Journal of Multidisciplinary Healthcare

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Bibliometric and Bioinformatics Analysis of Renal Impairment in Multiple Myeloma: Trends and Research Hotspots, and Associated Genetic Pathways (2000-2023)

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Objective: This study aims to perform a bibliometric visual analysis and bioinformatics analysis to explore the research hotspots and trends of renal impairment in multiple myeloma, including the associated genes and signal pathways over the past two decades.

Methods: The Web of Science Core Collection database was utilized as the data source to retrieve literature on renal impairment in multiple myeloma from 2000 to 2023. The selected literature was analyzed using bibliometric and bioinformatics software, including Bibliometrix, VOSviewer 1.6.16, Citespace 5.7R5 and Cytoscape 3.7.1 software.

Results: This study encompassed 2152 articles that were published from 2000 to 2023, demonstrating an overall upward trend in annual publications and citations. Among the set of 27 core journals examined, the "CUREUS JOURNAL OF MEDICAL SCIENCE" exhibited the highest frequency of publications, while "BLOOD" emerged as the most frequently cited source. The global research on renal impairment in multiple myeloma research included contributions from 84 countries/regions, with the United States leading in terms of publication output and Mayo Clinic playing a central role in fostering inter-agency collaboration. Keywords such as "daratumumab", "carfilzomib", "diagnostic criteria" and "kidney biopsy" included recent research hotspots. We hypothesized that the TP53, AKT1, MYC, and CTNNB1 genes were involved in epithelial cell proliferation and the positive regulation of the MAPK cascade through signaling receptor activator activity, receptor-ligand interactions, and cytokine receptor binding. Simultaneously, they were implicated in renal impairment in multiple myeloma via the PI3K/Akt and MAPK signaling pathways.

Conclusion: This research employed bibliometric visual analysis and bioinformatics analysis to identify the current focus and future directions of studying renal impairment in multiple myeloma, as well as to explore the associated genes and signaling pathways. The management of renal impairment in patients with multiple myeloma has a significant impact on medical costs. Clinical physicians need to consider how to allocate medical resources reasonably, ensure that patients can receive necessary diagnosis and treatment, and explore cost-effective treatment options. The management of these patients requires interdisciplinary medical services, which should integrate basic and clinical research, especially the development of new treatment plans, to improve patients' quality of life and guide future treatment choices.

Keywords: multiple myeloma, renal impairment, bibliometrics, bioinformatics

Introduction

Multiple myeloma (MM) is a malignant condition characterized by the abnormal proliferation of clonal plasma cells, primarily affecting middle-aged and elderly individuals.[1,2] The distinctive biological features often lead to primary drug resistance or disease recurrence, rendering the condition currently incurable.[3] At the time of initial diagnosis, up to 50% of patients present with renal impairment (RI),[4] with 2–4% requiring dialysis.[5] The reported incidence of RI varies across the studies, potentially due to differing definitions, such as elevated serum creatinine levels exceeding 2 mg/dL or above

Received: 20 October 2024
Accepted: 12 February 2025
Published: 26 February 2025

the normal range, and reduced estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 or 40 mL/min/1.73 m^2. RI can significantly affect the overall survival (OS) in MM patients and increase the risk of premature mortality.[6] Previous studies have found the median OS of newly diagnosed MM (NDMM) patients with eGFR ≥40 mL/min and<40 mL/min after anti-myeloma treatment were 122 months and 43 months, respectively; Compared to MM patients without RI, newly diagnosed patients with RI have a relative risk of 1.07 for myeloma progression or death, while recurrent or refractory patients have a risk of 1.20. In addition, patients with RI who have undergone treatment will have better survival outcomes with improved renal function recovery. RI not only affects the immediate health status of MM patients, but also directly affects the selection and efficacy of treatment plans. Some patients rely on mechanical methods and hemodialysis, which greatly increases treatment costs and reduces their quality of life. Anemia, bone destruction, and hypercalcemia associated with MM can be relatively recovered through a brief treatment cycle. However, the treatment cycle for RI is relatively long, and some patients may not be able to leave dialysis. It is urgent to find more powerful and targeted treatment measures.

The causes of RI in MM patients are diverse. In the early stages of monoclonal gammopathy of undetermined significance (MGUS), patients may exhibit abnormally high M protein levels that generate excessive free light chains (FLCs), leading to accumulation in the kidneys, even in the absence of evident anemia, hypercalcemia, or osteolytic lesions. This condition can evolve into monoclonal gammopathy of renal significance (MGRS).[7] Furthermore, elevated M protein in patients with MM may deposit in the glomerulus, resulting in secondary amyloidosis, proteinuria, and renal dysfunction.[8] When the diagnosis is uncertain, a renal biopsy is essential for determining the specific pathological characteristics of RI. However, patient acceptance of renal biopsies tends to be low due to their invasive nature. Therefore, accurate identification of the type of MM-related RI is crucial for effective diagnosis and treatment.

Given the compromised renal function, treatment options these for patients are often limited, potentially leading to significant drug-related adverse events. Consequently, careful management of patients with RI is paramount. It is imperative not only to promptly and effectively reduce tumor burden and lower serum FLCs levels, but also to ensure adequate fluid intake. Achieving rapid hematologic remission is critical for mitigating renal damage.[9] In recent years, there have been ongoing changes in the evaluation and evidence-based recommendations for treatment strategies. The management of patients with RI requires continuous attention and further discussion.

Bibliometrics is a research methodology that focuses on analyzing the quantitative aspects of scientific literature.[10] This approach employs mathematical and statistical techniques to characterize, assess, and forecast the current state and future trajectories of science and technology. The primary outcome of bibliometric analysis is the generation of quantitative data regarding scholarly outputs. Over time, this methodology has expanded beyond its origins in library and information studies to include disciplines within both the natural and social sciences. In this study, bibliometrics was employed to investigate the distribution patterns and evolutionary trends in the literature concerning RI in patients with MM.

Materials and Methods

Data Sources and Retrieval Strategies

The study employed the Web of Science Core Collection (WOSCC) database for data retrieval. The search strategy was designed as follows: (((((((((TS=(multiple myeloma)) OR TS=(plasma cell myeloma)) OR TS=(myelomatosis)) OR TS=(kahler disease)) OR TS=(mutiple myeloma)) OR TS=(multiplex myeloma)) OR TS=(multiply myeloma)) OR TS=(multiple myelomas)) AND ((((((((((((((((TS=(renal insufficiency)) OR TS=(kidney dysfunction)) OR TS=(renal injury)) OR TS=(kidney disease)) OR TS=(renal dysfunction)) OR TS=(renal inadequacy)) OR TS=(renal failure)) OR TS=(renal impairment)) OR TS=(kidney insufficiency)) OR TS=(kidney injury)) OR TS=(renal damage)) OR TS=(renal impairment)) OR TS=(kidney damage)) OR TS=(renal injuries)) OR TS=(kidney damages)) OR TS=(kidney injure)), with a time span from 2000 to 2023, no language restrictions, and limited to articles only. To ensure accuracy and avoid any discrepancies caused by database updates, the search was completed on January 1, 2024. Two researchers (Jiang Huinan and Bai Xue) independently reviewed and excluded irrelevant literature by examining titles, abstracts, and full-text articles requiring further evaluation. After the initial screening, the inter-rater consistency rate for included literature

between the two researchers was 94%. In cases where disagreements arose, a third researcher participated in discussions to reach a final consensus on the number of included literatures.

Data Analysis

The distribution and trends of journals, countries, authors, citations, topics, and other variables were analyzed utilizing the R language-based data analysis tool, Bibliometrix. Visual representations, including lollipop charts, line graphs, and world maps, were generated to enhance data visualization. Furthermore, literature coupling analysis and keyword co-occurrence analysis were conducted using VOSviewer version 1.6.16, while journal double-image overlay charts and co-citation analysis were produced using Citespace version 5.7R5.

The GeneCards database (https://www.genecards.org/) and the Online Mendelian Inheritance in Man (OMIM) database (https://omim.org/) were utilized as primary sources for human genetic information. Searches were conducted using the terms "multiple myeloma" and "renal impairment", followed by the download of relevant gene data. The acquired gene dataset was then imported into Cytoscape version 3.7.1 to facilitate the construction of a visual network diagram of the target genes. Subsequently, intersecting genes related to "multiple myeloma" and "renal impairment" were imported into the STRING database, with species restricted "Homo sapiens". Network data with a Combined score of $\geq$ 0.9 from STRING were utilized in Cytoscape to establish a protein-protein interaction (PPI) network and identify core genes. The "clusterProfiler" package in R was employed to perform GO, KEGG, and Disease Ontology (DO) enrichment analysis for the intersection genes, specifying the species as 'Homo sapiens'. The GO function enrichment analysis includes biological processes (BP), cellular components (CC), and molecular functions (MF), while KEGG pathway enrichment analysis explores relevant signaling pathways; additionally, the DO enrichment analysis investigates potential associations between core genes involved in MM-induced RI and other diseases. A significance threshold was set at $P < 0.05$, with results presented using bar charts and bubble charts.

Statistical Analysis

All the databases used in this study, A P-value less than 0.05 indicated that the difference was statistically significant.

Results

Annual Publications and Journal Analysis

A comprehensive analysis of 2152 articles focused on RI in MM spanning from the years 2000 to 2023 was conducted (Figure 1A). The study revealed a notable upward trend, with the number of publications increasing from 25 articles in 2000 to 155 articles in 2021, reflecting a growth rate of 6.04%. The citation count peaked at 5363 articles in 2021 (Figure 1B). The journal that published the most articles on RI in MM was the "Cureus Journal of Medical Science" with 45 publications, followed closely by "Clinical Lymphoma Myeloma & Leukemia" (43), "Annals of Hematology" (40), "American Journal of Hematology" (39), and "American Journal of Kidney Diseases" (37) (Figure 1C). Notably, "Blood", published by the American Society of Hematology, emerged as the most cited journal, with a total citation count of 5343, followed by "Journal of Clinical Oncology" (2895), "New England Journal of Medicine" (2448), "British Journal of Hematology" (1940), and "Leukemia" (1828). Figure 1D illustrated the publication trends of the top ten journals from 2000 to 2023, demonstrating significant growth trajectories for specific journals. Regression analysis utilizing the Loess smoothing technique depicted distinct growth patterns for individual journals, with the "Cureus Journal of Medical Science" exhibiting substantial expansion, indicative of sustained research focus on RI in MM. Furthermore, "Clinical Lymphoma Myeloma & Leukemia" experienced a remarkable surge in publications from 2012 to 2022. Applying Bradford's Law, 27 core journals were identified as pivotal in disseminating studies on RI in MM. Through dual-map overlay visualization (Figure 1E), the flow of knowledge between disciplines at a journal level was observed, where the left area represented cited domains and the right area denoted citing domains. Within this framework, two primary distribution groups targeting MM with RI were delineated (Figure 1F): molecular. biology, immunology, and medicine. medical clinical domains. In contrast, the main cited journal groups encompassed molecular. biology. genetics and health. nursing. medicine, with a significant emphasis on medicine. medical. clinical as the domains as the

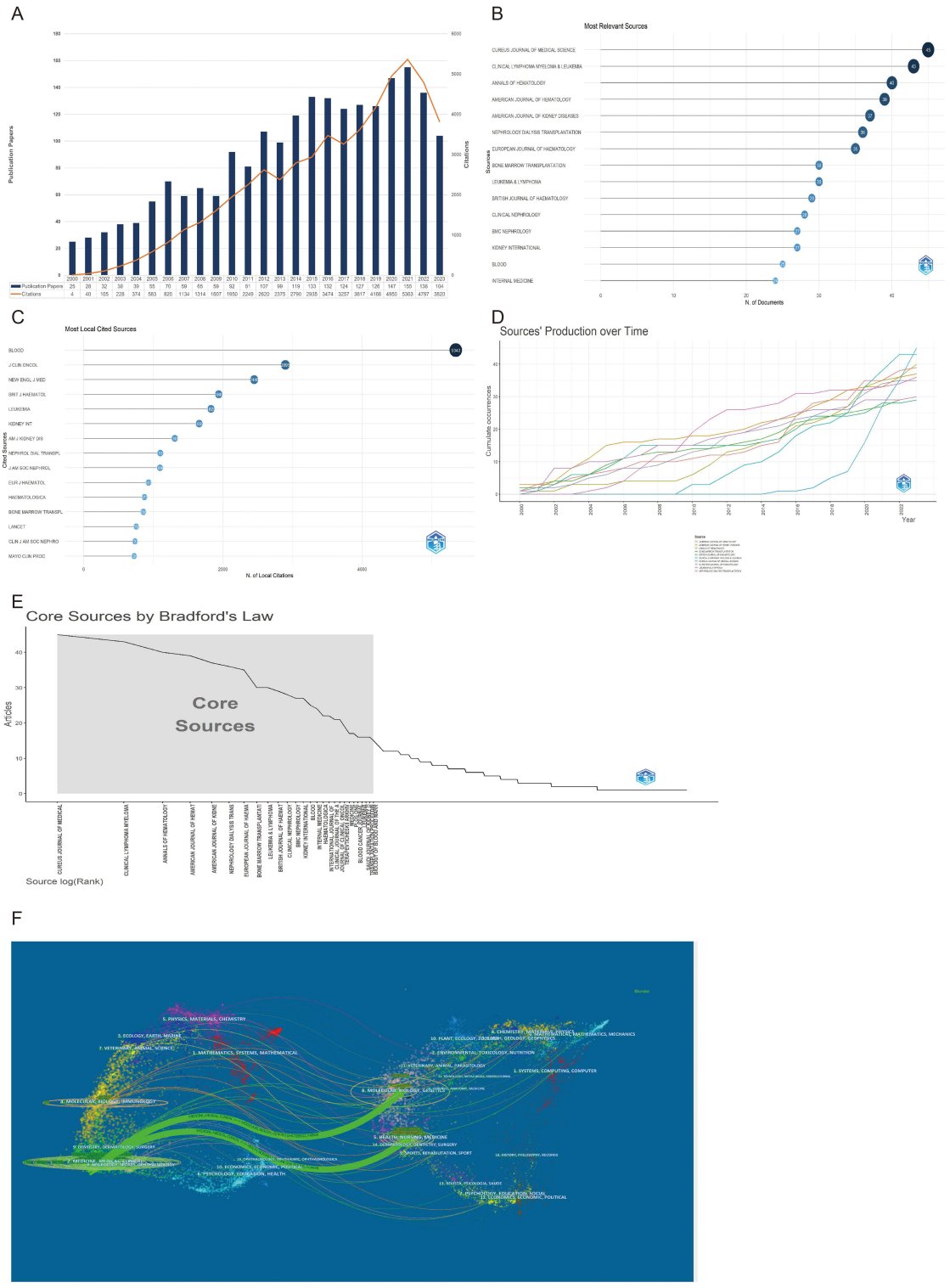

Figure 1 The bibliometric analysis of publications and journals. (**A**) Annual publication and citation trends for MM-related RI from 2000 to 2023. (**B**) The top 15 relevant journals contributing the most articles to the field. (**C**) The top 15 most local cited journals in MM-related RI. (**D**) Trends in annual publication output over time for the top 10 journals. (**E**) Identification of 27 core journals pivotal for disseminating MM-related RI studies according to Bradford's law. (**F**) A dual-map overlay illustrating the flow of knowledge between disciplines at the journal level. The citing papers were primarily focused: (1) Medicine. Medical. Clinical; (2) Molecular. Biology. Genetics; The cited papers were mainly focused: (1) Medicine. Medical. Clinical; (2) Health. Nursing. Medicine. The citing literature in the direction of Medicine. Medical. Clinical is divided into two data streams (green flow line), in which the upper flow line represents that the journals cited by the citing literature are mainly from Molecular. Biology. Genetics. The lower flow line represents the cited journals mainly in Health. Nursing. Medicine. reflecting that molecular biology (including molecular genetics) and drug research and development provide a theoretical basis for the clinical research of multiple myeloma kidney damage.

Abbreviations: MM, multiple myeloma; RI renal impairment.

central citation cluster boasting two outward citation paths. Notably, health. nursing. medicine exhibited the highest citation volume and Z value.

Country-Institution-Author Analysis

A total of 2152 studies on MM RI originated from 84 countries/regions, with the United States leading with 700 publications, accounting for 32.53% of the total—a substantial margin above other countries/regions. Following closely were China (168), Japan (125), France (111), Germany (108), Italy (103), India (96), UK (84), Spain (56), and Turkey (53) (Table 1). These data highlight the varying levels of attention given to MM-related RI across different nations.

Figure 2A illustrated that the top-cited countries remained consistent, with the United States garnering 28,137 citations, followed by the UK (3719), Italy (3018), Greece (2738), and Germany (2452). In terms of international collaboration, the United States engaged in the most multiple-country publications (Figure 2B), with cooperative efforts among various nations depicted in Figure 2C.

In Figure 3A and B, the top 15 most productive authors and key locally cited authors were listed. Notably, LEUNG N from the Mayo Clinic in Rochester, Minnesota, USA emerged as both the most productive relevant author and a key locally cited author, focusing on light chain cast nephropathy (LCCN) in patients with MM. The analysis, grouped in Lotka's Law, revealed that approximately 60% of authors contributed only one relevant research paper (Figure 3C). Furthermore, the bibliographic coupling analysis, presented in Figure 3D and E, showcased collaborations between authors and their affiliated institutions. The Mayo Clinic in the USA stands at the epicenter of institutional cooperation, engaging with entities such as the University of Texas MD Anderson Cancer Center (USA), Dana-Farber Cancer Institute (USA), University of Athens (Greece), University of Birmingham (UK), and other prominent cancer treatment centers. Figure 3F illustrates the author collaboration network. It is evident that the collaboration relationships among authors are relatively dispersed, forming smaller clusters.

Table 1 Top 20 Most Productive Countries in the Field of Multiple Myeloma Kidney Injury

Country	Number of Publications
USA	700
China	168
Japan	125
France	111
Germany	108
Italy	103
India	96
UK	84
Spain	56
Turkey	53
Canada	44
Greece	43
South Korea	43
Australia	38
Russia	36
Poland	31
Austria	29
Switzerland	28
Brazil	19
Netherlands	18

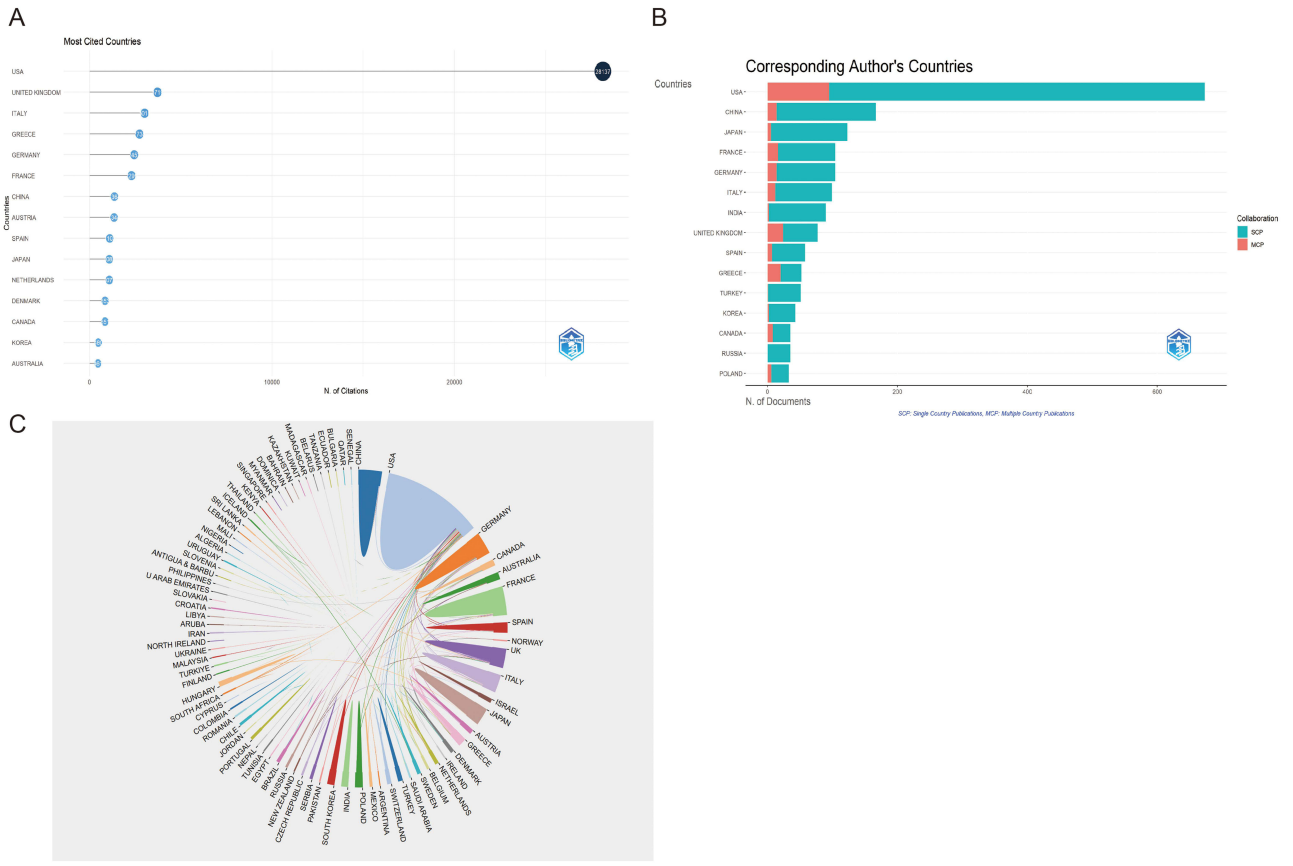

Figure 2 Bibliometric analysis of countries in the field of MM-related RI. (**A**) The top 15 most cited countries contributing to the literature on MM-related RI. (**B**) The top 15 countries with the highest number of corresponding authors in MM-related RI research. (**C**) A chordal diagram illustrating international collaboration patterns among countries in the field of MM-related RI.

Abbreviations: MM, multiple myeloma; RI renal impairment.

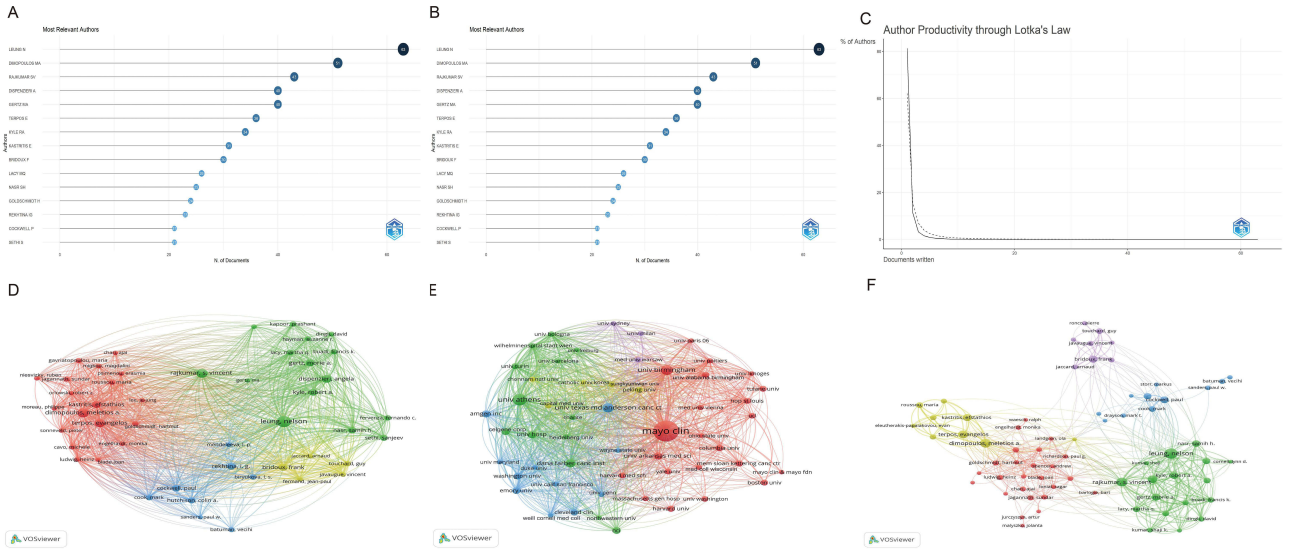

Figure 3 Bibliometric analysis of authors and their affiliations in the field of MM-related RI. (**A**) The top 15 most productive relevant authors in the field of MM-related RI. (**B**) The top 15 most locally cited authors in the field of MM-related RI. (**C**) The frequency distribution of author productivity in the field of MM-related RI. (**D**) Bibliographic coupling analysis of the authors in the field of MM-related RI. (**E**) Bibliographic coupling analysis of the authors' affiliations. (**F**) Co-authorship analysis in the field of MM-related RI.

Abbreviations: MM, multiple myeloma; RI renal impairment.

Bibliometric Analysis of the Documents and References

Figure 4A and Table 2 presented the top 20 most locally cited documents in MM-related RI research. Notably, the study by KNUDSEN LM published in 2000 in *European Journal of Haematology* was cited 198 times, ranking first and primarily focusing on the early intervention of renal failure in MM and its prognostic implications. Subsequent influential studies by researchers KYLE RA, AUGUSTSON BM, CLARK WF, and CHANAN-KHAN AA emphasized updates to diagnostic criteria for MM-related RI and elucidated various factors affecting prognosis. The pivotal findings by KYLE RA and colleagues illuminated the correlation between MM-related RI and prognostic outcomes. They highlighted factors such as advanced age, hypertension, anemia, and high urinary protein excretion as contributors to RI, which stemmed from various sources including abnormal immunoglobulin deposition and treatment-related toxicity.

Table 3 highlighted the top 20 most cited references in the field of MM-related RI. Notably, the study by KYLE RA published in 2003 in *Mayo Clinic Proceedings* stands out as the most cited references. Other highly references included the diagnostic criteria for MM-related RI proposed by the International Myeloma Working Group (IMWG). The IMWG has continuously updated these diagnostic criteria, gradually introducing glomerular filtration rate (GFR) as an evaluation indicator of renal function. In addition, the IMWG has clarified the evaluation criteria for proteinuria according to the 24-hour urinary protein value, while emphasizing the assessment of renal tubular function.

Figure 4B presented the co-citation analysis of reference clusters. The red cluster focused on the diagnostic criteria for MM and the clinical characteristics of renal involvement in MM; the blue cluster pertained to the disease evaluation and clinical outcomes of MM; the yellow and green clusters analyzed the studies of MM-related RI, including

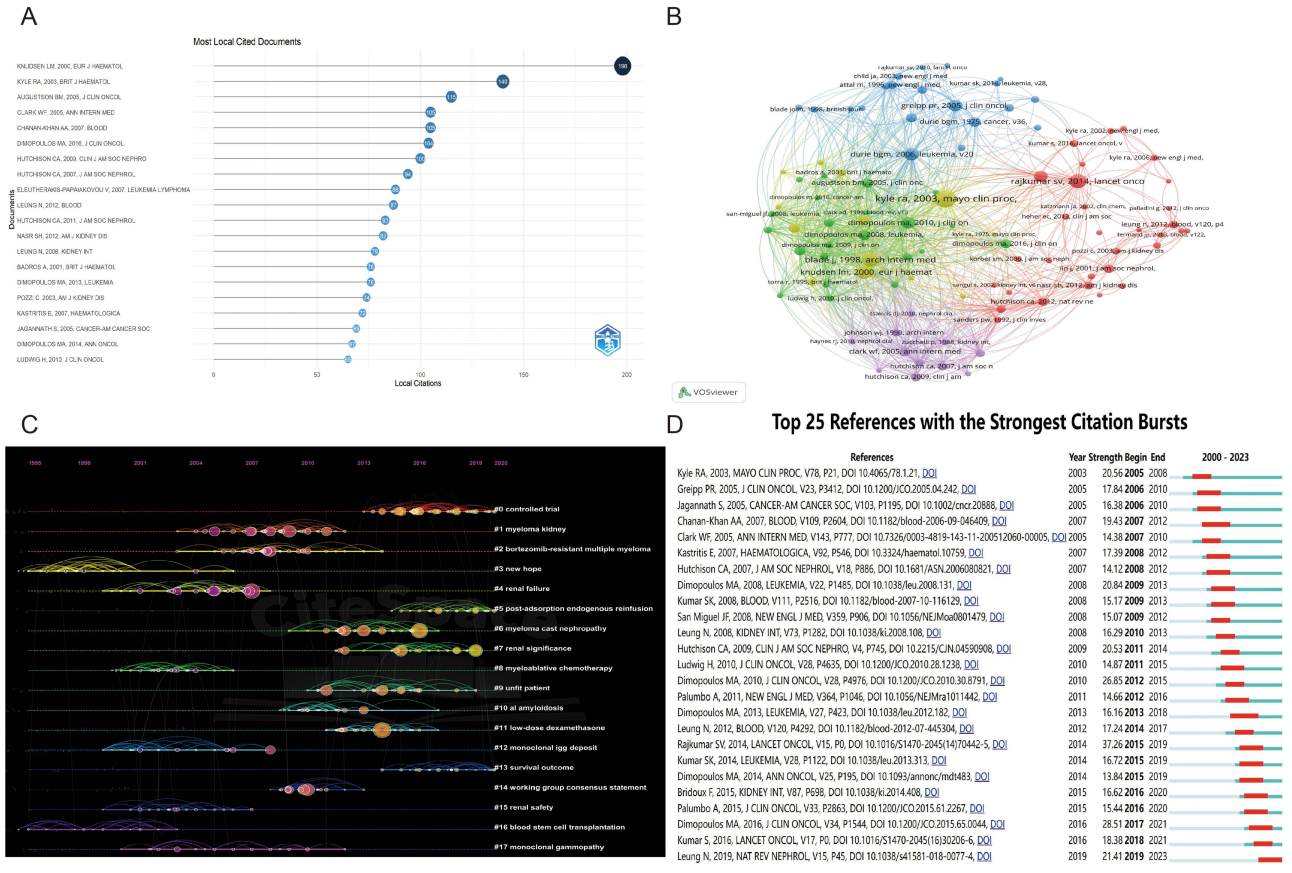

Figure 4 Bibliometric analysis of the documents and references in the field of MM-related RI. (**A**) The top 20 most local cited documents of MM-related RI. (**B**) Co-citation analysis of references of MM-related RI. (**C**) Co-citation analysis of references shown in timeline scope. (**D**) The top 25 references with the strongest citation bursts in the field of MM-related RI.

Abbreviations: MM, multiple myeloma; RI renal impairment.

Table 2 Top 20 Most Local Cited Documents in the Field of Multiple Myeloma Kidney Injury

Documents	Year	Local Citations
KNUDSEN LM, 2000, EUR J HAEMATOL[11]	2000	198
KYLE RA, 2003, BRIT J HAEMATOL[12]	2003	140
AUGUSTSON BM, 2005, J CLIN ONCOL[13]	2005	115
CLARK WF, 2005, ANN INTERN MED[14]	2005	105
CHANAN-KHAN AA, 2007, BLOOD[15]	2007	105
DIMOPOULOS MA, 2016, J CLIN ONCOL[16]	2016	104
HUTCHISON CA, 2009, CLIN J AM SOC NEPHRO[17]	2009	100
HUTCHISON CA, 2007, J AM SOC NEPHROL[18]	2007	94
ELEUTHERAKIS-PAPAIAKOVOU V, 2007, LEUKEMIA LYMPHOMA[19]	2007	88
LEUNG N, 2012, BLOOD[20]	2012	87
HUTCHISON CA, 2011, J AM SOC NEPHROL[21]	2011	83
NASR SH, 2012, AM J KIDNEY DIS[22]	2012	82
LEUNG N, 2008, KIDNEY INT[23]	2008	78
BADROS A, 2001, BRIT J HAEMATOL[24]	2001	76
DIMOPOULOS MA, 2013, LEUKEMIA[25]	2013	76
POZZI C, 2003, AM J KIDNEY DIS[26]	2003	74
KASTRITIS E, 2007, HAEMATOLOGICA[27]	2007	72
JAGANNATH S, 2005, CANCER-AM CANCER SOC[28]	2005	69
DIMOPOULOS MA, 2014, ANN ONCOL[29]	2014	67
LUDWIG H, 2010, J CLIN ONCOL[30]	2010	65

Table 3 Top 20 Most Cited References in the Field of Multiple Myeloma Kidney Injury

Cited References	Year	Citations
Review of 1027 patients with newly diagnosed multiple myeloma[31]	2003	272
Renal failure in multiple myeloma: presenting features and predictors of outcome in 94 patients from a single institution[32]	1998	203
International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma[33]	2014	201
Renal failure in multiple myeloma: reversibility and impact on the prognosis.[11]	2000	198
International uniform response criteria for multiple myeloma[34]	2006	165
International staging system for multiple myeloma[35]	2005	152
Renal impairment in patients with multiple myeloma: a consensus statement on behalf of the International Myeloma Working Group[36]	2010	148
Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group[12]	2003	140
Pathogenesis and treatment of renal failure in multiple myeloma[37]	2008	126
A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival[38]	1975	118
Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United Kingdom Medical Research Council trials between 1980 and 2002–Medical Research Council Adult Leukaemia Working Party[13]	2005	115
Renal failure in multiple myeloma. Pathogenesis and prognostic implications[39]	1990	111
Renal function in newly diagnosed multiple myeloma–a demographic study of 1353 patients. The Nordic Myeloma Study Group[40]	1994	109
Activity and safety of bortezomib in multiple myeloma patients with advanced renal failure: a multicenter retrospective study[15]	2007	105
Plasma exchange when myeloma presents as acute renal failure: a randomized, controlled trial[14]	2005	105
International Myeloma Working Group Recommendations for the Diagnosis and Management of Myeloma-Related Renal Impairment[16]	2016	104
Improved survival in multiple myeloma and the impact of novel therapies[41]	2008	102
Treatment of acute renal failure secondary to multiple myeloma with chemotherapy and extended high cut-off hemodialysis[17]	2009	100
Renal monoclonal immunoglobulin deposition disease: the disease spectrum[42]	2001	97
A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma[43]	1996	94

pathogenesis, treatment options, and prognostic factors; and the purple cluster addressed alternative treatments for MM renal failure, such as hemodialysis, plasma exchange, and high-flux hemodialysis.

Figure 4C showed the timeline of the references, which was divided into three clusters. Cluster1 (#1 myeloma kidney, #6 myeloma cast nephropathy, #10 al amyloidosis, #12 monoclonal igg deposit, #17 monoclonal gammopathy) focused

on the study of "pathogenesis of MM RI". Cluster 2 (#4 renal failure, #7 renal significance, #9 unfit patient, #13 survival outcome, #15 renal safety) focused on "the interactive effects of MM RI on kidney and the prognosis of myeloma". Cluster 3 (#0 controlled trial, #2 bortezomib-resistant multiple myeloma, #3 new hope, #5 post-adsorption endogenous reinfusion, #8 myeloablative chemotherapy, #11 low-dose dexamethasone, #14 working group consensus statement, #16 blood stem cell transplantation) focused on the study of "treatment options for MM RI". Figure 4D showed the top 25 references with the strongest citation bursts in chronological order, highlighting recent advancements in updates to diagnostic criteria, prognosis assessments, and treatment efficacy evaluations.

Key Words Analysis

The co-occurrence analysis of keywords with a frequency greater 12 was shown in Figure 5A, which included terms such as multiple myeloma, pathogenesis, survival, chemotherapy, and bisphosphonate. Figure 5B categorized the keywords into four groups. The red category represented the pathological mechanisms of MM-related RI, encompassing 30 keywords, including myeloma, monoclonal gammopathy, and amyloidosis. The green category pertained to the risk factors and prognosis of RI, featuring 17 keywords, including MM, renal insufficiency, and prognosis. The blue category focused on treatment strategies for MM-related RI, comprising 16 keywords, including bortezomib, lenalidomide, autologous stem cell transplantation (ASCT). The yellow category was the alternative treatments for MM-related RI, with 14 keywords, including renal failure, hemodialysis, plasmapheresis. According to the time distribution (Figure 5C), the yellow nodes represented keywords that gained significant attention from 2018 to 2023, including renal biopsy, MGRS, daratumumab, and carfilzomib. This indicated that the research related to these keywords had become a hot topic in recent years. Additionally, based on the trend analysis descried in Figure 5D, the drugs aimed at improving MM-related RI had primarily centered on thalidomide (2010), melphalan (2012), lenalidomide (2014), bortezomib (2014),

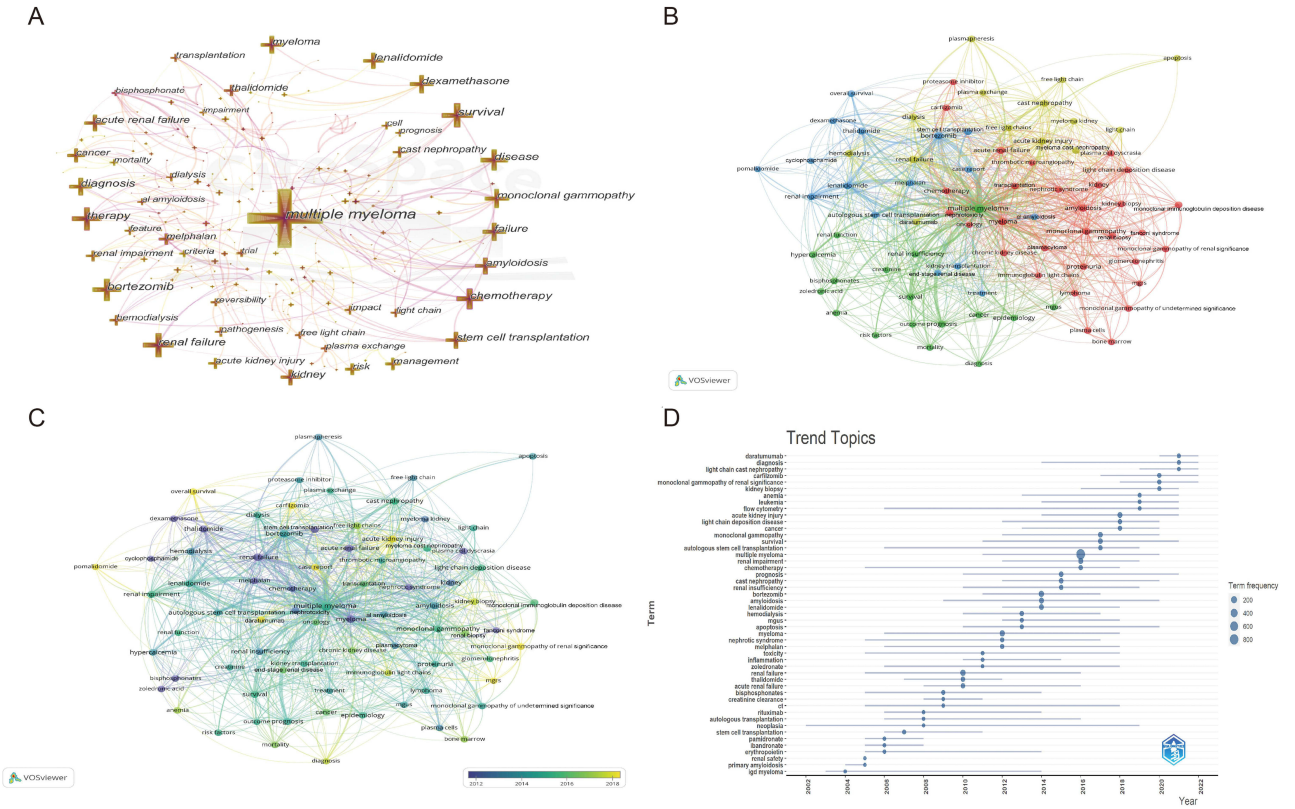

Figure 5 Bibliometric analysis of the keywords in the field of MM-related RI. (**A**) Co-occurrence analysis of keywords in the field of MM-related RI. (**B**) Clusters analysis of author keywords in the field of MM-related RI. (**C**) Timeline distribution of author keywords in the field of MM-related RI. (**D**) Trend topics of MM renal impairment from 2000 to 2023.

Abbreviations: MM, multiple myeloma; RI renal impairment.

https://doi.org/10.2147/JMDH.S501551

carfilzomib (2020), and daratumumab (2022). In the past three years, renal biopsy and updates to the diagnostic criteria for MM-related RI had attracted increased attention.

Genetic Factors Underlying Both MM and RI

We extracted the intersection genes between MM (n=377) and renal impairment (n=558), and identified a total of 237 intersection targets (Figure 6A and B). The genes were imported into the STRING database to determine the top 29 core genes, such as TP53, AKT1, MYC and CTNNB1 (Figure 6C). To investigate the biological function of RI in MM, GO functional enrichment analysis of core genes was performed. The results showed that the BP of the core genes included epithelial cell proliferation and positive regulation of the MAPK cascade. The CC associated with these genes comprised membrane raft, membrane microdomain, the external side of plasma membrane. The MF included signaling receptor activator activity, receptor ligand activity, and cytokine receptor binding (Figure 7A). Based on the enrichment results and related literature, two major pathways associated with RI in MM were identified: the PI3K/Akt signaling pathway and the MAPK signaling pathway (Figure 7B). In addition, DO enrichment analysis of the core genes showed that these

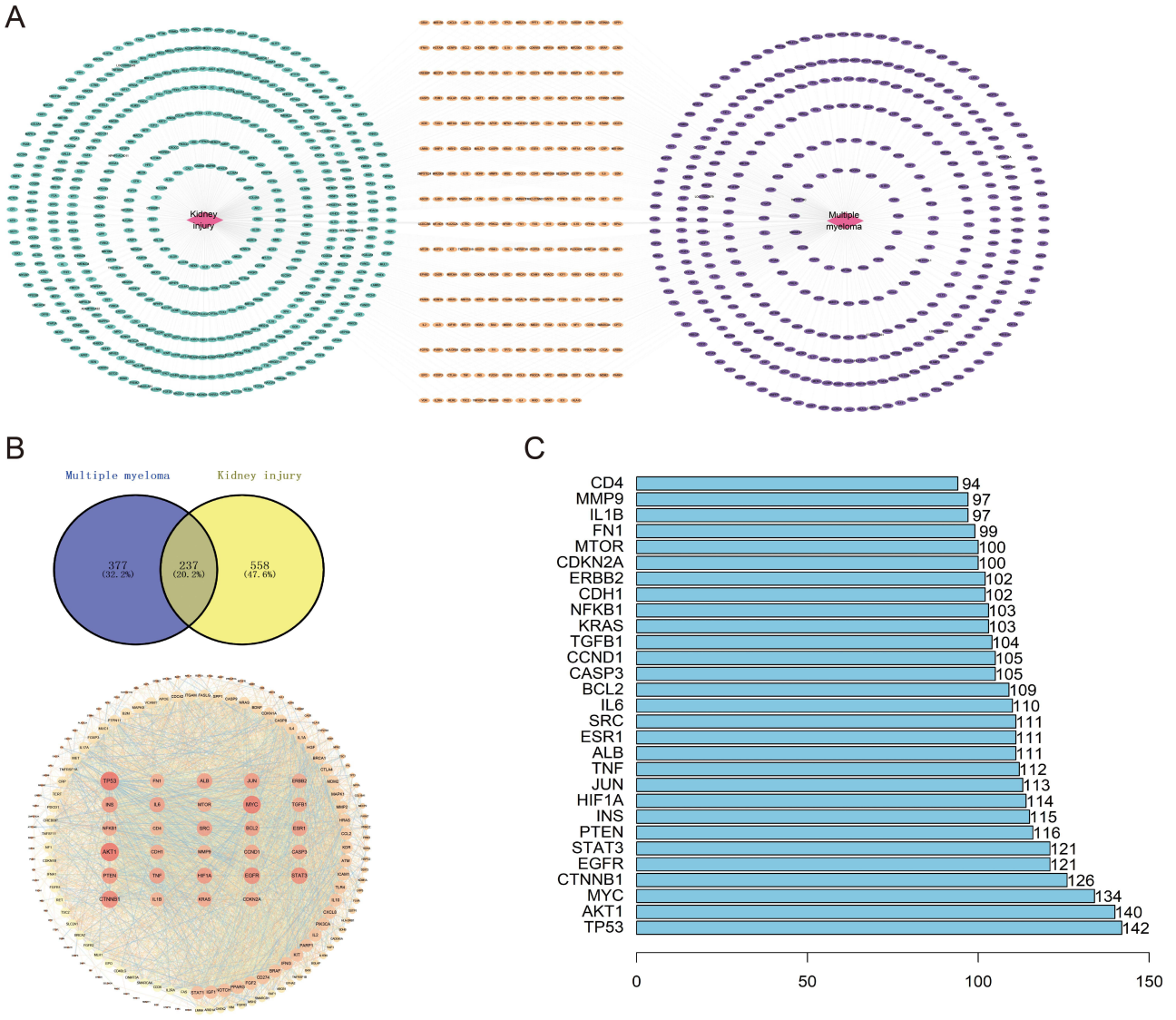

Figure 6 Analysis of disease-related databases in the field of MM-related RI. (**A**) Incorporating Cytoscape for visualization revealed distinct and shared targets of MM and renal impairment. (**B**) Interaction of MM related targets and renal impairment related targets. (**C**)The top 20 core genes of common targets.
Abbreviations: MM, multiple myeloma; RI renal impairment.

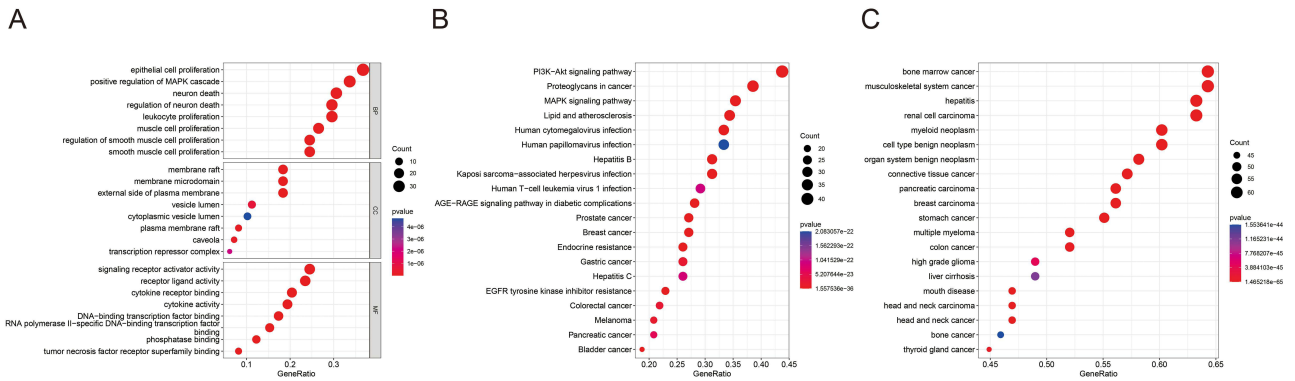

Figure 7 Analysis of the common target genes of MM and RI. (**A**) GO enrichment analysis of common targets. (**B**) KEGG pathway enrichment analysis of common targets. (**C**) DO analysis of common targets.
Abbreviations: MM, multiple myeloma; RI renal impairment; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes Genomes; DO, Disease Ontology.

genes may also play a role in musculoskeletal system cancer, renal cell carcinoma, myeloid neoplasm and other diseases (Figure 7C).

Discussion

The present study aimed to elucidate the research landscape concerning RI in MM through a comprehensive bibliometric and bioinformatics analysis spanning the last two decades. Our findings indicate a notable upward trend in the volume and impact of research in this domain, as evidenced by the increase in publications and citations from 2000 to 2023. The "CUREUS JOURNAL OF MEDICAL SCIENCE" was identified as the most prolific source of publications, while "BLOOD" garnered the highest citation frequency, underscoring its influence and reputation in the field. Our analysis included 2152 articles from diverse countries, with the United States emerging as the leading contributor to this body of work. The Mayo Clinic was highlighted as a pivotal institution, fostering inter-agency collaboration and driving innovation in research. Key research hotspots were identified, including therapeutic agents such as daratumumab and carfilzomib, alongside diagnostic advancements involving diagnostic criteria and renal biopsy. These findings align with the emerging trends in personalized medicine and targeted therapy in MM.

RI is a prevalent complication in MM, significantly affecting patient prognosis and quality of life.[13] The pathogenesis of RI in MM is multifactorial, involving both direct and indirect mechanisms. Myeloma tubular nephropathy is one of the most common renal complications associated with MM. It is characterized by the accumulation of FLCs in the renal tubules, leading to tubular obstruction and damage. These FLCs are filtered by the glomeruli and reabsorbed by the proximal tubules, resulting in cast formation and subsequent tubular injury.[14] The overproduction of monoclonal immunoglobulin light chains by malignant plasma cells is central to this process. Monoclonal immunoglobulin deposition disease (MIDD) is a condition wherein monoclonal immunoglobulins, predominantly light chains, deposit in the glomerular and tubular basement membranes. This deposition results in glomerulopathy and interstitial nephritis, contributing to progressive renal dysfunction.[15] The light chains form granular deposits that alter the normal structure and function of renal tissues. Amyloidosis occurs when misfolded light chains form insoluble amyloid fibrils that deposit in various organs, including the kidneys. These fibrils disrupt normal tissue architecture and function, leading to proteinuria and nephrotic syndrome.[16] Moreover, RI in MM is further exacerbated by non-immune factors such as hypercalcemia, dehydration, and the use of nephrotoxic drugs. Hypercalcemia, often a result of increased bone resorption in MM, can lead to nephrocalcinosis and acute kidney injury (AKI). Additionally, dehydration, secondary to hypercalcemia or other causes, reduces renal perfusion and exacerbates renal damage.[17] The bone-protecting drugs such as bisphosphonates are also implicated in contributing to kidney injury.[18] The intricate interplay between these mechanisms underscores the complexity of RI in MM. The identification of these pathophysiological processes provides a framework for understanding disease progression and potential therapeutic targets.

The management of RI in MM necessitates a multifaceted approach, addressing both the underlying myeloma and renal-specific complications. Plasmapheresis and high-cutoff hemodialysis are employed to rapidly reduce circulating FLCs, alleviating their nephrotoxic effects.[19,20] Plasmapheresis involves the removal and replacement of plasma to decrease the concentration of pathogenic proteins, while high-cutoff hemodialysis utilizes specialized membranes to effectively clear FLCs from the bloodstream. The advent of novel agents such as bortezomib, daratumumab, and carfilzomib has transformed the treatment landscape of MM. These agents target specific molecular pathways involved in myeloma cell survival and proliferation. Bortezomib, a proteasome inhibitor, induces apoptosis in myeloma cells and has shown efficacy in improving renal outcomes.[21] Daratumumab, a monoclonal antibody targeting CD38, and carfilzomib, a selective proteasome inhibitor, have also demonstrated renal protective effects.[44,45] Early and aggressive treatment of MM can lead to significant renal recovery, enhancing overall prognosis. Bispecific T-cell junction antibodies are a promising new immunotherapy for treating myeloma, which can achieve deep and lasting remission in patients with recurrent or refractory MM. The results announced at the ASTCT-CIBMTR conference in 2023 showed that adult patients with advanced MM and RI who received BCMA CAR-T drug ide cel treatment achieved similar outcomes to those with normal renal function. In RI patients, a single dose of CAR-T cell therapy does not increase the risk of treatment-related toxicity and there are no signs of renal function deterioration. However, the current reported studies are all on patients with creatinine clearance rates above 40mL/min and no significant renal toxicity, but research conducted in patients with moderate or severe RI is worth looking forward to.

Recent research identified through burst analysis of the references shows a primary focus on "diagnostic criteria, prognosis, and treatment evaluation". The co-occurrence timeline of keywords from the author's publication showed that "renal biopsy, monoclonal gammopathy of renal significance (MGRS), daratumumab, carfilzomib" were frequently published around 2018. Furthermore, trend analysis revealed an increased emphasis on "daratumumab" and "diagnostic criteria" in 2022, while significant research on "carfilzomib, MGRS, renal biopsy" was conducted in 2020. Daratumumab is the world's first fully human monoclonal antibody that targets CD38 with a unique "dual action mechanism". It binds directly to the CD38 antigen on the surface of MM cells, leading to the direct killing of myeloma cells and induction of apoptosis through cross-linking.[46] Additionally, daratumumab activates the immune system and modulates the immune microenvironment, thereby contributing to the ongoing death of myeloma cells and enabling MM patients to achieve long-lasting deep remission.[47] A key advantage of daratumumab is that it does not undergo renal metabolism, making it safe for use in patients with RI. Furthermore, it helps in rapidly reducing light chains, which helps to alleviate kidney damage.[21,46] Despite the development of numerous drugs for the treatment of MM in recent years, proteasome inhibitors (PIs) remain indispensable cornerstone therapies. Carfilzomib, a novel generation PI, irreversibly binds to the N-terminal active site of the 20S proteasome, which contains threonine. Additionally, within 24 hours of administration, approximately 25% of carfilzomib is excreted as metabolites in the urine, exerting minimal impact on renal function. In patients with renal dysfunction, carfilzomib can improve renal function, with a positive correlation observed between renal response and improved survival rates.[48] Ball conducted a systematic review and meta-analysis of four Phase III studies regarding carfilzomib to evaluate the incidence and relative risk of renal toxicity in MM patients receiving this treatment.[49] The results showed that the incidence of all-grade renal toxicity in the carfilzomib group was 21.3%, with a severe (Grade 3–5) renal toxicity incidence of 8.3%. More than half of carfilzomib-related renal toxicity events were transient, and the pharmacokinetics of carfilzomib are not influenced by the degree of renal impairment. Therefore, a careful assessment of the benefit-risk profile of carfilzomib is necessary for its clinical application.

The definition of RI in MM is continually being refined, and establishing this concept serves as the fundamental basis for subsequent pathological, physiological research, and treatment planning studies. In addition to LCCN, monoclonal proteins can contribute to various kidney diseases collectively referred to MGRS. Renal biopsy is considered the gold standard for distinguishing between LCCN, MGRS lesions, and other unrelated causes of AKI.[50] When non-selective proteinuria (primarily albuminuria) is detected, with a FLC value of less than 500 mg/L and no other known factors exacerbating kidney damage, a renal biopsy should be performed to identify the underlying cause of RI,[51] especially in the absence of amyloid substances in subcutaneous fat or other tissues. Identifying the cause of RI is crucial for implementing appropriate management strategies in subsequent therapy, ultimately improving survival outcomes for patients with MM. These trends underscore the importance of innovation and personalized approaches in managing RI in

MM. Ongoing research and collaboration among clinicians, researchers, and industry partners are essential to driving these advancements and improving patient outcomes.

The exploration of genetic factors in MM and RI has provided new insights into disease pathogenesis and potential therapeutic targets. Our analysis identified several key genes, including TP53, AKT1, MYC, CTNNB1, and EGFR, implicated in both MM pathogenesis and RI. These genes are involved in critical cellular processes such as proliferation, migration, apoptosis, and survival, and positive MAPK pathway regulation. Their dysregulation contributes to the malignant phenotype of myeloma cells and their interaction with the renal microenvironment. In the classification of CC, the most significantly enriched GO terms are "membrane raft" and "membrane microdomain", both of which are specialized regions of the plasma membrane characterized by a high concentration of cholesterol and sphingomyelin. In the context of MF, it mainly focuses on signal receptor activator activity, receptor ligand activity, and cytokine receptor binding. Research has demonstrated that phospholipid ether adenosine can accumulate in the membrane rafts of MM cells, thereby inducing apoptosis through the co-aggregation of these rafts with death receptors.[52] Moreover, CD38 expressed on the surface of myeloma cells can upregulate several proteins, including MDM2, cyclin A1, CDK4, cyclin D1, NF-κB, p65, and c-REL, while simultaneously downregulating p53, p21, and p38.[53] This regulatory mechanism enhances the proliferation of CD38-overexpressing cells and inhibits their apoptosis. Therefore, inducing cell apoptosis through the CD38-BTK-p53-c-MYC axis, in association with lipid rafts, may provide a novel target for future treatment of MM.[54] KEGG pathway analysis revealed that the intersection of common related genes between MM and RI primarily resides within the PI3K/Akt and MAPK signaling pathways. Both the two pathways play crucial roles in MM and its associated RI. The PI3K/Akt pathway supports the growth of myeloma cells by promoting cell survival, proliferation, and metabolism while contributing to tubular injury and fibrosis in the kidneys.[55,56] AKT phosphorylates FOXO transcription factors, causing them to be eliminated from the nucleus, thereby inhibiting FOXO mediated gene expression. FOXO family transcription factors are involved in regulating the expression of cell cycle, apoptosis, and metabolism related genes, promoting the survival, proliferation, and metabolism of myeloma cells. In patients with MM, inflammatory reactions may lead to kidney damage. The Akt signaling pathway is associated with the NLRP3/NF-κB and PI3K/Akt/GSK-3β/MAPK axes, exacerbating inflammatory responses and thus exacerbating renal damage in patients with MM.[57] Furthermore, activation of the Akt signaling pathway may lead to changes in energy metabolism of kidney cells, affecting their function and survival. The MAPK pathway, including ERK1/2, JNK, and p38, regulates cell proliferation, stress responses, and differentiation, and is involved in renal inflammation and repair processes.[58,59] Similarly, MAPK is also involved in the NLRP3/NF-κB and PI3K/Akt/GSK-3β/MAPK axes of inflammasomes, overactivating inflammatory factors and exacerbating kidney damage. And the MAPK signaling pathway is involved in regulating cell apoptosis, leading to the loss of renal tubular epithelial cells, which in turn affects the filtration and excretion functions of the kidneys. The interaction between these pathways, along with genetic mutations causing dysregulated signaling, further exacerbates the progression of MM and renal damage. It is worth mentioning that angiogenesis is also a key pathophysiological process in RI caused by MM. Myeloma cells can secrete various angiogenic factors, such as vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF), which can promote the formation of new blood vessels, provide nutrition and oxygen for myeloma cells, and support their growth and spread.[60] And the newly formed blood vessels may help myeloma cells evade immune system surveillance, promoting their spread. The increase in angiogenesis may exacerbate renal tubular blockage, affect renal filtration function, and further impair renal function. Moreover, abnormal angiogenesis may lead to changes in renal microvascular structure, affecting renal hemodynamics and exacerbating renal dysfunction.[61] Research has shown that in the pathophysiological process of angiogenesis, MP0250 acts as a multi-specific DARPin molecule that can simultaneously block VEGF and HGF with high specificity and affinity. Research has shown that MP0250 can reduce microvascular density (MVD) and enhance the effect of bortezomib, which may improve the therapeutic efficacy of myeloma treatment and reduce further damage to the kidneys. MP0250 has the potential to be a novel combination drug for treating patients with myeloma, improving hematological efficacy while enhancing renal response rates.[62] Inhibitors targeting these pathways and combination therapies show potential in reducing myeloma progression and alleviating renal impairment, offering new hope for personalized treatment.

This study provides a comprehensive analysis of the research trends and underlying mechanisms of RI in multiple myeloma. Through a combination of bibliometric and bioinformatics approaches, we have identified key research areas, therapeutic advancements, and genetic factors contributing to this complex condition. Our findings highlight the importance of early diagnosis, personalized treatment strategies, and a deeper understanding of the genetic underpinnings of MM and its renal complications. While our study provides valuable insights, several limitations must be acknowledged. The reliance on the

WOSCC may have excluded relevant studies not indexed within this database. There exists a latency issue in the data updates from the WOSCC data source, which may result in the failure to incorporate the most recent research findings or trends during the analysis process. This could consequently impact the timeliness and accuracy of the analysis outcomes.Future research should incorporate a broader range of data sources to capture a more comprehensive picture of the research landscape. We have not adequately addressed the impact of cross-regional variations in healthcare infrastructure and practices on the management and outcomes of MM-associated RI. The uneven distribution of medical resources across regions can result in limited access to essential services such as dialysis and transplantation for patients with severely impaired renal function, potentially leading to treatment interruptions and accelerated disease progression. Additionally, adherence to diagnostic criteria and treatment guidelines for MM and its complications may vary between regions. Variations in patient education efforts can also influence patient adherence and overall outcomes. In addition, as new therapies and biomarkers continue to emerge, ongoing research is needed to evaluate their efficacy and integration into clinical practice. The dynamic nature of the field necessitates continuous monitoring and adaptation to incorporate novel advancements.

Conclusion

In conclusion, this study underscores the critical need for continued research and collaboration in understanding and managing RI in MM. The integration of advanced diagnostic tools, targeted therapies, and genetic insights holds promise for improving patient outcomes and reducing the burden of renal complications in this patient population. Our research contributes to the ongoing efforts to optimize care for patients with MM, particularly those at risk of or experiencing RI, reinforcing the importance of innovation and personalized approaches in modern healthcare.

Data Sharing Statement

The data that support the findings of this study are openly available in WOS Core Collection.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgments

The authors would particularly like to acknowledge their team members, for their wonderful collaboration and professional writing services.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

All the authors have no financial or non-financial conflicts of interest.

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