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Treatment patterns and clinical outcomes for multiple myeloma in Korean patients: a database study

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Abstract

Background The treatment landscape for multiple myeloma (MM) has significantly progressed in recent decades.

Methods We analyzed the treatment patterns and clinical outcomes in Korean patients using data from the National Health Insurance Service database. Patients diagnosed with MM between 2010 and 2018 were included. Survival analysis with a Cox regression model was performed.

Results A total of 8,367 patients with MM were identified, from which 2,442 patients underwent stem cell transplantation (SCT). The mean patients' age at diagnosis was 67.1 years. Since 2011, the combination of a proteasome inhibitor (PI) and an alkylating agent has been most common, with a significant increase in the PI and immunomodulatory drug (IMiD) combination after 2015. The attrition rates after first-line therapy were 45% and 56% for the SCT and non-SCT groups, respectively. Patients on bortezomib, melphalan, and prednisolone were younger with less renal insufficiency compared to those on lenalidomide and dexamethasone. The SCT group had a median overall survival (OS) of 7.04 years, significantly higher than the non-SCT group's 2.52 years.

Conclusions SCT eligibility and the reimbursement status of new drugs impact the treatment pattern of MM. Expanding access to new agents and identifying patients who can benefit from SCT are essential.

Keywords Multiple myeloma, Therapy, Stem cell transplantation, Survival

Background

Multiple myeloma (MM) is a hematological neoplasm characterized by the proliferation of monoclonal plasma cells, accounting for approximately 10% of hematologic malignancies and an annual incidence of seven per 100,000 individuals according to data from the US Surveillance, Epidemiology, and End Results (SEER) registry [1, 2]. Although the incidence of MM has been relatively lower in Asians than that in Caucasians, it has rapidly increased in Asian countries including Korea [3].

After the introduction of novel agents such as proteasome inhibitors (PI) and immunomodulatory drugs (IMiDs), the treatment landscape of MM has rapidly

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improved. The introduction of anti-CD38 monoclonal antibodies such as daratumumab has proven to be effective regardless of the treatment line [4]. The availability of these novel agents significantly affects the clinical outcomes [5]. For example, the survival rates have significantly improved alongside the introduction of new drugs in the United States and Japan over the past two decades [6, 7]. Meanwhile, despite the introduction of these new drugs, the efficacy of autologous stem cell transplantation (SCT) continues to be recognized [8]. In Korea, the age limit for coverage by the National Health Insurance Service (NHIS) was expanded from < 65 to < 70 years due to its efficacy in this age group [9]. Such changes in the diverse treatment landscape are deemed to have had a significant impact on the treatment patterns and outcomes of patients with MM in Korea. In Korea, national health insurance is mandatory and covers almost the entire population. Therefore, health insurance claims data include comprehensive information on treatment patterns along with other important information, such as the subscriber's demographic characteristics (sex, age, residential area, occupation), insurance premiums (indicator of socioeconomic status), medical use (diagnosis, hospitalization, prescription details) based on a fee-for-service insurance system, and health check-ups. Thus, we used these data to understand the treatment patterns and survival outcomes of patients with MM in Korea.

MM is a disease of the older population, with a median age at diagnosis of almost 70 years, which means that approximately half of the patients are not eligible for transplantation. In this age group, bortezomib, melphalan, prednisolone (VMP), lenalidomide, and dexamethasone (Rd) are critical as induction therapies. However, there are no definite criteria for selecting an induction regimen with comparable outcomes in older patients [10]. We also analyzed factors to choose the induction regimen in patients who did not undergo SCT along with survival comparison according to the induction regimen to elucidate the tendency to choose the treatment regimen. This study examined the treatment patterns and survival outcomes based on NHIS drug-approval policy changes, focusing on trends in selecting VMP vs. Rd regimens and their associated survival outcomes among elderly patients.

Methods

Data source and study population

We used data from the NHIS database between January 2010 and December 2018. Data on patients with MM and malignant plasma cell neoplasms with the International Classification of Diseases (ICD)-10 code C90 and rare and intractable disease (RID) codes were extracted from the NHIS database. Patients diagnosed with severe diseases, including cancer and rare and incurable diseases, receive support for medical expenses by registering with the NHIS RID program. Thus, the definition of cancer diagnosis based on the RID codes in the NHIS database has shown high accuracy. Patients lacking baseline information for the 12 months preceding diagnosis were excluded. Additionally, patients with diagnostic codes for plasma cell leukemia (C90.1), extramedullary plasmacytoma (C90.2), or solitary plasmacytoma (C90.3) were excluded. Only patients with a diagnostic code for multiple myeloma (C90.0) were included, with no cases of primary amyloidosis (C90.4) identified in the data. In addition, patients with a diagnostic code of C90.1 (plasma cell leukemia) within 2 months of MM (C90.0) diagnosis were also excluded because of the possibility of secondary disease from MM. Patients were excluded if they had another primary cancer or had received anticancer treatment prior to the diagnosis of MM. The study subjects were aged ≥ 18 years, and those without any anticancer prescription history after MM diagnosis were also excluded (Fig. 1).

Line of therapy

MM treatment was investigated using the NHIS records of medical claims. The treatment regimens for patients with MM were identified using the main ingredient codes in the prescription records from the NHIS database. Treatment regimens were defined by the presence of a combination of core drugs of anticancer treatment for MM in the line of therapy (LOT) (Additional file 1, Supplementary Table S1). The non-core drugs in the LOT did not affect the definition of each regimen. Treatments that did not fall under the defined regimen were classified as "Other." LOT was defined as the combination of drugs administered within 14 days from the start of the prescription of the core drug, and the LOT was terminated when the core drug belonging to the defined regimen was changed without considering the duration of the treatment. Exceptions were applied to induction therapies followed by upfront SCT, in which induction therapy and SCT were considered as one LOT. The first LOT was initiated on the date of the first prescription claim for MM treatment following the diagnosis index date.

The treatment pattern of MM from the first to the fifth LOT was described. The treatment duration of LOT was defined as the number of days from the start date of the LOT to the last prescription date, plus the number of prescription days. The treatment-free interval (TFI), which is the period between LOTs, was defined as the time from the last dose of one regimen to the time of initiation of the subsequent regimen.

The LOT outcomes for patients with MM were classified as "progression", "death", and "no treatment". Patients who were administered a different treatment regimen from their previous regimen or who underwent

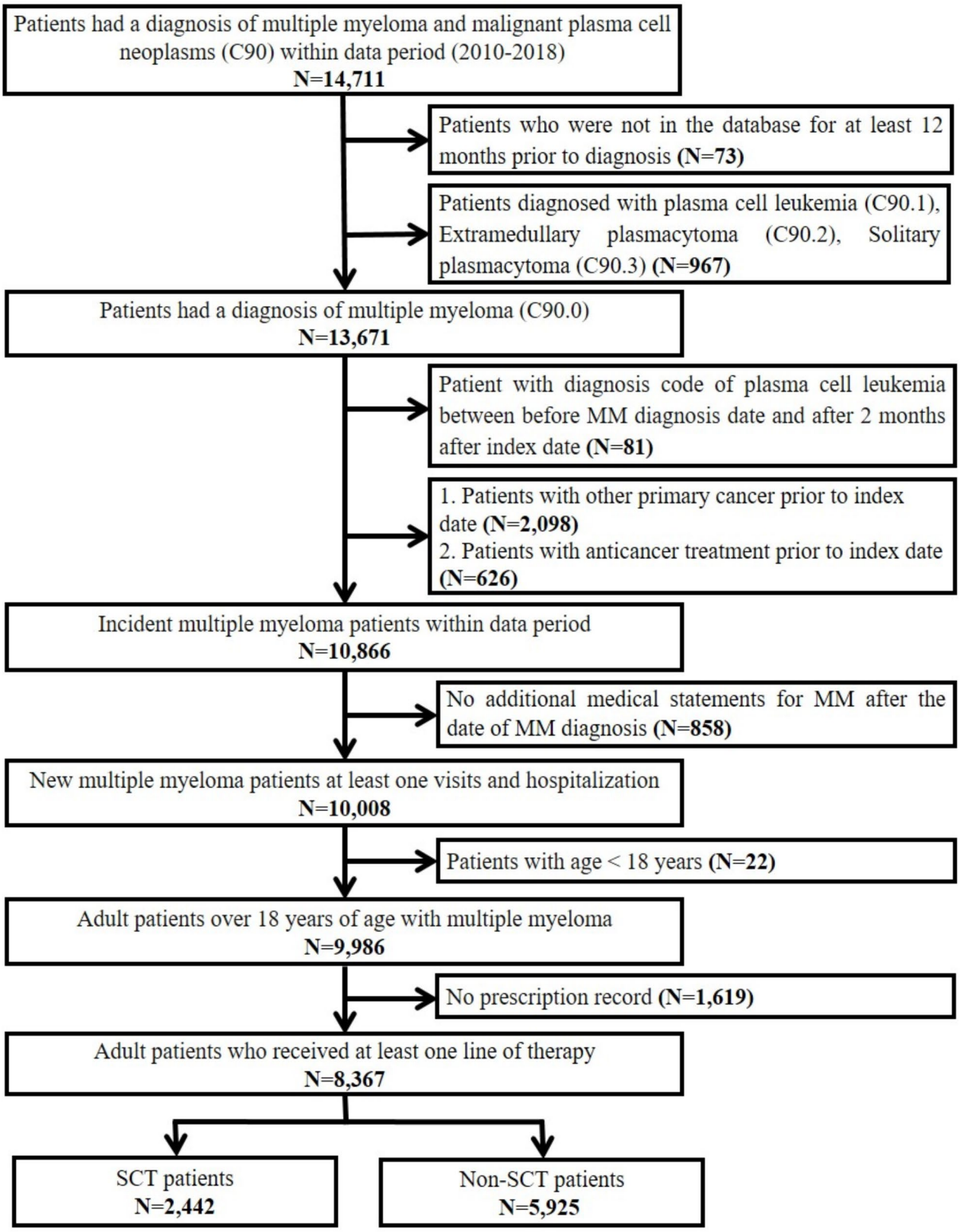

Fig. 1 Flowchart of selection of patients with multiple myeloma

retreatment (reinitiating the same treatment regimen after a gap of >180 days) were considered to have progressed. As the Korean NHIS halts reimbursement for treatments only upon evidence of progression and does not permit switching to alternative therapies solely due to toxicity, we assumed that treatment changes in our data closely align with instances of disease progression. Patients who did not proceed to the next LOT by the end of the study were considered untreated. Death was defined by the death of a patient within the study period after completion of the LOT.

Clinical characteristics

The severity of comorbidities before MM diagnosis was assessed using the Charlson Comorbidity Index (CCI). The look-back period of the CCI was 12 months prior to the start date of the first LOT and was defined for all diseases diagnosed during this period. The components of the ICD-10 codes used to define CCI are listed in Supplementary Table S2 (Additional file 1). Among the components of the CCI, cancer was excluded as a comorbidity owing to the potential for overestimation because the study population included patients with MM who were already diagnosed with cancer. Clinical symptoms of MM were defined by the presence of the following diagnostic codes within 12 months prior to the date of MM diagnosis: renal failure (ICD-10 codes N17–N19), anemia (ICD-10 codes D55–D59 and D60–D64), bone fracture (ICD-10 codes T02, T08, T10, T12, T14.2), and recurrent bacterial infections (ICD-10 codes A30–A49).

Healthcare utilization was evaluated by summarizing the number of hospitalizations, emergency room visits, and outpatient visits. Patients who visited the hospital with a main diagnosis of C90.0 after being diagnosed with MM were considered for healthcare utilization. Healthcare utilization was confirmed using inpatient and outpatient classification codes and treatment department codes from the health insurance claims data.

Statistical methods

The baseline characteristics, distribution of treatment regimens, and LOT sequences were descriptively analyzed. Considering the status of SCT (SCT-conducted and non-SCT-conducted) and the timing of medical insurance coverage in Korea, the diagnosis period of patients with MM was divided, and treatment patterns were depicted. When VMP (coverage in the NHIS from 2011) and Rd (coverage in the NHIS from 2017) were prescribed as first-line therapies in patients with MM diagnosed after January 2018, an analysis of factors affecting each treatment regimen was performed using binomial logistic regression only in patients with MM diagnosed in 2018. The odds ratios (OR) and 95% confidence intervals (CI) were calculated after adjusting for socioeconomic variables and clinical characteristics. These patients were classified according to age (divided at 75 years). Survival distribution was estimated using the Kaplan–Meier method, and the log-rank test was used to evaluate significant differences in each survival rate. In addition, overall survival (OS) and median survival time were confirmed by analyzing the Kaplan–Meier curve for all patients with MM according to the SCT status and age (based on the age of 65 years). All analyses were performed using the SAS Enterprise Guide version 8.3 (SAS Institute, Inc., Cary, NC, USA) and R version 4.2.2 (The R Foundation for Statistical Computing, Vienna, Austria). The significance level for all p-values was set at 0.05.

Results

Baseline characteristics of patients

This study included 8,367 patients with at least one prescription claim after MM diagnosis. The mean age at diagnosis of the treated patients was 67.1 years, and the proportion of men was higher than that of women. In the first LOT, 2442 patients received SCT, whereas 5925 patients did not. In total, 91.7% of patients in the SCT group were aged < 65 years, and 82.4% of the patients in the non-SCT group were aged > 65 years; therefore, the average age of starting the first LOT in the SCT group was lower. Regarding the income distribution of patients, the 4th quartile income group was the most prevalent. Compared to the SCT group, the average CCI score in the non-SCT group was higher, and the likelihood of developing renal disease was high. Healthcare utilization, including hospitalization, outpatient visits, and emergency visits, was higher in the SCT group than in the non-SCT group. These findings are summarized in Table 1.

Treatment pattern

From 2011 to 2017, the most commonly used initial treatment was a combination of PI and an alkylating agent. Combination therapy was one of the primary treatment approaches initially attempted in patients. Following the PI and alkylating agent combination treatment, IMiD (immunomodulatory drug) class therapy was used. As the use of IMiDs in combination with PI therapy has increased rapidly since 2015, the proportion of patients receiving IMiD treatment (without PI and/or alkylators) has significantly decreased. In 2018, the use of IMiD and PI combination therapy as the initial treatment regimen surpassed that of the previously dominant PI and alkylating agent combination therapies (Fig. 2).

Before December 2017, patients who were not eligible for SCT had commonly chosen PI/alkylator agents as their initial treatment. Most of these patients opted for PI/alkylator agents only as the first LOT without proceeding to the second LOT (29.8%). Subsequently, some

Table 1 Demographic and clinical characteristics of patients with MM based on SCT status

	Overall	Non-SCT group	SCT group	*p*-value
Total	8,367	5,925	2,442	
Sex				
Male	4,447 (53.1)	3,050 (51.5)	1,397 (57.2)	< 0.0001
Female	3,920 (46.9)	2,875 (48.5)	1,045 (42.8)	
Age				
Mean ± SD	67.1 ± 10.5	71.4 ± 8.7	56.7 ± 6.7	< 0.0001
18–29	2 (0.0)	0	2 (0.08)	< 0.0001
30–39	64 (0.8)	11 (0.2)	53 (2.2)	
40–49	422 (5.0)	111 (1.87)	311 (12.7)	
50–59	1,544 (18.5)	456 (7.7)	1,088 (44.6)	
60–69	2,605 (31.1)	1,620 (27.3)	985 (40.3)	
70–79	2,765 (33.0)	2,762 (46.6)	3 (0.1)	
80+	965 (11.5)	965 (16.3)	0	
Eligible age for SCT				
18–64	3,284 (39.2)	1,044 (17.6)	2,240 (91.7)	< 0.0001
65+	5,083 (60.8)	4,881 (82.4)	202 (8.3)	
Income				
1st quartile (lowest)	1,456 (17.4)	1,011 (17.1)	445 (18.2)	< 0.0001
2nd quartile	1,358 (16.2)	870 (14.7)	488 (20.0)	
3rd quartile	1,840 (22.0)	1,258 (21.2)	582 (23.8)	
4th quartile (highest)	3,270 (39.1)	2,414 (40.7)	856 (35.1)	
Unknown	443 (5.3)	372 (6.3)	71 (2.9)	
CCI score				
Mean ± SD	1.4 ± 1.4	1.5 ± 1.5	1.0 ± 1.3	< 0.0001
0	2,653 (31.7)	1,606 (27.1)	1,047 (42.8)	< 0.0001
1	2,606 (31.1)	1,817 (30.7)	789 (32.3)	
2	1,642 (19.6)	1,266 (21.4)	376 (15.4)	
3	839 (10.0)	711 (12.0)	128 (5.2)	
4+	627 (7.5)	525(8.9)	102 (4.2)	
Comorbidities associated with MM				
Renal failure	1,203 (35.1)	972 (37.1)	231 (28.6)	< 0.0001
Anemia	2,077 (60.7)	1,533 (58.6)	544 (67.4)	< 0.0001
Factures	55 (1.6)	42 (1.6)	13 (1.6)	< 0.0001
Bacterial disease	89 (2.6)	70 (2.7)	19 (2.4)	< 0.0001
Hospitalizations[a)]				
Mean ± SD	8.6 ± 11.2	6.7 ± 9.2	13.2 ± 14.0	< 0.0001
Hospital stays (days)				
Mean ± SD	99.3 ± 139.8	88.7 ± 138.2	125.0 ± 140.2	< 0.0001
Outpatient visits*				
Mean ± SD	53.4 ± 55.1	43.7 ± 51.8	76.9 ± 55.8	< 0.0001
Emergency visits*				
Mean ± SD	0.3 ± 1.3	0.3 ± 1.2	0.4 ± 1.5	0.0005

All results are presented as n (%)

MM, multiple myeloma; SCT, stem cell transplantation; SD, standard deviation; CCI, Charlson Comorbidity Index

[a)] Hospitalization, outpatient visits, and emergency visits were measured as the number of events

patients used IMiDs after PI/alkylator therapy (13.6%). Even after Rd was covered by national insurance in December 2017, the use of PI/alkylator agents remained highest. However, the number of patients receiving IMiD therapy rapidly increased, rising from 3.1 to 27.1% as of December 2017. The proportion of patients who received IMiD as initial therapy and did not receive any additional treatment was highest (17.7%). After undergoing IMiD treatment, 14.5% of patients received PI as a second LOT. In patients with MM who underwent SCT, IMiDs were primarily used as induction therapy for the first LOT. The highest proportion of these patients received IMiD therapy alone (17.7%), followed by those who received PI therapy sequentially after IMiD therapy (14.5%). Since the introduction of insurance coverage for bortezomib, thalidomide, and dexamethasone (VTd, a combination therapy of PI/IMiD) in October 2015, the proportion of patients who received PI/IMiD therapy as their first treatment regimen increased to 64.5% (Fig. 3).

In the SCT group, the first treatment was initiated within one month of MM diagnosis, whereas it was initiated on average, at 1.6 months in the non-SCT group. The proportion of patients transitioning through consecutive LOTs from the first to the fifth line was higher in the SCT group, with 8% of the patients remaining in the fifth LOT (compared to 3% in the non-SCT group). Regardless of the SCT status, the proportion of patients progressing to subsequent LOTs decreased. Patients who did not receive SCT experienced a continuous decrease in treatment duration and TFI as they progressed through the LOTs. In contrast, the patients in the SCT group were treated for a relatively short period during the first LOT and had the longest TFI of 17.7 months after the first treatment (Fig. 4).

VMP and rd as frontline therapy

Among the patients diagnosed after 2018 who received VMP (352 patients) or Rd (262 patients) as their initial treatment, the likelihood of choosing Rd over VMP was approximately twice as high in women as in men (Table 2). The VMP and Rd regimens were administered according to the approval criteria in Korea, adhering to the protocols established in the VISTA trial for VMP and FIRST trial for Rd. Rd treatment was continued until disease progression or the occurrence of unacceptable toxicity [11, 12]. Compared to patients in their 70s, patients in their 60s were 46% less likely to choose Rd over VMP, whereas patients in their 80s or older had an approximately 3.8 times higher chance of choosing Rd. There was either no patient or only one patient aged < 50 years who was treated with VMP or Rd; therefore, statistical estimation was not possible (Additional file 1, Supplementary Table S3). Among the patients with specific complications related to MM, those with renal failure

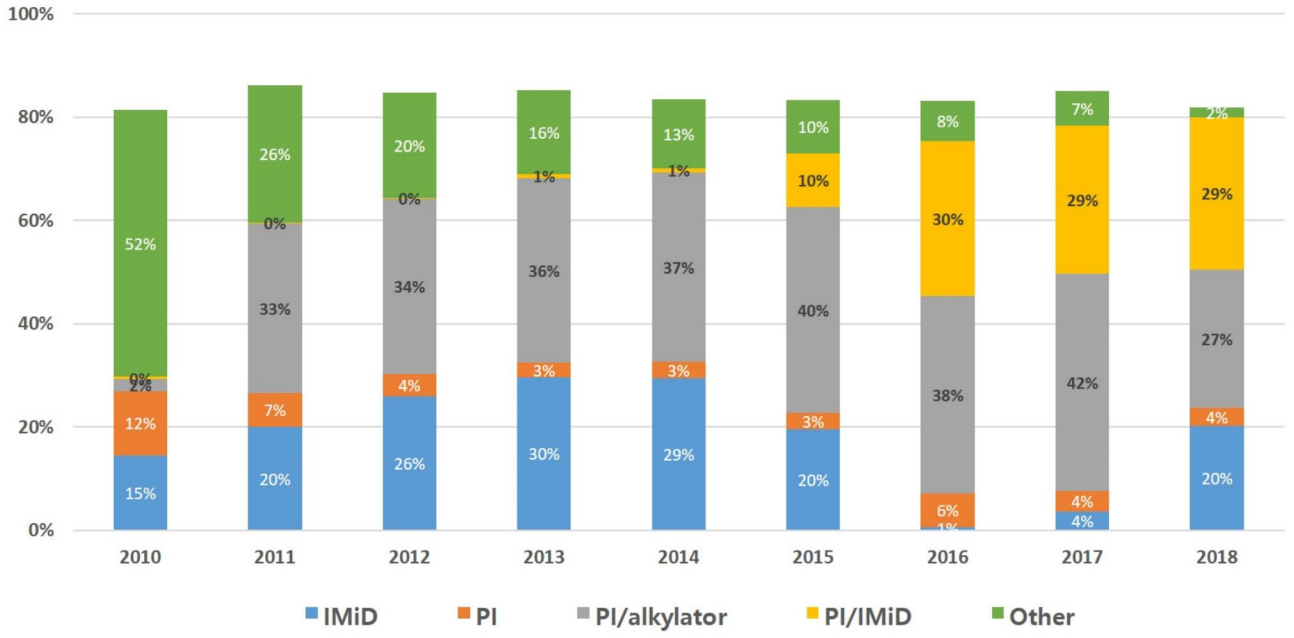

Fig. 2 Distribution of first line of therapy in patients with multiple myeloma by year

as a comorbidity were 62% less likely to choose Rd over VMP compared to those without.

Survival outcomes

The 9-year survival rate among all patients (including untreated patients) was 22.4%, and the median OS was 3.36 years (95% CI: 3.22–3.50). Regarding SCT eligibility, patients in the SCT group had significantly higher survival rate ($p < 0.0001$). The 9-year survival rates were 14.2% and 44.7% in the non-SCT and SCT groups, respectively. The median OS for the non-SCT group and SCT group was 2.52 years (95% CI: 2.02–3.00) and 7.04 years (95% CI: 6.49–8.11), respectively, indicating a longer survival in the SCT group (Fig. 5a and 5b).

Survival rates were analyzed by stratifying patients by age (based on age 65) and SCT eligibility. The survival rate was significantly higher ($p < 0.0001$) among patients aged < 65 years who underwent SCT. In the non-SCT group, the 9-year survival rate was higher in patients aged < 65 years compared to patients aged > 65 years. When compared within each age group, patients who underwent SCT showed significantly better survival rates in both age groups compared to those who did not receive SCT. However, in cases of early death, the survival rate decreased sharply in patients aged < 65 years (Fig. 5c).

Among the patients diagnosed in 2018, the OS of those who received VMP and Rd as the first-line treatment is shown in Fig. 5d, stratified by age. Regardless of treatment, patients aged < 75 years showed a high survival rate ($p = 0.0004$). The 1-year survival rate for patients aged < 75 years was 82.3% and 87.4% in those who were first treated with Rd and VMP, respectively. Patients aged ≥ 75 years who received the Rd regimen had the poorest prognosis in terms of the 1-year survival rate (62.6%).

Discussion

The current analysis demonstrated how the treatment patterns of MM have changed according to the introduction of new drugs and reimbursement status of the national health insurance in Korea using NHIS data, which is a comprehensive registry that covers all South Korean residents [13]. We analyzed 9,985 Korean patients with MM diagnosed between 2010 and 2018, and to the best of our knowledge, this is the largest population study of Korean patients with integrative analysis of current MM treatment patterns.

Novel agent-based regimens were introduced for both induction and salvage treatments in our analysis. The reimbursement of these new regimens dramatically altered the choice of treatment for the SCT group, in whom VTd has been administered most frequently since October 2015. In real-world data from Korea, the 2-year OS for patients under 65 years who received VTd followed by SCT was reported as 95.4%, demonstrating better outcomes compared to the overall SCT cohort in our study (2-year OS: 88.5%) [14]. While our study has limitations in directly comparing the outcomes across specific regimens, these findings indirectly suggest that the introduction of novel drugs significantly improves patient outcomes. In the non-SCT group, the approval of Rd as the first-line therapy in December 2017 expanded

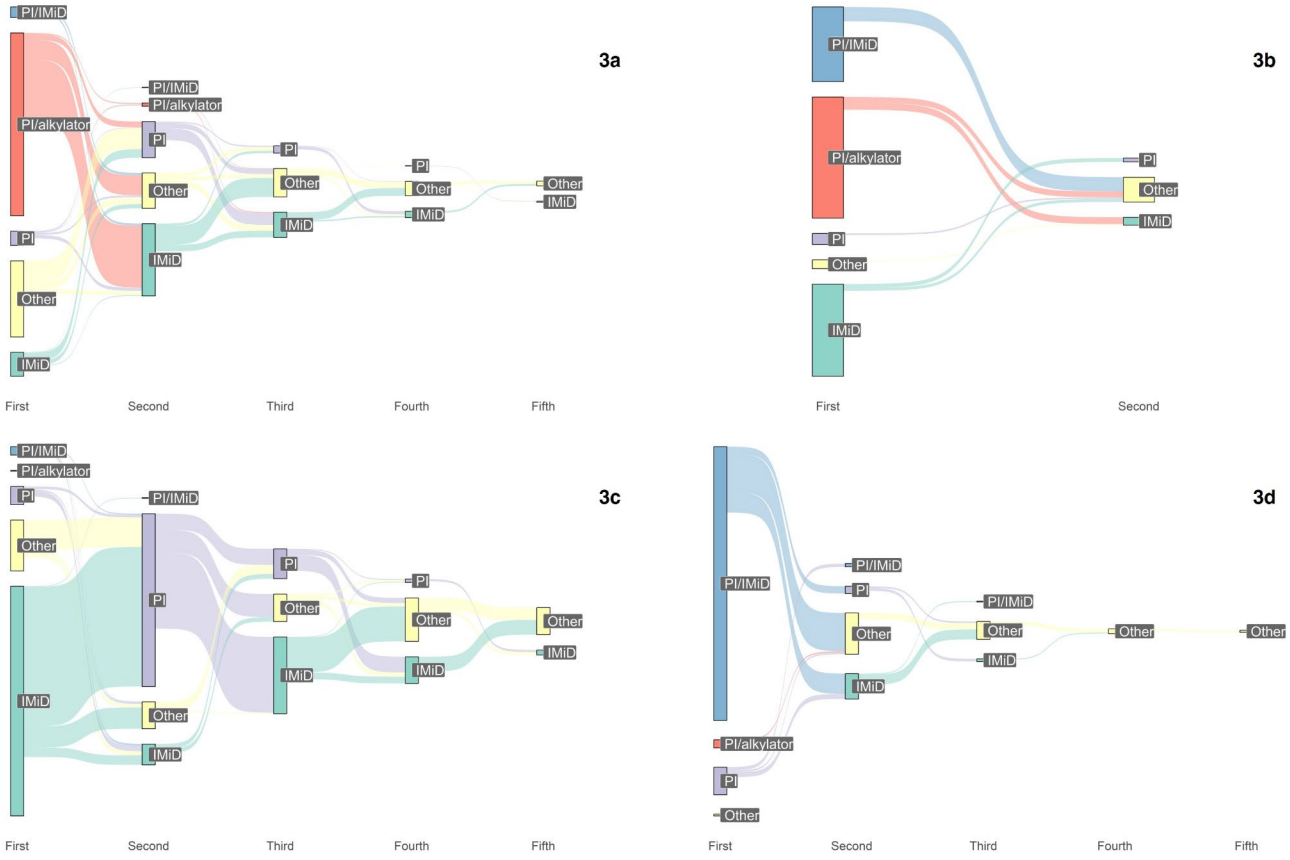

Fig. 3 Treatment patterns of patients with MM according to eligibility for SCT and reimbursement status. (**a**) Sequenced treatment of patients with MM who did not receive SCT before Rd (IMiD class) was covered by insurance (January 1, 2010, to November 30, 2017), (**b**) patients with MM who did not receive SCT after Rd was covered by insurance (December 1, 2017, to December 31, 2018), (**c**) sequenced treatment of patients with MM who received SCT before VTd (PI/IMiD class) was covered by insurance (January 1, 2010, to September 30, 2015), (**d**) patients with MM who received SCT after VTd (PI/IMiD class) was covered by insurance (October 1, 2015, to December 31, 2018). SCT, stem cell transplantation; MM, multiple myeloma; VTd, bortezomib, thalidomide, and dexamethasone; PI, proteasome inhibitor; IMiD, immunomodulatory drug; Rd, lenalidomide, and dexamethasone

the range of treatment options. The Rd regimen has been widely used among older patients aged ≥ 80 years, likely due to the preference for oral medications over injectable agents, such as bortezomib. This pattern underscores the influence of economic factors on treatment preferences and accessibility, as shown in other studies where reimbursement policies facilitated increased drug utilization and improved patient outcomes [15]. Such policy-driven changes enhance treatment accessibility and improve survival rates, particularly among frail patients, by enabling consistent care.

Similar trends have been observed in Japan. Suzuki et al. reported an increase in triplet regimens combining PIs and IMiDs around 2016, attributed to the broader availability of novel agents [16]. Handa et al. noted that, among SCT-conducted groups, bortezomib and dexamethasone (VD) therapy constituted 53.9% of treatments before 2015, whereas bortezomib, lenalidomide, and dexamethasone (VRd) emerged as the most common regimen (44.3%) after 2016 [6]. In non-SCT groups, Rd usage increased approximately 2.5-fold post-2016, with greater utilization among patients aged ≥ 70 years compared to those under 70 years, which is consistent with our findings. Additionally, attrition rates in Japanese studies rose to 48.9% in second-line treatment groups after 2015, aligning with our observations (44% for the non-SCT group and 55% for the SCT group). These results emphasize that the introduction of novel agents has enabled more patients to access subsequent treatments, ultimately improving overall outcomes. Together, these findings highlight the critical role of national policies in accelerating the adoption of innovative therapies to enhance patient care.

Recently, there have been significant advancements in MM treatment, leading to an ongoing question regarding the necessity of SCT. In the DETERMINATION trial published in 2022, patients who received lenalidomide, bortezomib, and dexamethasone (RVD) followed by SCT showed significantly better progression-free survival (PFS) (median 67.5 vs. 46.2 months) than patients who received RVD without SCT. However, no OS benefit was associated with SCT in the present study [17].

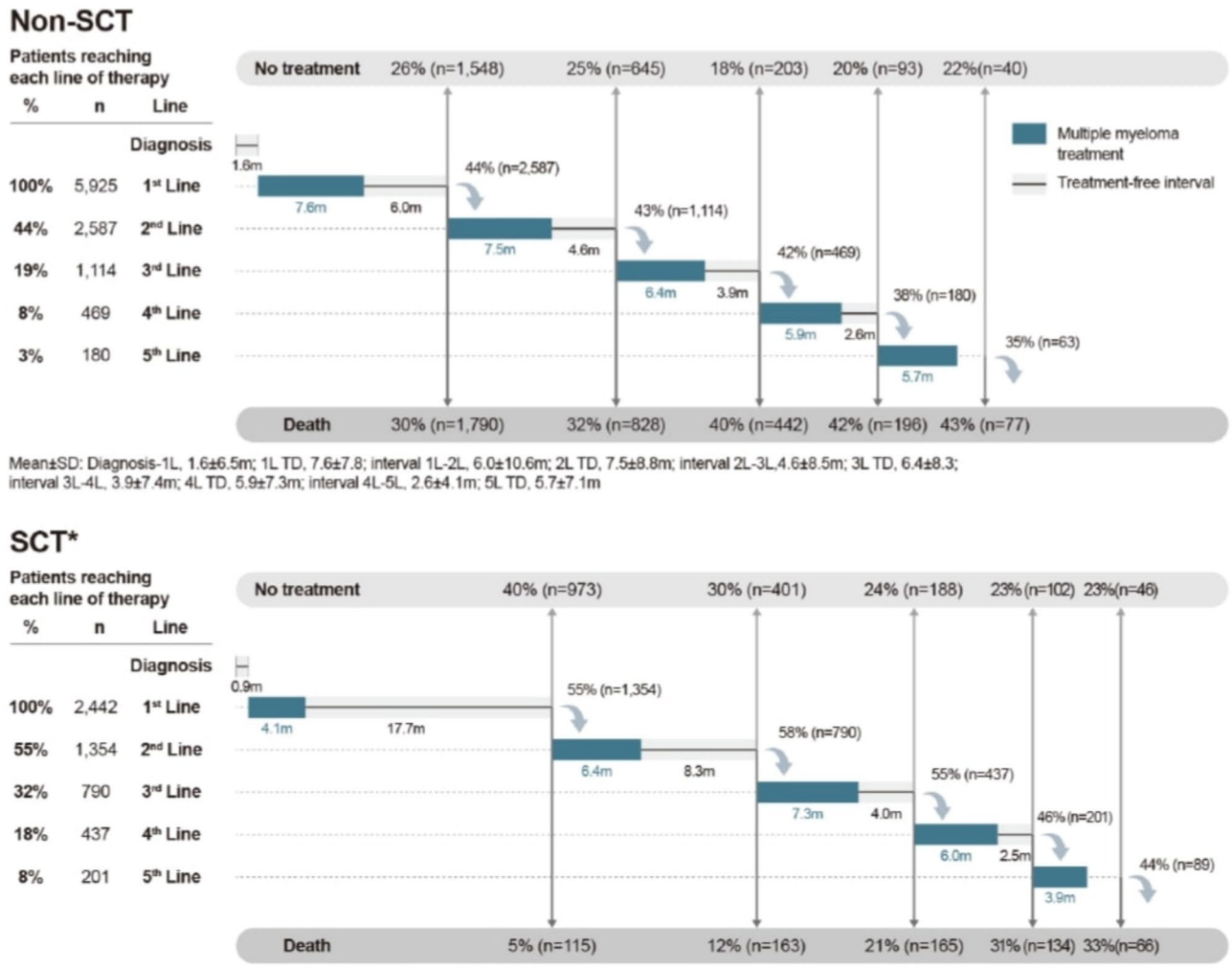

Fig. 4 Mean treatment duration and TFI, and fraction of patients with MM reaching each LOT according to SCT status. SCT, stem cell transplantation; LOT, line of therapy; TFI, treatment-free interval; VMP, bortezomib, melphalan, and prednisolone

This outcome may be attributed to the continued availability of various new treatments, even after the failure of first-line therapy. For instance, B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T cell (CAR-T) therapy may be helpful for patients in which other available treatments for MM have failed. In the CARTITUDE-4 trial, which included patients with lenalidomide-refractory MM and more than a quarter of patients with triple-class exposure, patients who received ciltacabtagene autoleucel showed significantly improved 12-month PFS (75.9% vs. 48.6%) compared to those who received standard care [18]. Bispecific antibodies, such as talquetamab and teclistamab, also represent newly available options with various molecular targets and relatively tolerable safety issues [19–21]. Even in older patients who are ineligible for SCT, new agent-combined regimens have shown outcomes comparable to those of SCT. For instance, patients who received daratumumab, lenalidomide, and dexamethasone (D-Rd) as frontline therapy had a median PFS of 62 months and an estimated 5-year OS of 66.5% [22]. These achievements in new therapies continue to raise questions regarding the necessity of SCT. However, most of these new agents are expensive, making their use challenging in many resource-poor countries. In contrast, SCT offers the advantage of providing sufficient efficacy with relatively reasonable costs compared with many newly developed high-cost treatments. In our analysis, SCT was related to superior survival outcomes regardless of age group. Furthermore, SCT demonstrated the longest treatment-free period among all the diverse regimens across the various lines of therapy analyzed. These results suggest that SCT may contribute to improved survival rates and an enhanced quality of life for patients in many resource-poor

Table 2 Analysis of factors associated with considering Rd regimen (with VMP as reference) as first LOT

Variables	Rd (ref = VMP)		
	OR	95% CI	*p*-value
Sex			
Male	Ref		0.0002
Female	1.94	1.37–2.76	
Age[a)]			
60–69	0.54	0.33–0.88	< 0.0001
70–79	Ref		
80+	3.76	2.43–5.84	
Income			
1st quartile (lowest)	Ref		0.5847
2nd quartile	1.26	0.66–2.42	
3rd quartile	1.63	0.92–2.87	
4th quartile (highest)	1.25	0.78–2.00	
CCI score			
0	Ref		0.1889
1	0.77	0.44–1.34	
2	1.02	0.58–1.79	
3	1.55	0.86–2.81	
4+	1.13	0.62–2.07	
Comorbidities associated with MM[b)]			
Renal failure	0.38	0.24–0.61	< 0.0001
Anemia	0.93	0.64–1.35	0.7039
Factures	-	–	0.9911
Bacterial disease	3.19	0.91–11.17	0.0702

ORs were adjusted for all variables in the table

OR, odds ratio; CI, confidence interval; MM, multiple myeloma; SCT, stem cell transplantation; CCI, Charlson Comorbidity Index; VMP, bortezomib, melphalan, and prednisolone; Rd, lenalidomide, and dexamethasone

[a)] Either no patient or only one patient under the age of 50 years was treated with VMP or Rd; thus, the OR is not presented

[b)] For each of the comorbidities associated with MM, the reference was 'no disease'

countries. Additionally, SCT could play an important role as standard therapy until accessibility to newly developed agents expands worldwide.

MM is an incurable disease that is characterized by frequent relapses and refractoriness. In the treatment of MM, therapy generally becomes less effective with subsequent LOT [23]. In other words, as the LOT increases, the number of patients receiving treatment decreases; therefore, the most effective treatment modality should be used as early as possible. Fonseca et al. presented the effect of treatment sequence on the survival rate of newly diagnosed transplant-ineligible patients [24]. In this study, the attrition rate between the first and second LOT was 27.7–58.8%, strongly supporting the use of D-Rd as an initial therapy without delaying subsequent LOT. In our study, the attrition rates were approximately 50% after induction therapies in both SCT- and non-SCT-conducted groups. In addition, the interval times between each LOT and TFI tended to decrease as the number of LOTs increased. This finding highlights the importance of the availability of optimal regimens for induction therapy. Recently, increasingly efficient treatment regimens have demonstrated improved efficacy. For transplant-eligible patients, the combination of daratumumab, bortezomib, lenalidomide, and dexamethasone (D-VRd) with lenalidomide for maintenance showed a significant benefit compared to VRd regimen, which is currently the most widely used regimen in Korea [25]. For transplant-ineligible patients, the combination of daratumumab, bortezomib, melphalan, and prednisolone (D-VMP) presented superior outcomes in both global and Asian populations, along with D-Rd [22, 26, 27]. However, all these regimens currently have limited accessibility in Korea due to reimbursement issues. The use of regimens with relatively low efficacy ultimately leads to a decrease in survival rates and increases the burden of additional treatments, thereby increasing the patient burden, socioeconomic costs, and reducing quality of life. Therefore, a proactive direction for the national insurance policy is necessary. Furthermore, ongoing research is needed to evaluate the outcomes of patients treated with newer regimens, such as VRd, D-VMP, and D-Rd, as well as to investigate how treatment patterns continue to evolve in response to changes in reimbursement policies.

Our study had several limitations. First, we could not assess each patient's disease stage, cytogenetic risk, or laboratory data, all of which are important information for MM. The absence of detailed clinical and molecular data, such as genetic profiles or ISS staging, may have introduced residual confounding, as these factors are essential for refining survival outcomes. Moreover, the NHIS database does not capture clinical signs, response status, progression dates, or information on uninsured treatments, potentially leading to an incomplete therapeutic landscape. Additionally, the NHIS database lacks details on treatment intent, such as whether chemotherapy was administered as consolidation or maintenance therapy. This is a limitation of database studies of the national insurance system. However, we obtained accurate information on the time to the next treatment and survival data, which could be the most important indicators directly affecting patients. Second, we could not access specific information on how treatments, including SCT, were performed because we could not check the medical records of each patient. Consequently, it was impossible to distinguish treatment changes due to planned therapeutic strategies from those resulting from true progression. All changes in treatment regimens were classified as progression, which may have introduced some misclassification. However, in the analysis of the non-SCT group, we identified patient characteristics regarding the treatment selection of VMP and Rd, allowing us to indirectly assess how these two regimens with equal selection criteria were chosen based on patient

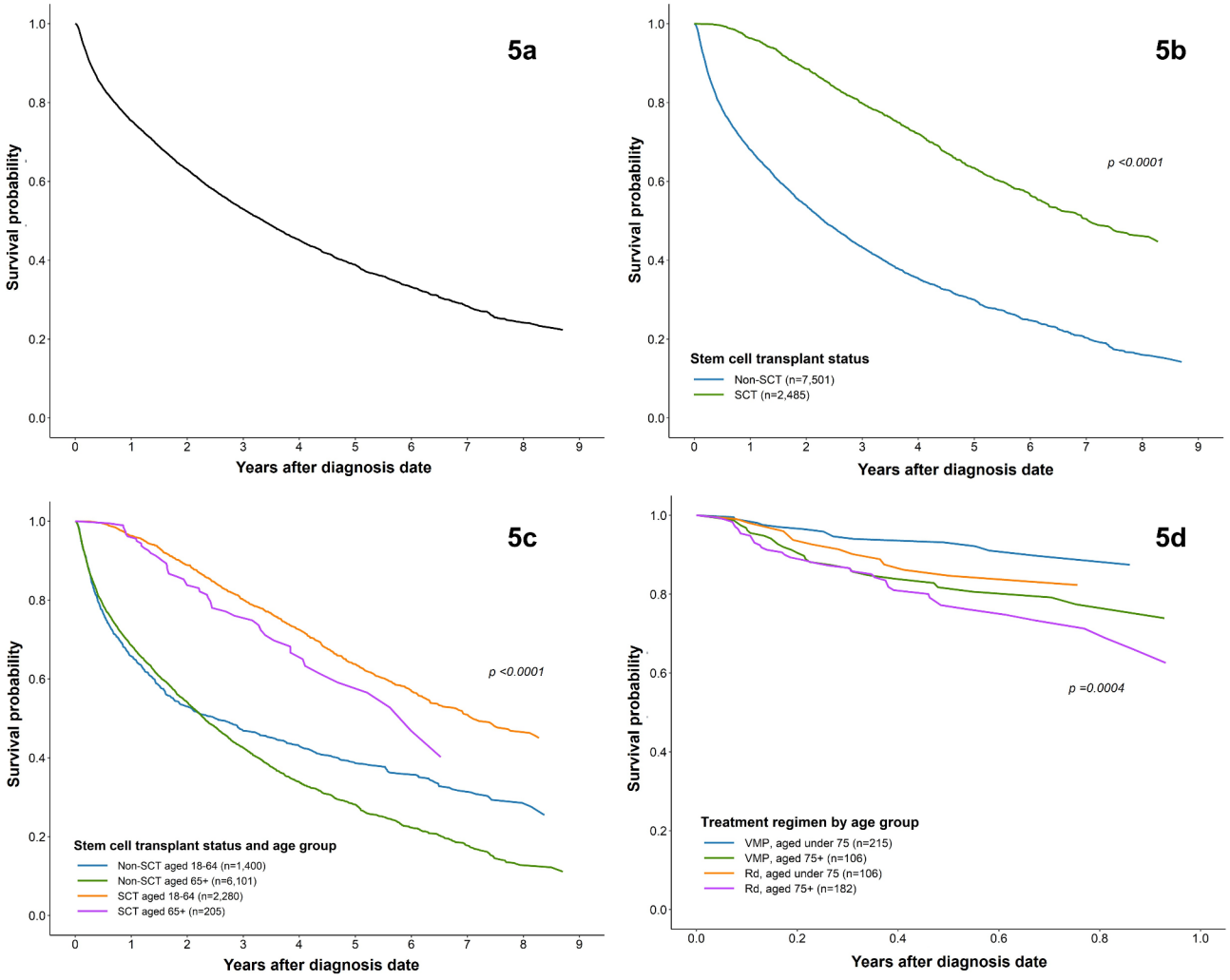

Fig. 5 Patients' probability of survival after date of MM diagnosis. (**a**) All patients with MM, including untreated patients, (**b**) all patients with MM with and without SCT, (**c**) all patients with MM stratified by the age of 65 years and SCT status, (**d**) patients with MM diagnosed in 2018 and treated with VMP and Rd therapy, stratified by age of 75 years. MM, multiple myeloma; SCT, stem cell transplantation; Rd, lenalidomide, and dexamethasone

characteristics. Third, although we analyzed data from approximately 10 years, the data on the regimens primarily used recently had relatively short follow-up periods. As a result, some findings in our analysis may have been subject to bias. Novel agents and combination regimens are associated with improved OS in patients with MM, as suggested by findings from other studies [28, 29]. Longer follow-up is essential to validate the findings of this study and better understand evolving treatment outcomes. For instance, a significant proportion of the patients who received IMiD did not receive further treatment, and fewer patients underwent more than four lines of therapy. This may be attributed to the relatively short follow-up period after the reimbursement of Rd as a first-line therapy in Korea. For the same reasons, we could not compare long-term survival outcomes between the VMP and Rd groups. Therefore, our study may not fully capture the outcomes of the continuous Rd regimen, limiting us to a comparison of 1-year OS. In our data, the 1-year OS was 82.3% for patients aged < 75 years and 62.6% for those aged ≥ 75 years. These outcomes appear slightly lower than those reported in the subgroup analysis of the FIRST trial. However, the proportion of older patients (aged ≥ 75 years) was higher among those receiving Rd in our study, and these patients had less favorable CCI scores. Consequently, it is likely that our cohort included more patients who would have been excluded from the FIRST trial. Although blood test results were unavailable in our analysis, compared to the FIRST trial, prior studies on Asian populations have reported a higher incidence of grades 3–4 thrombocytopenia (13.9% vs. 8%) [12, 30]. This disparity may have contributed to challenges in maintaining treatment for some patients. However, a detailed comparison in this regard was not feasible, which we acknowledge as a limitation of our study. Despite these limitations, our study had several strengths. Korea

is one of the few countries to have a national unified insurance system covering almost the entire population. Therefore, analyzing such data is invaluable, as it can demonstrate changes in treatment selection for diseases exhibiting rapidly changing treatment patterns. Furthermore, our analysis may provide valuable data for future comparisons of treatment patterns and outcomes after the introduction of new therapies.

Conclusions

In conclusion, the introduction of novel agents and new combination regimens has significantly influenced the choice of MM therapy in Korea. The findings of our study highlight the impact of SCT eligibility and reimbursement status for new drugs on the treatment patterns of MM. Continued efforts to expand access to novel agents and identify patients who could benefit from SCT are essential.

Abbreviations

BCMA	B-cell maturation antigen
CCI	Charlson Comorbidity Index
CAR-T	Chimeric antigen receptor T cell
Rd	Lenalidomide and dexamethasone
RVD	Lenalidomide, bortezomib, and dexamethasone
VMP	Bortezomib, melphalan, and prednisolone
VRd	Bortezomib, lenalidomide, and dexamethasone
IMiDs	Immunomodulatory drugs
ICD	International Classification of Diseases
IRB	Institutional Review Board
LOT	Line of therapy
MM	Multiple myeloma
NHIS	National Health Insurance Service
OS	Overall survival
PFS	Progression-free survival
PI	Proteasome inhibitors
RID	Rare and intractable disease
SCT	Stem cell transplantation
SEER	Surveillance, Epidemiology, and End Results
TFI	Treatment-free interval
VD	Bortezomib and dexamethasone
D-VMP	Daratumumab, bortezomib, melphalan, and prednisolone
D-VRd	Daratumumab, bortezomib, lenalidomide, and dexamethasone
D-Rd	Daratumumab, lenalidomide, and dexamethasone

Supplementary Information

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Supplementary Material 1

Author contributions

JY, JJ, and BP conceived and designed the study. JY collected and assembled data, performed data analysis and interpretation, and wrote the manuscript. JJ contributed to data analysis, interpretation, and manuscript writing. BP participated in data collection and assembly and interpretation. EL, YP, and SM provided statistical guidance and interpretation. HE was responsible for the study's concept, design, and interpretation. All authors reviewed and approved the final manuscript.

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Data availability

The data supporting the findings of this study are available from the National Health Insurance Service (NHIS), Korea. Access to these data is restricted by the Personal Information Protection Act of Korea. The data were used under a license for this study and are not publicly accessible. However, they can be made available from the authors upon reasonable request and with the approval of NHIS.

Declarations

Ethics approval and consent to participate

The research protocol for this study was reviewed and approved by the Institutional Review Board (IRB) of Hanyang University (approval number: HYU-2020-05-018-1) and the National Cancer Center, Korea (approval number: NCC2019-0238). Given that this study used anonymized data from the National Health Insurance Service database, the IRBs of Hanyang University and the National Cancer Center waived the requirement for informed consent. All data were anonymized to ensure the confidentiality and privacy of the participants. All methods were performed in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74:12–49.
2. Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. Am J Hematol. 2020;95:548–67.
3. Kang MJ, Won YJ, Lee JJ, Jung KW, Kim HJ, Kong HJ, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2019. Cancer Res Treat. 2022;54:330–44.
4. Atrash S, Thompson-Leduc P, Tai MH, Kaila S, Gray K, Ghelerter I, et al. Treatment patterns and effectiveness of patients with multiple myeloma initiating daratumumab across different lines of therapy: a real-world chart review study. BMC Cancer. 2021;21:1207.
5. Kouroukis TC, Baldassarre FG, Haynes AE, Imrie K, Reece DE, Cheung MC. Bortezomib in multiple myeloma: systematic review and clinical considerations. Curr Oncol. 2014;21:e573–603.
6. Handa H, Ishida T, Ozaki S, Mori A, Kato K, Iida S. Treatment pattern and clinical outcomes in multiple myeloma patients in Japan using the Medical Data Vision claims database. PLoS ONE. 2023;18:e0283931.
7. Ailawadhi S, Jagannath S, Narang M, Rifkin RM, Terebelo HR, Toomey K, et al. Connect MM Registry as a national reference for United States multiple myeloma patients. Cancer Med. 2020;9:35–42.
8. Mizuno S, Kawamura K, Hanamura I, Sunami K, Mori T, Nakamura F, et al. Efficacy and safety of autologous stem cell transplantation in patients aged >/= 65 years with multiple myeloma in the era of novel agents. Bone Marrow Transpl. 2019;54:1595–604.
9. Jung J, Choi YS, Lee JH, Lee WS, Kim SH, Park Y, et al. Autologous stem cell transplantation in elderly patients with multiple myeloma in Korea: the KMM1807 study. Int J Hematol. 2020;112:84–95.
10. Facon T, San-Miguel J, Dimopoulos MA, Mateos MV, Cavo M, van Beekhuizen S, et al. Treatment regimens for transplant-ineligible patients with newly diagnosed multiple myeloma: a systematic literature review and network meta-analysis. Adv Ther. 2022;39:1976–92.
11. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Bortezomib plus Melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008;359(9):906–17.
12. Benboubker L, Dimopoulos MA, Dispenzieri A, Catalano J, Belch AR, Cavo M, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2014;371(10):906–17.

13. Park B, Lee E, Yoon J, Park Y, Eom HS. Secondary malignancies in multiple myeloma in Korean patients: a nationwide population-based study. Cancer Res Treat. 2024;56:936–44.
14. Lee YJ, Moon JH, Sohn SK, Kim SJ, Jung SH, Lee JJ, et al. Benefits of additional cycles of bortezomib/thalidomide/dexamethasone (VTD) induction therapy compared to four cycles of VTD for newly diagnosed multiple myeloma. Bone Marrow Transplant. 2019;54(12):2051–9.
15. Xu J, Xu P, Han Q, Sun J, Chen B, Dong X. Socioeconomic status-based survival disparities and nomogram prediction for patients with multiple myeloma: results from American and Chinese populations. Front Oncol. 2022;12:941714.
16. Kenshi SUZUKI, Amy BUCHANAN-HUGHES, Alvin NG, Yan Ran WEE, Iro CHATZIDAKI, Jose GARNICAEK, et al. Real-world treatment patterns in multiple myeloma: retrospective observational study using the Japan Medical Data Vision claims database (2012–2020). Int J Myeloma. 2024;14(5):27–41.
17. Richardson PG, Jacobus SJ, Weller EA, Hassoun H, Lonial S, Raje NS, et al. Triplet therapy, transplantation, and maintenance until progression in myeloma. N Engl J Med. 2022;387:132–47.
18. San-Miguel J, Dhakal B, Yong K, Spencer A, Anguille S, Mateos MV, et al. Ciltacel or standard care in lenalidomide-refractory multiple myeloma. N Engl J Med. 2023;389:335–47.
19. Swan D, Murphy P, Glavey S, Quinn J. Bispecific antibodies in multiple myeloma: opportunities to enhance efficacy and improve safety. Cancers (Basel). 2023;15.
20. Chari A, Minnema MC, Berdeja JG, Oriol A, van de Donk NWCJ, Rodríguez-Otero P, et al. Talquetamab, a T-cell-redirecting GPRC5D bispecific antibody for multiple myeloma. N Engl J Med. 2022;387:2232–44.
21. Moreau P, Garfall AL, van de Donk NWCJ, Nahi H, San-Miguel JF, Oriol A, et al. Teclistamab in relapsed or refractory multiple myeloma. N Engl J Med. 2022;387:495–505.
22. Kumar SK, Moreau P, Bahlis NJ, Facon T, Plesner T, Orlowski RZ et al. Daratumumab plus Lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (rd) alone in transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM): updated analysis of the phase 3 Maia Study. Blood. 2022;140;Suppl 1:10150–3.
23. Szabo AG, Iversen KF, Möller S, Plesner T. The clinical course of multiple myeloma in the era of novel agents: a retrospective, single-center, real-world study. Clin Hematol Int. 2019;1:220–8.
24. Fonseca R, Facon T, Hashim M, Nair S, He J, Ammann E, et al. Impact of treatment sequencing on overall survival in patients with transplant-ineligible newly diagnosed myeloma. Oncologist. 2023;28:e263–9.
25. Sonneveld P, Dimopoulos MA, Boccadoro M, Quach H, Ho PJ, Beksac M, et al. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2024;390:301–13.
26. Mateos MV, Dimopoulos MA, Cavo M, Suzuki K, Jakubowiak A, Knop S, et al. Daratumumab plus Bortezomib, melphalan, and prednisone for untreated myeloma. N Engl J Med. 2018;378:518–28.
27. Fu W, Bang SM, Huang H, Kim K, Li W, An G, et al. Bortezomib, melphalan, and prednisone with or without daratumumab in transplant-ineligible Asian patients with newly diagnosed multiple myeloma: the phase 3 OCTANS study. Clin Lymphoma Myeloma Leuk. 2023;23:446–55..e4 e444.
28. Puertas B, González-Calle V, Sobejano-Fuertes E, Escalante F, Queizán JA, Bárez A, et al. Novel agents as Main drivers for continued improvement in Survival in multiple myeloma. Cancers (Basel). 2023;15(5):1558.
29. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008;111(5):2516–20.
30. Lu J, Lee JH, Huang SY, Qiu L, Lee JJ, Liu T, et al. Continuous treatment with lenalidomide and low-dose dexamethasone in transplant-ineligible patients with newly diagnosed multiple myeloma in Asia: subanalysis of the FIRST trial. Br J Haematol. 2017;176(5):743–9.

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