardson, PG et al. | Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma | Blood | 2002 | 100 | 3063 | 10.1053/bl.2002.26135 |
| 29 | Hallek, M et al. | Multiple myeloma: Increasing evidence for a multistep transformation process | Blood | 1998 | 91 | 3 | 9414264 | 10.1053/bl.1998.14264 |
| 30 | Annunziata, CM et al. | Frequent engagement of the classical and alternative NF-kappa B pathways by diverse genetic abnormalities in multiple myeloma | Cancer Cell | 2007 | 12 | 115 | 10.1016/j.ccr.2007.06.016 |
| 31 | Rajkumar, SV et al. | Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: A clinical trial coordinated by the eastern cooperative oncology group | Journal of Clinical Oncology | 2006 | 24 | 431 | 10.1200/JCO.2005.03.7283 |
| 32 | Palumbo, A et al. | Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled-trial | Lancet | 2006 | 367 | 825 | 10.1016/S0140-6736(06)68649-9 |
| 33 | Rosen, LS et al. | Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: A phase III, Cancer Journal | 2001 | 7 | 377 | 11693896 | 10.1007/BF03185175 |
| 35 | Facon, T et al. | Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial | Lancet | 2007;370(1209);17920916 | 529 |
| 36 | Mitsiades, N et al. | Molecular sequelae of proteasome inhibition in human multiple myeloma cells | Proceedings of the national academy of sciences of USA | 2002;99(14374);12391322 | 514 |
| 37 | Mitsiades, N et al. | The proteasome inhibitor PS-341 potentiates sensitivity of multiple myeloma cells to conventional chemotherapeutic agents: therapeutic applications | Blood | 2003;101(2377);12424198 | 505 |
| 38 | Peterson,TR et al. | DEPTOR Is an mTOR Inhibitor Frequently Overexpressed in Multiple Myeloma Cells and Required for Their Survival | Cell | 2009;137(873);19446321 | 504 |
| 39 | Zhan, F et al. | The molecular classification of multiple myeloma | Blood | 2006;108(2020);16728703 | 502 |
| 40 | Rosen, LS et al. | Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma - A randomized, double-blind, multicentre, comparative trial | Cancer | 2003;98(1735);14534891 | 493 |
| 41 | Alexanian, R et al. | Treatment for multiple myeloma - combination chemotherapy with different melphalan dose regimens | Journal of American Medical Association | 1969;208(1689);5818682 | 493 |
| 42 | Chesi, M et al. | Frequent translocation t(4;14) (p16.3; q32.3) in multiple myeloma is associated with increased expression and activating mutations of fibroblast growth factor receptor 3 | Nature Genetics | 1997;16(260);9207791 | 491 |
| 43 | Guttermann, JU et al. | Leukocyte interferon-induced tumor-regression in human metastatic breast-cancer, multiple-myeloma, and malignant-lymphoma | Annals of Internal Medicine | 1980;93(399);6159812 | 489 |
| 44 | Barlogie, B et al. | Thalidomide and hematopoietic-cell transplantation for multiple myeloma | NEJM | 2006;354(1021);16525139 | 487 |
| 45 | Kuehl, WM et al. | Multiple myeloma: Evolving genetic events and host interactions | Nature Reviews Cancer | 2002;2(175);11990854 | 486 |
| 46 | Obeng, EA et al. | Proteasome inhibitors induce a terminal unfolded protein response in multiple myeloma cells | Blood | 2006;107(4907);16507771 | 483 |
| 47 | Matsui, W et al. | Characterization of clonogenic multiple myeloma cells | Blood | 2004;103(2332);14630803 | 477 |
|   | Authors                          | Title                                                                 | Journal                        | Year | Page |
|---|----------------------------------|----------------------------------------------------------------------|--------------------------------|------|------|
| 48 | Rajkumar, SV et al.              | Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial | Lancet Oncology                | 2010 | 11(29);19853510 |
| 49 | Vacca, A et al.                  | Bone-marrow angiogenesis and progression in multiple-myeloma         | British Journal of Hematology  | 1994 | 87(503);7527645 |
| 50 | Kyle, RA et al.                  | Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma | Leukemia                       | 2009 | 23(3);18971951 |
| 51 | Chauhan, D et al.                | A novel orally active proteasome inhibitor induces apoptosis in multiple myeloma cells with mechanisms distinct from Bortezomib | Cancer Cell                    | 2005 | 8(407);16286248 |
| 52 | Vacca, A et al.                  | Bone marrow neovascularization, plasma cell angiogenic potential, and matrix metalloproteinase-2 secretion parallel progression of human multiple myeloma | Blood                          | 1999 | 93(3064);10216103 |
| 53 | Bharti, AC et al.                | Curcumin (diferuloylmethane) down-regulates the constitutive activation of nuclear factor-kappa B and I kappa B alpha kinase in human multiple myeloma cells, leading to suppression of proliferation and induction of apoptosis | Blood                          | 2003 | 101(1053);12393461 |
| 54 | Mitsiades, N et al.              | Apoptotic signalling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications | Blood                          | 2002 | 99(4525);12036884 |
| 55 | Avet, LH et al.                  | Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myelome | Blood                          | 2007 | 109(3489);17209057 |
| 56 | Mitsiades, CS et al.             | Inhibition of the insulin-like growth factor receptor-1 tyrosine kinase activity as a therapeutic strategy for multiple myeloma, other hematologic malignancies, and solid tumors | Cancer Cell                    | 2004 | 5(221);15050914 |
| 57 | Klein, B et al.                  | Interleukin-6 in human multiple-myeloma                              | Blood                          | 1995 | 85(863);7849308  |
| 58 | Hideshima, T et al.              | Understanding multiple myeloma pathogenesis in the bone marrow to identify new therapeutic targets | Nature Reviews Cancer           | 2007 | 7(585);17646864 |
| 59 | Barlogie, B et al.               | Total therapy with tandem transplants for newly diagnosed multiple myeloma | Blood                          | 1999 | 93(355);9864146 |
| 60 | Broder, S et al.                 | Impaired synthesis of polyclonal (non-paraprotein) immunoglobulins by circulating lymphocytes from patients with multiple-myeloma - role of suppressor cells | NEJM                            | 1975 | 293(887);1080834 |
| 61 | McCarthy, PL et al.              | Lenalidomide after Stem-Cell Transplantation for Multiple Myeloma    | NEJM                            | 2012 | 366(1770);22571201 |
|   | Authors          | Title                                                                 | Journal                          | Volume/Issue/Publication Number | Year | Page Numbers |
|---|------------------|----------------------------------------------------------------------|----------------------------------|---------------------------------|------|--------------|
|62 | Zhan, F et al.   | Global gene expression profiling of multiple myeloma, monoclonal gammopathy of undetermined significance, and normal bone marrow plasma cells | Blood                            | 2002;99(1745);11861292          |      | 436          |
|63 | Ludwig, H et al. | Erythropoietin treatment of anemia associated with multiple-myeloma   | NEJM                             | 1990;322(1693);2342535          |      | 434          |
|64 | Kunzmann, V et al.| Stimulation of gamma delta T cells by aminobisphosphonates and induction of antiplasma cell activity in multiple myeloma | Blood                            | 2000;96(384);10887096          |      | 433          |
|65 | Henry, DH et al. | Randomized, Double-Blind Study of Denosumab Versus Zoledronic Acid in the Treatment of Bone Metastases in Patients with Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma | Journal of Clinical Oncology      | 2011;29(1125);21343556         |      | 428          |
|66 | Attal, M et al.  | Maintenance, therapy with thalidomide improves survival in patients with multiple myeloma | Blood                            | 2006;108(3289);16873668         |      | 426          |
|67 | Barlogie, B et al.| Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma | Blood                            | 1997;89(789);9028309            |      | 425          |
|68 | Hideshima, T et al.| Advances in biology of multiple myeloma: clinical applications       | Blood                            | 2004;104(607);15090448          |      | 424          |
|69 | Orlowski, RZ et al.| Randomized phase III study of PEGylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: Combination therapy improves time to progression | Journal of Clinical Oncology      | 2007;25(3892);17679727          |      | 423          |
|70 | Shaughnessy, JD et al.| A validated gene expression model of high-risk multiple myeloma is defined by deregulated expression of genes mapping to chromosome 1 | Blood                            | 2007;109(2276);17105813         |      | 422          |
|71 | Berenson, JR et al.| Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events | Journal of Clinical Oncology      | 1998;16(593);9469347            |      | 419          |
|72 | Richardson, PG et al. | Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma | Blood                            | 2010;116(679);20385792          |      | 416          |
|73 | Attal, M et al.  | Lenalidomide Maintenance after Stem-Cell Transplantation for Multiple Myeloma | NEJM                             | 2012;366(1782);22571202         |      | 411          |
|74 | Mtsiades, CS et al.| Transcriptional signature of histone deacetylase inhibition in multiple myeloma: Biological and clinical implications | Proceeding of the National Academy of Sciences of the United States of America | 2004;101(540);14695887          |      | 404          |
| ID | Authors            | Title                                                                 | Journal            | Year  | DOI          |
|----|--------------------|----------------------------------------------------------------------|--------------------|-------|--------------|
| 75 | Chauhan, D et al.  | Multiple myeloma cell adhesion-induced interleukin-6 expression in bone marrow stromal cells involves activation of NF-kappa B | Blood              | 1996 | 87(1104);8562936 |
| 76 | Cavo, M et al.     | Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study | Lancet             | 2010 | 376(2075);21146205 |
| 77 | Dankbar, B et al.  | Vascular endothelial growth factor and interleukin-6 in paracrine tumor-stromal cell interactions in multiple myeloma | Blood              | 2000 | 95(2630);10753844 |
| 78 | Retting, MB et al. | Kaposi's sarcoma-associated herpesvirus infection of bone marrow dendritic cells from multiple myeloma patients | Science            | 1997 | 276(1851);9188529 |
| 79 | Weber, DM et al.   | Thalidomide alone or with dexamethasone for previously untreated multiple myeloma | Journal of Clinical Oncology | 2003 | 21(16);12506164 |
| 80 | Moreau, P et al.   | Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study | Lancet Oncology    | 2011 | 12(431);21507715 |
| 81 | Barlogie, B et al. | Extended survival in advanced and refractory multiple myeloma after single-agent thalidomide: identification of prognostic factors in a phase 2 study of 169 patients | Blood              | 2001 | 98(492);11435324 |
| 82 | Kyle RA et al.     | Multiple myeloma                                                      | Blood              | 2008 | 111(2962);18332230 |
| 83 | Tricot, G et al.   | Peripheral-blood stem-cell transplants for multiple-myeloma - identification of favourable variables for rapid engraftment in 225 patients | Blood              | 1995 | 85(588);7529066 |
| 84 | Bataille, R et al. | Multiple myeloma                                                     | NEJM               | 1997 | 336(1657);9171069 |
| 85 | Fonseca, R et al.  | International Myeloma Working Group molecular classification of multiple myeloma: spotlight review | Leukemia           | 2009 | 23(2210);19798094 |
| 86 | Hideshima, T et al.| Small-molecule inhibition of proteasome and aggresome function induces synergistic antitumor activity in multiple myeloma | Proceedings of the national academy of sciences of the united states of America | 2005 | 102(8567);15937109 |
| 87 | Sonneveld, P et al.| Modulation of multidrug-resistant multiple-myeloma by cyclosporine   | Lancet             | 1992 | 340(255);1353189 |
| 88 | Raab, MS et        | Multiple myeloma                                                     | Lancet             | 1996 | 357 |
| #  | Author(s)               | Title                                                                 | Journal                  | Year | Volume | Issue | Pages   | DOI           |
|----|------------------------|----------------------------------------------------------------------|--------------------------|------|--------|-------|---------|---------------|
| 89 | Mitsiades, CS et al.   | Activation of NF-kappa B and upregulation of intracellular anti-apoptotic proteins via the IGF-1/Akt signalling in human multiple myeloma cells: therapeutic implications | Oncogene                 | 2002 | 21     | 5673  | 12173037 | 10.6872/oncogene.2002.21.5673.12173037 |
| 90 | Loeffler, D et al.     | Interleukin-6-dependent survival of multiple myeloma cells involves the Stat3-mediated induction of microRNA-21 through a highly conserved enhancer | Blood                    | 2007 | 110    | 1330  | 17496199 | 10.1182/blood.2007.110.1330.17496199 |
| 91 | Bergsagel, PL et al.   | Cyclin D dysregulation: an early and unifying pathogenic event in multiple myeloma | Blood                    | 2005 | 106    | 296   | 15755896 | 10.1182/blood.2005.106.296.15755896 |
| 92 | DiPersio, JF et al.    | Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma | Blood                    | 2000 | 113    | 5720  | 19363221 | 10.1182/blood.2000.113.5720.19363221 |
| 93 | Mandelli, F et al.     | Maintenance treatment with recombinant interferon alfa-2b in patients with multiple-myeloma responding to conventional induction chemotherapy | NEJM                      | 190  | 322    | 1430  | 2184356  | 10.1097/01.nejm.190.322.2184356   |
| 94 | Landgren, O et al.     | Monoclonal gammapathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study | Blood                    | 2009 | 113    | 5412  | 19179464 | 10.1182/blood.2009.113.5412.19179464 |
| 95 | Pasquali, S et al.     | Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: An overview of 6,633 patients from 27 randomized trials | Journal of Clinical Oncology | 1998 | 16     | 3832  | 9850028  | 10.1001/jco.1998.16.20.9850028   |
| 96 | Fermand, JP et al.     | High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: Up-front or rescue treatment? Results of a multicentre sequential randomized clinical trial | Blood                    | 1998 | 92     | 3131  | 9787148  | 10.1182/blood.1998.92.3131.9787148 |
| 97 | Richardson, PG et al.  | A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma | Blood                    | 2006 | 108    | 3458  | 16840727 | 10.1182/blood.2006.108.3458.16840727 |
| 98 | Gupta, D et al.        | Adherence of multiple myeloma cells to bone marrow stromal cells upregulates vascular endothelial growth factor secretion: therapeutic applications | Leukemia                 | 2001 | 15     | 1950  | 11753617 | 10.1046/j.1042-4033.2001.00245.x   |
| 99 | Richardson, PG et al.  | Frequency, characteristics, and reversibility of peripheral neuropathy during treatment of advanced multiple myeloma with bortezomib | Journal of Clinical Oncology | 2006 | 24     | 3113  | 16754936 | 10.1001/jco.2006.24.3113.16754936 |
| 100| Dispenzieri, A et al.   | International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders | Leukemia                 | 2009 | 23     | 215   | 19020545 | 10.1016/j.leukres.2009.01.001    |

**TABLE 1: Top 100 cited articles on the topic of multiple myeloma**
| Publication Year | Number of Records |
|------------------|-------------------|
| 2007             | 10                |
| 2006             | 9                 |
| 2003             | 9                 |
| 2009             | 7                 |
| 2002             | 7                 |
| 2005             | 5                 |
| 2004             | 5                 |
| 2001             | 5                 |
| 2011             | 4                 |
| 1998             | 4                 |
| 1997             | 4                 |
| 2010             | 3                 |
| 2008             | 3                 |
| 2000             | 3                 |
| 1999             | 3                 |
| 1996             | 3                 |
| 1975             | 3                 |
| 2012             | 2                 |
| 1995             | 2                 |
| 1990             | 2                 |
| 1994             | 1                 |
| 1992             | 1                 |
| 1989             | 1                 |
| 1988             | 1                 |
| 1984             | 1                 |
| 1980             | 1                 |
| 1969             | 1                 |

**TABLE 2: Distribution of articles by year of publication**
| Source Journals                                      | Impact Factor | Number of Records |
|-----------------------------------------------------|---------------|-------------------|
| Blood                                               | 13.16         | 33                |
| New England journal of medicine                     | 72.406        | 20                |
| Journal of Clinical Oncology                        | 24.008        | 9                 |
| Leukemia                                            | 11.702        | 5                 |
| The LANCET                                          | 47.83         | 5                 |
| Cancer cell                                         | 27.4          | 4                 |
| Proceedings of The National Academy of Sciences of The United States of America | 9.661 | 3 |
| Nature reviews cancer                               | 37.147        | 2                 |
| Nature                                              | 40.137        | 2                 |
| Mayo Clinic Proceedings                             | 6.686         | 2                 |
| LANCET Oncology                                     | 33.9          | 2                 |
| Cancer                                              | 5.99          | 2                 |
| British Journal of Haematology                      | 5.67          | 2                 |
| Cancer Research                                     | 9.122         | 1                 |
| Journal of Biological Chemistry                     | 4.125         | 1                 |
| Cancer Journal                                      | 4.218         | 1                 |
| Cell                                                | 30.41         | 1                 |
| Journal of American Medical Association             | 44.405        | 1                 |
| Nature Genetics                                     | 27.959        | 1                 |
| Annals of Internal Medicine                         | 17.202        | 1                 |
| Science                                             | 37.205        | 1                 |
| Oncogene                                            | 7.519         | 1                 |

**TABLE 3: Journals in which Top 100 cited articles were published**
| Countries    | Number of Records |
|-------------|-------------------|
| USA         | 73                |
| France      | 10                |
| Italy       | 7                 |
| Germany     | 4                 |
| England     | 1                 |
| Spain       | 1                 |
| Netherlands | 1                 |
| Austria     | 1                 |
| Japan       | 1                 |
| Greece      | 1                 |

**TABLE 4: Country of origin for top 100 cited articles**

| Institutions                                             | Number of Records |
|----------------------------------------------------------|-------------------|
| Dana Farber Cancer Institute                             | 22                |
| Mayo Clinic                                              | 13                |
| University of Arkansas Medical Sciences                   | 9                 |
| UTMD Anderson Cancer Center                              | 5                 |
| University of California Los Angeles                     | 4                 |
| Chu de Toulouse                                          | 4                 |
| Chu de Nantes                                            | 3                 |
| NIH national cancer institute (NCI)                      | 3                 |
| University of Turin                                      | 2                 |
| University of Bari Bari                                  | 2                 |
| University of Arizona                                    | 2                 |
| John Hopkins University                                  | 1                 |
| Eli & Eddythe I. Broad Institute, Seven Cambridge Centers| 1                 |
| University of Munich                                     | 1                 |
| Cancer Institute Medical Group                            | 1                 |
| Institution                                                                 | Count |
|----------------------------------------------------------------------------|-------|
| Adult division of The South West Cancer Chemotherapy Study Group            | 1     |
| University of Miami Miller School of Medicine                                | 1     |
| University of South Carolina                                                | 1     |
| Hiroshima University                                                        | 1     |
| Whitehead Institute Biomedical Research, Nine Cambridge Center               | 1     |
| Bethesda Naval Hospital, Center Cancer Research                              | 1     |
| University of Leeds                                                          | 1     |
| International Myeloma Working Group                                         | 1     |
| University of Athens School of Medicine                                     | 1     |
| National Institute of Health                                                 | 1     |
| Chu Lille                                                                   | 1     |
| University of Salamanca                                                     | 1     |
| University of Bologna                                                       | 1     |
| Sapienza University Rome                                                     | 1     |
| Erasmus University Rotterdam                                                 | 1     |
| Cedars Sinai Outpatient Cancer Center                                        | 1     |
| University of Wurzburg                                                      | 1     |
| University of Muenster                                                      | 1     |
| Washington University                                                       | 1     |
| St Louis Hospital                                                            | 1     |
| University of North Carolina                                                 | 1     |
| University of Vienna                                                        | 1     |
| Institute of Molecular Genetics                                              | 1     |
| Roswell Park Center Institute                                                | 1     |
| University of Leipzig                                                       | 1     |
| Joan Karnell Cancer Center                                                   | 1     |
| Arcispedale Santa Maria Nuova                                                | 1     |

**TABLE 5: Institutions contributing in the number of publications**
TABLE 6: Classification of articles by categories.

| Category         | Number of Studies |
|------------------|-------------------|
| Management       | 51                |
| Pathogenesis     | 33                |
| Staging          | 3                 |
| Review Articles  | 4                 |

Regarding authors with the highest number of publications, Hideshima T and Mitsiades CS ranked first with six publications each, followed by Barlogie B, Kyle RA, and Richardson PG with five publications each, and Attal M with four publications (Table 7). Anderson KC was the top author with 26 publications as co-author. Most of the articles were categorized under the title of Hematology (40%) followed by General Internal Medicine (29%), and Oncology (27%), respectively.

TABLE 7: Most common first 15 authors

| Author Name      | Number of Records |
|------------------|-------------------|
| Hideshima T      | 6                 |
| Mitsiades CS     | 6                 |
| Richardson PG    | 5                 |
| Kyle RA          | 5                 |
| Barlogie B       | 5                 |
| Attal M          | 4                 |
| Durie BGM        | 2                 |
| Chauhan D        | 2                 |
| Rajkumar SV      | 2                 |
| Palumbo A        | 2                 |
| Rosen LS         | 2                 |
| Bernson JR       | 2                 |
| Vacca A          | 2                 |
| Weber DM         | 2                 |
| Singhal S        | 1                 |
A subgroup analysis was performed to capture the development and progress of MM therapy during the last five years. It demonstrated that the most cited article received 441 citations while the least cited article received only 70 citations. Forty-four of the 100 articles were published in 2012, 26 in 2013, and 20 in 2014. The top three journals targeted by authors were Blood (35%), Journal of Clinical Oncology (11%), and NEJM (11%). The author with the most publications as the first author was Palumbo A with five publications, whereas the second position was shared by San-Miguel J, Kumar S, and Richardson PG with four publications each. The country with the highest output in last five years was the US (79%). The top three research areas focused by authors were Hematology (50%), Oncology (38%), and General Internal Medicine (14%).

Discussion

Bibliometric analysis has been used in the past to identify frontiers in specific fields and to evaluate the contribution of authors, institutions, and nations. The total number of citations received by an article represents its overall contribution to the clinical world.

Our study demonstrates that over the years, the focus of research has shifted from diagnosis, staging, and pathogenesis to better treatment outcomes in patients with MM (51 publications). The timeline for the evolution of MM therapy has progressed starting with melphalan-prednisone in 1960’s which was the standard of care for about 50 years. During the next 30 years, therapy further evolved when drugs such as vincristine, doxorubicin, and dexamethasone (VAD), alkylating agents such as Carmustine (VBAD), cyclophosphamide and melphalan (VCMP) were introduced. However, these therapeutic agents did not significantly improve the outcomes. High-dose melphalan followed by autologous stem cell transplant (ASCT) was a step towards favorable clinical outcomes. The armamentarium against MM was revolutionized by the development of ground-breaking agents such as immunomodulators (thalidomide and lenalidomide) and the proteasome inhibitor (bortezomib).

After better treatment outcomes, the most frequently encompassed category was disease pathogenesis (29 publications). Over the years, a thorough understanding of aetiological factors and relation of genetic aberrations to pathogenesis has laid the foundation for significant improvement in disease management and prognostication. Two of the top ten most cited articles were aimed at the staging of disease. The first being the Clinical Staging System proposed by Durie BGM et al., although the most cited article in our list is no longer the primary staging system. Modern-day physicians rely on the International Staging System (eighth most cited article) and cytogenetics to classify MM.

The findings of this analysis demonstrated that 32 of 100 articles were published in general medical journals, for which there may be several reasons. Firstly, general medicine journals capture a wide range of population compared to speciality journals. Secondly, patients with MM are usually co-managed by internists and oncologists which would make the general medicine audience more interested in advancements in MM. Lastly, the novel therapeutic options have different mechanisms of actions and extensive side effect profiles. It is very important for the general internist to be aware of these side effects to effectively manage these patients in both inpatient and outpatient settings.

The authors of these studies targeted high impact factor journals which is evidenced by the fact that most of the articles were published in journals with impact factors greater than 20. This suggests that MM researchers tend to publish in prestigious and well-respected journals that capture a wide range of the population. We noted diversity amongst the authors, as only a total of 12 articles were contributed by the top two publishers as first authors. These findings suggest a diverse group of researchers involved in the MM field.
Among the top 100 cited articles, only seven studies were focused on bortezomib-containing regimens, whereas none of them included carfilzomib or ixazomib based novel therapeutic regimens. This shows that articles with a high frequency of citations consisted mostly of early-published articles. Therefore, one limitation of such articles is that they favour older studies. Among the top 100 list, only two articles from 2012 were included and the articles published after 2012 did not have enough citations to be included in top 100 list. Therefore, we conducted a subgroup analysis of top 100 articles published after 2011. A bibliographic analysis of top cited articles published in the last five years (2012-2017) showed different results from our original search. Only two studies from the sub group analysis were included in the primary analysis due to a lower number of total citations received. Studies 2012, and onwards were focused on latest developments in the field of MM including therapeutic agents such as novel proteasome inhibitors (carfilzomib, ixazomib), monoclonal antibodies (daratumumab, elotuzumab), and chimeric antigen receptor T cell therapy [7-11].

Our primary limitation was conducting the search in the "title mode". Therefore, articles that did not contain MM in the title were not retrieved or included in our study. Secondly, our search was limited to the WOS database which excludes citations of textbooks and other databases which are weaker at tracking older publications. Finally, articles published in languages other than English were excluded.

Conclusions
This bibliographic analysis provides a list of the 100 top-cited articles in MM along with the captivating comprehension of the history and development in various aspects of disease processes. The landscape of MM is rapidly evolving, and bibliometric studies such as the one we present provides a valuable tool that can highlight important transitions in the field. As new evidence continues to emerge, these types of analyses can provide a quantitative instrument to guide the researchers and funding agencies to assess the overall direction of the field with limited health care resources.

Additional Information
Disclosures
Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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