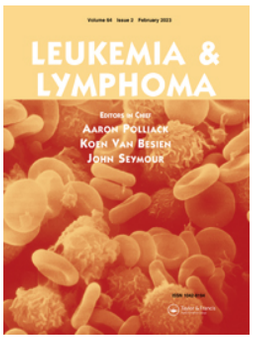

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ORIGINAL ARTICLE

Real-world assessment of the treatment patterns and outcomes among patients with multiple myeloma across different risk stratification criteria in the United States: a retrospective cohort study

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ABSTRACT

This study evaluated prognostic performance of International Staging System (ISS), revised ISS, and chromosomal abnormalities (CA) in newly diagnosed multiple myeloma patients to describe treatment patterns (cohort 1; $n = 1979$) and survival outcomes (cohort 2; $n = 1382$). In both cohorts, ~18%, 41%, and 37% of patients were high-risk according to the R-ISS, ISS, and high-risk CA criteria, respectively. Across all risk stratification criteria, 60% of patients received triplets. In cohort 2, the median modified progression-free survival decreased with each increasing risk stage (23.5, 12.1, and 8.8 months in R-ISS I, II, and III, respectively, and 16.0, 12.7, and 10.4 months in ISS I, II, and III). Similar trends were observed in the proportions of two-year overall survival. In conclusion, R-ISS has greater discriminatory power than ISS or high-risk CA alone and can be implemented in a real-world setting. Accordingly, a more risk-adapted approach can be feasible, with a greater population-level impact.

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Electronic health records; overall survival; prognosis; progression-free survival; triplets

Introduction

The worldwide incidence of multiple myeloma (MM), a plasma cell neoplasm, was estimated to be 176,000 cases, with an estimated mortality in 117,000 cases [1]. In the United States (US), MM accounts for 1.8% of all incident cancer cases [2]. The prognosis and survival outcomes in patients with MM have significantly improved due to high-dose chemotherapy with stem cell support and the introduction of three new drug classes, namely immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and monoclonal antibodies, along with systemic steroids [3–8]. However, the improvement in survival does not extend equally to all patients with MM, especially among high-risk subgroups.

To develop a prognostic staging system, the International Myeloma Working Group (IMWG) developed the International Staging System (ISS) based on the serum levels of albumin and β_2-microglobulin [9]. Subsequently, the importance of chromosomal abnormalities (CA), defined as the presence of del(17p), t(4;14), t(14;16), t(14;20), p53 mutation, gain 1q, and lactate dehydrogenase (LDH) level above the upper limit of normal, were reported in the prognostication of MM [10–12]. In 2015, the IMWG proposed the revised ISS (R-ISS) as a prognostic risk stratification system with better discrimination for overall survival (OS) and progression-free survival (PFS) that integrated the presence of high-risk CA as a function of disease biology and LDH as a function of tumor burden into the ISS [11]. In R-ISS, patients were stratified into three groups, namely R-ISS I, comprising ISS I, no high-risk CA, and normal LDH levels; R-ISS III, comprising ISS III and high-risk CA or high LDH levels; and R-ISS II, comprising all other possible combinations. The 5-year OS rates were 82%, 62%, and 40% in the R-ISS I, II, and III groups, respectively; the 5-year PFS rates were 55%, 36%, and 24%, respectively [11]. Although R-ISS has been successfully evaluated in various settings [13–15], real-world studies using electronic health records (EHRs) have not evaluated the performance of risk stratification systems with real-world outcomes. Further, there is a difference between efficacy outcomes observed in clinical trials and real-world studies in patients with MM [16]. Results obtained in the real-

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world studies tend to demonstrate poorer long-term outcomes than those from clinical trials due to stringent patient enrollment criteria and strict study protocols in clinical trials. This study aims to evaluate the prognostic performance of ISS, R-ISS, and high-risk CA to characterize treatment patterns and evaluate survival outcomes, including OS and modified PFS (mPFS), among patients with newly diagnosed MM (NDMM) in the US community practice.

Materials and methods

Data source

Data from the Flatiron MM Enhanced EHR (New York, NY) were used in this retrospective cohort study. The Flatiron network represents a longitudinal, and demographically and geographically diverse database with data from over 280 cancer clinics representing over two million active patients treated at primarily community-based hematology/oncology practices in the US. Flatiron Health generates a real-world, longitudinal dataset derived from EHRs and other real-world data sources that can support observational research to improve cancer care. Flatiron Health collects both structured (extracted from the EHR and harmonized to a standard terminology) and unstructured (abstracted from the EHR through technology-enabled human review based on standardized processes) data elements and applies algorithms to combine structured and/or unstructured data into derived data. For all patients treated in the Flatiron network, the entire patient chart in the EHR is available to Flatiron, thus enabling a complete view of the longitudinal data of cancer patients with resolution at the disease and treatment level. Further details are available in Supplemental Methods.

Patient selection

This study included adult ($\geq$18 years old) patients with NDMM who received treatment following MM diagnosis as the first line of therapy (LOT1). The International Classification of Diseases, Ninth Revision (ICD-9) diagnosis code 203.00 or ICD-10 diagnosis code 90.00 was used to identify the diagnosis of MM.

Two study periods were used to evaluate treatment distribution and survival outcomes. For the assessment of treatment distribution, cohort 1 included patients diagnosed with MM from 1 January 2015 to 30 June 2020, with a 6-month follow-up through 31 December 2020. For mPFS and OS outcomes assessment, cohort 2 included patients diagnosed with MM from 1 January 2015 to 31 December 2018, with a 2-year follow-up through 31 December 2020. Based on the IMWG criteria, these patients were stratified into three risk categories (stages I, II, and III) at baseline using the ISS and R-ISS risk stratification criteria, and two categories (high-risk and standard-risk) based on CA [9,11]. High-risk CA was characterized by the presence of at least one of the abnormalities such as del(17p), t(4;14), t(14;16), t(14;20), p53 mutation, and gain 1q. Patients classifiable by R-ISS risk categories were included in the study and those with multiple malignancies other than MM were excluded.

The disease index date and the treatment index date were defined as the date when the patient was first diagnosed with MM and when the treatment with LOT1 was initiated, respectively. The baseline period was from up to 30 days prior to the disease index date to seven days after the treatment index date. The follow-up period for each patient started on the treatment index date.

Research objectives

The primary objectives were to describe the demographic and clinical characteristics of patients with NDMM and to characterize the distribution of MM treatments by LOT1 and drug classes. The secondary objectives were to describe mPFS and two-year OS, and the proportion of patients who received stem cell transplant (SCT) after initiation of LOT1 and before initiation of the second LOT (LOT2).

Outcomes

Clinical and demographic characteristics were assessed at baseline, and the distribution of MM treatments was determined at the LOT index date. The primary outcomes of the study were to examine treatment distribution by LOT1 and drug classes used in the treatment of MM in patients included in cohort 1. Treatment patterns were described by regimen (all drugs in a regimen, drug/regimen classes), and number of agents in the regimen, i.e. monotherapy, doublets, triplets, and quadruplets. A detailed description of the treatment regimens is provided in Supplemental Table 1. Patient outcomes, including mPFS and two-year OS, were assessed for LOT1. The proportion of patients who received SCT after initiation of LOT1 but before initiation of LOT2 in the follow-up period was also evaluated.

Lines of therapy

Line of therapy is defined in Flatiron based on an MM algorithm developed by a cross-functional team of oncologists, engineers, and biostatisticians with clinical expertise using a step-wise approach based on the review and summary of medication administrations recorded in the EHR from structured and unstructured data. The full description of the Flatiron LOT is provided in Supplemental Table 2.

Statistical analyses

The primary analysis characterized the clinical and demographic characteristics at MM diagnosis. Results of the analyses were stratified across ISS and R-ISS stratification criteria (stages I–III) and CA (high-risk or standard-risk). All study variables were analyzed by descriptive statistics. Continuous variables were summarized by mean and standard deviation, and categorical variables were summarized by frequencies and percentages. For categorical variables, *p* values were determined via Chi-square test or Monte Carlo simulation of Fisher's exact test for small sample sizes; means were determined via one-way ANOVA; and Kruskal–Wallis tests were performed for medians. Treatment patterns and transplant distributions were reported as frequencies and percentages. The median mPFS was measured from treatment initiation until death, progression, or at the start of LOT2. The proportion of two-year OS was measured from treatment initiation until death. Both were summarized using Kaplan–Meier estimates and 95% confidence intervals (CIs). Wilcoxon's rank-sum tests were used to generate *p* values for survival curves. Statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC).

Results

Patient characteristics

A total of 1979 and 1382 patients were eligible and included in cohorts 1 and 2, respectively (Figure 1). In cohort 1, 367 (18.6%), 805 (40.7%), and 738 (37.3%) patients were stratified as R-ISS III, ISS III, and high-risk CA, respectively. A similar trend was observed in cohort 2, with 248 (18.0%), 566 (41.0%), and 508 (36.8%) patients stratified as R-ISS III, ISS III, and high-risk CA, respectively.

Baseline and disease characteristics of patients enrolled in cohorts 1 and 2 are shown in Table 1 and Supplemental Table 3, respectively. We observed

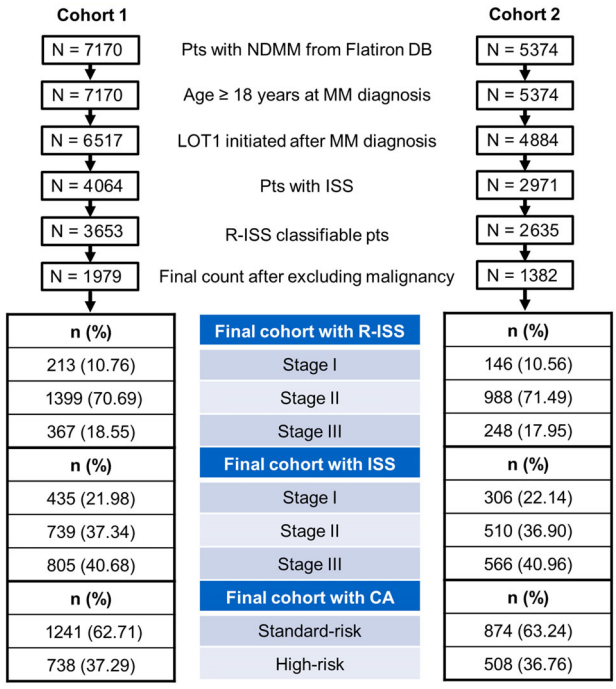

Figure 1. Patient identification. CA: chromosomal abnormalities; DB: database; ISS: International Staging System; LOT1: first line of therapy; NDMM: newly diagnosed multiple myeloma; pts: patients; R-ISS: revised ISS.

similar demographics and baseline characteristics among patients in cohorts 1 and 2. In cohort 1, the proportion of men was slightly greater than that of women. Approximately, 60% of the patients were white and aged ≥60 years (Table 1). A higher proportion of patients aged ≥75 years belonged to the high-risk categories of R-ISS and ISS. The proportion of patients stratified in low-risk categories remained constant from 2015 to 2019. During the same period, the number of high-risk patients gradually increased. A greater proportion of high-risk patients stratified by R-ISS and ISS risk stratification criteria had an Eastern Cooperative Oncology Group (ECOG) score ≥2 than that in the low-risk patients. Hypercalcemia was observed in high-risk and low-risk patients, ranging from 3.9% to 5.1% and 2.3% to 3.1%, respectively. A greater proportion of patients stratified in R-ISS III (198; 54.0%) had a poor renal function with estimated glomerular filtration rate ≥3 than those stratified in R-ISS I (28; 13.1%, $p < 0.0001$). A similar trend was observed in patients stratified by the ISS risk stratification criteria. Further, approximately 63% of high-risk patients and 23% of low-risk patients had anemia. The proportion of patients with anemia with standard-risk and high-risk CA was similar. Among the patients included in this study, 60% of high-risk patients and

Table 1. Baseline and disease characteristics of patients included in cohort 1 for studying treatment distribution.

	R-ISS				ISS				CA		
	I ($N=213$)	II ($N=1399$)	III ($N=367$)	p value[a]	I ($N=435$)	II ($N=739$)	III ($N=805$)	p value	Standard risk ($N=1241$)	High risk ($N=738$)	p value
Age, years, mean (SD)	67.21 (10.75)	67.93 (10.20)	68.40 (11.10)	0.4111	66.01 (10.82)	68.17 (9.88)	68.76 (10.59)	<0.0001	68.25 (10.35)	67.42 (10.55)	0.0864
Age, years				0.1963				0.0006			0.0804
<65	82 (38.49)	475 (33.95)	121 (32.97)		184 (42.29)	240 (32.47)	254 (31.55)		419 (33.76)	259 (35.09)	
65–74	71 (33.33)	514 (36.74)	120 (32.69)		149 (34.25)	285 (38.56)	271 (33.66)		423 (34.08)	282 (38.21)	
≥75	60 (28.17)	410 (29.31)	126 (34.33)		102 (23.45)	214 (28.96)	280 (34.78)		399 (32.15)	197 (26.69)	
Sex				0.2140				0.3042			0.0571
Male	116 (54.46)	765 (54.68)	182 (49.59)		223 (51.26)	412 (55.75)	428 (53.17)		687 (55.36)	376 (50.95)	
Female	97 (45.54)	634 (45.32)	185 (50.41)		212 (48.74)	327 (44.25)	377 (46.83)		554 (44.64)	362 (49.05)	
Race				0.2218				0.3650			0.2474
Asian	0	32 (2.29)	10 (2.72)		7 (1.61)	14 (1.89)	21 (2.61)		25 (2.01)	17 (2.30)	
Black or African American	35 (16.43)	218 (15.58)	71 (19.35)		75 (17.24)	115 (15.56)	134 (16.65)		193 (15.55)	131 (17.75)	
White	132 (61.97)	842 (60.19)	203 (55.31)		259 (59.54)	459 (62.11)	459 (57.02)		751 (60.52)	426 (57.72)	
Hispanic or Latino	0	4 (0.29)	1 (0.27)		0	1 (0.14)	4 (0.50)		4 (0.32)	1 (0.14)	
Other	24 (11.27)	143 (10.22)	44 (11.99)		43 (9.89)	69 (9.34)	99 (12.30)		141 (11.36)	70 (9.49)	
Unknown	22 (10.33)	160 (11.44)	38 (10.35)		51 (11.72)	81 (10.96)	88 (10.93)		127 (10.23)	93 (12.60)	
Year of MM diagnosis				0.1750				0.7445			0.0567
2015	42 (19.72)	255 (18.23)	45 (12.26)		75 (17.24)	142 (19.22)	125 (15.53)		239 (19.26)	103 (13.96)	
2016	37 (17.37)	249 (17.80)	67 (18.26)		82 (18.85)	119 (16.10)	152 (18.88)		223 (17.97)	130 (17.62)	
2017	33 (15.49)	215 (15.37)	68 (18.53)		68 (15.63)	116 (15.70)	132 (16.40)		186 (14.99)	130 (17.62)	
2018	34 (15.96)	269 (19.23)	68 (18.53)		81 (18.62)	133 (18.00)	157 (19.50)		226 (18.21)	145 (19.65)	
2019	52 (24.41)	290 (20.73)	92 (25.07)		97 (22.30)	162 (21.92)	175 (21.74)		264 (21.27)	170 (23.04)	
2020	15 (7.04)	121 (8.65)	27 (7.36)		32 (7.36)	67 (9.07)	64 (7.95)		103 (8.30)	60 (8.13)	
ECOG score				0.0010				<0.0001			0.4621
0	73 (34.27)	297 (21.23)	69 (18.80)		133 (30.57)	169 (22.87)	137 (17.02)		262 (21.11)	177 (23.98)	
1	53 (24.88)	402 (28.73)	96 (26.16)		115 (26.44)	219 (29.63)	217 (26.96)		348 (28.04)	203 (27.51)	
2	16 (7.51)	166 (11.87)	48 (13.08)		34 (7.82)	89 (12.04)	107 (13.29)		147 (11.85)	83 (11.25)	
3	3 (1.41)	51 (3.65)	18 (4.90)		7 (1.61)	21 (2.84)	44 (5.47)		49 (3.95)	23 (3.12)	
4	1 (0.47)	2 (0.14)	0		1 (0.23)	1 (0.14)	1 (0.12)		3 (0.24)	0	
Missing	67 (31.46)	481 (34.38)	136 (37.06)		145 (33.33)	240 (32.48)	299 (37.14)		432 (34.81)	252 (34.15)	
Hypercalcemia	5 (2.35)	44 (3.15)	18 (4.90)	0.1705	10 (2.30)	16 (2.17)	41 (5.09)	0.0023	38 (3.06)	29 (3.93)	0.3021
eGFR stage[b]				<0.0001				<0.0001			0.0037
1	54 (25.35)	164 (11.72)	21 (5.72)		111 (25.52)	89 (12.04)	39 (4.84)		156 (12.57)	83 (11.25)	
2	106 (49.77)	389 (27.81)	53 (14.44)		182 (41.84)	248 (33.56)	118 (14.66)		357 (28.77)	191 (25.88)	
3A	20 (9.39)	193 (13.80)	42 (11.44)		40 (9.20)	130 (17.59)	85 (10.56)		160 (12.89)	95 (12.87)	
3B	8 (3.76)	152 (10.86)	63 (17.17)		15 (3.45)	66 (8.93)	142 (17.64)		151 (12.17)	72 (9.76)	
4	0	106 (7.58)	66 (17.98)		4 (0.92)	26 (3.52)	142 (17.64)		107 (8.62)	65 (8.81)	
5	0	50 (3.57)	27 (7.36)		0	8 (1.08)	69 (8.57)		55 (4.43)	22 (2.98)	
Unknown	25 (11.74)	345 (24.66)	95 (25.89)		83 (19.08)	172 (23.27)	210 (26.09)		255 (20.55)	210 (28.46)	
Anemia	50 (23.47)	651 (46.53)	233 (63.49)	<0.0001	106 (24.37)	323 (43.71)	505 (62.73)	<0.0001	578 (46.58)	356 (48.24)	0.4736
Bone-targeting agents[c]	155 (72.77)	887 (63.40)	220 (59.95)	0.0072	308 (70.80)	479 (64.82)	475 (59.01)	0.0002	786 (63.34)	476 (64.50)	0.6028

CA: chromosomal abnormalities; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; ISS: International Staging System; MM: multiple myeloma; R-ISS: revised ISS; SD: standard deviation.

Data are reported as n (%) unless specified otherwise.

[a]p values for frequencies were determined by Chi-square test or Monte Carlo simulation of Fisher's exact test for small sample sizes. Statistical significance for means were determined by one-way ANOVA.

[b]Estimated using the CKD-EPI equation [17].

[c]Defined as the use of zoledronic acid, pamidronate disodium, or denosumab.

Table 2. Treatment distribution in patients included in cohort 1 and treated with LOT1.

	R-ISS			ISS			CA	
	I (*N* = 213)	II (*N* = 1399)	III (*N* = 367)	I (*N* = 435)	II (*N* = 739)	III (*N* = 805)	Standard risk (*N* = 1241)	High risk (*N* = 738)
Doublets	47 (22.07)	388 (27.73)	88 (23.98)	105 (24.14)	193 (26.12)	225 (27.95)	347 (27.96)	176 (23.85)
PIs + dexamethasone	16 (7.51)	160 (11.44)	42 (11.44)	29 (6.67)	73 (9.88)	116 (14.41)	152 (12.25)	66 (8.94)
IMiDs + dexamethasone	26 (12.21)	200 (14.3)	35 (9.54)	67 (15.4)	110 (14.88)	84 (10.43)	167 (13.46)	94 (12.74)
MAbs + PIs	0	0	1 (0.27)	0	0	1 (0.12)	1 (0.08)	0
MAbs + corticosteroids	2 (0.94)	2 (0.14)	0	2 (0.46)	1 (0.14)	1 (0.12)	4 (0.32)	0
Triplets	140 (65.73)	868 (62.04)	227 (61.85)	283 (65.06)	478 (64.68)	474 (58.88)	754 (60.76)	481 (65.18)
PIs + IMiDs + dexamethasone	124 (58.22)	706 (50.46)	159 (43.32)	253 (58.16)	402 (54.4)	334 (41.49)	601 (48.43)	388 (52.57)
PIs + chemotherapy + dexamethasone	11 (5.16)	135 (9.65)	62 (16.89)	22 (5.06)	64 (8.66)	122 (15.16)	129 (10.39)	79 (10.7)
MAbs + PIs + corticosteroids	1 (0.47)	5 (0.36)	3 (0.82)	1 (0.23)	2 (0.27)	6 (0.75)	2 (0.27)	7 (0.56)
MAbs + IMiDs + corticosteroids	2 (0.94)	12 (0.86)	1 (0.27)	3 (0.69)	6 (0.81)	6 (0.75)	6 (0.81)	9 (0.73)
Quadruplets	7 (3.29)	50 (3.57)	25 (6.81)	12 (2.76)	19 (2.57)	51 (6.34)	52 (4.19)	30 (4.07)
PIs + IMiDs + chemotherapy + dexamethasone	4 (1.88)	39 (2.79)	21 (5.72)	6 (1.38)	13 (1.76)	45 (5.59)	42 (3.38)	22 (2.98)
MAbs + PIs + IMiDs + corticosteroids	2 (0.94)	10 (0.71)	1 (0.27)	5 (1.15)	6 (0.81)	2 (0.25)	5 (0.68)	8 (0.64)
MAbs + PIs + corticosteroids + chemotherapy	0	0	3 (0.82)	0	0	3 (0.37)	3 (0.41)	0

CA: chromosomal abnormalities; IMiD: immunomodulatory drugs; ISS: International Staging System; LOT1: first line of therapy; MAbs: monoclonal antibodies; PI: proteasome inhibitor; R-ISS: revised ISS.
Data are reported as *n* (%). Most frequent treatment regimens are included.

71% of low-risk patients were treated with bone-targeting agents (BTAs), namely zoledronic acid, pamidronate disodium, or denosumab. A similar proportion of patients with standard-risk and high-risk CA were treated with BTAs.

Treatment distribution in patients treated with first line of therapy (cohort 1)

Triplets were the most common treatment regimens across all risk stratification criteria, with approximately 60% of the patients receiving them (Table 2). Among them, the combination of PIs, IMiDs, and dexamethasone was used for the treatment of 41–58% of patients and that of PIs, chemotherapy, and dexamethasone was used for treating 5–17% of patients. Approximately 25% of the patients were treated with doublets across all risk stratification criteria (Table 2). Among the doublets, 7–15% of all patients received the combination of dexamethasone with either PIs or IMiDs. Further, quadruplets were used in the treatment of 3–7% of patients (Table 2). Of these, approximately, 7% stratified in R-ISS III and ISS III and 3% stratified in R-ISS I and ISS I received quadruplets. The combination of PIs, IMiDs, dexamethasone, and chemotherapy was the most frequently used quadruplet regimen.

Median modified progression-free survival and two-year overall survival proportion (cohort 2)

In all the treatment regimens, the median mPFS was 8.8 (95% CI, 7.1–11.0) months in patients stratified in R-ISS III and 23.5 (95% CI, 13.8–not estimable [NE]) months in those stratified in R-ISS I (Table 3). Similar trends were reported in the high-risk and low- or standard-risk patients according to ISS and CA risk stratification criteria (Figure 2(A–C)). Patients treated with doublets or triplets and stratified in the high-risk categories of R-ISS and ISS demonstrated lower mPFS as opposed to those stratified in the low-risk categories (Table 3). In patients treated with triplets, the median mPFS was 10.4 (95% CI, 9.0–12.6) months in those stratified in high-risk CA and 15.5 (95% CI, 12.9–18.1) months in those stratified in standard-risk CA. In contrast, the median mPFS in patients treated with doublets was similar in standard-risk and high-risk CA categories (Table 3).

Overall, the two-year OS proportion was 0.65 (95% CI, 0.59–0.70) months in patients stratified in R-ISS III, 0.79 (95% CI, 0.76–0.81) months in those stratified in R-ISS II, and 0.91 (95% CI, 0.85–0.95) months in those stratified in R-ISS I (Table 3). This trend was consistent in patients stratified by ISS and CA risk stratification criteria (Figure 2(D–F)). A numerically lower two-year OS proportion was reported in high-risk patients treated with doublets and triplets as opposed to low- and standard-risk patients (Table 3).

In general, across all risk stratification criteria, a numerically lower median mPFS was reported in patients aged $\geq$75 years than those aged $<$75 years (Supplemental Tables 4 and 5). A similar trend was observed in the findings of two-year OS proportions (Supplemental Tables 6 and 7).

Transplant distribution

Transplant distribution was studied after initiation of LOT1 and before initiation of LOT2. Among all patients

Table 3. Modified progression-free survival and two-year overall survival among patients with NDMM stratified across risk stratification criteria (cohort 2).

	R-ISS			ISS			CA	
	I	II	III	I	II	III	Standard risk	High risk
Modified progression-free survival								
All therapies, *N*[a]	146	988	248	306	510	566	874	508
Number of events	74	657	182	179	330	404	563	350
Median mPFS (95% CI), months	23.5 (13.8–NE)	12.1 (10.7–13.6)	8.8 (7.1–11.0)	16.0 (12.2–19.5)	12.7 (10.7–14.3)	10.4 (8.5–11.5)	13.1 (11.3–14.8)	10.1 (8.8–12.1)
Doublets, *N*	33	302	67	79	147	176	266	136
Number of events	18	201	53	43	99	130	179	93
Median mPFS (95% CI), months	15.9 (6.0–NE)	11.1 (8.8–13.8)	7.1 (4.3–11.0)	18.0 (11.3–NE)	10.8 (8.1–15.9)	8.3 (6.6–11.0)	10.4 (8.4–12.8)	11.0 (8.1–16.8)
Triplets, *N*	92	576	150	190	310	318	501	317
Number of events	43	375	106	109	193	222	312	212
Median mPFS (95% CI), months	NE (16.1–NE)	13.3 (11.5–15.5)	9.5 (7.1–12.1)	17.1 (12.2–23.8)	13.6 (11.4–16.3)	11.2 (9.5–13.01)	15.5 (12.9–18.1)	10.4 (9.0–12.6)
Two-year overall survival								
All therapies, *N*[a]	146	988	248	306	510	566	874	508
Number of events	13	212	87	33	98	181	186	126
OS, proportion (95% CI), months	0.91 (0.85–0.95)	0.79 (0.76–0.81)	0.65 (0.59–0.70)	0.89 (0.85–0.92)	0.81 (0.77–0.84)	0.68 (0.64–0.72)	0.79 (0.76–0.81)	0.75 (0.71–0.79)
Doublets, *N*	33	302	67	79	147	176	266	136
Number of events	2	77	34	10	30	73	68	45
OS, proportion (95% CI), months	0.94 (0.78–0.98)	0.75 (0.69–0.79)	0.49 (0.37–0.61)	0.87 (0.78–0.93)	0.80 (0.72–0.85)	0.59 (0.51–0.65)	0.74 (0.69–0.79)	0.67 (0.58–0.74)
Triplets, *N*	92	576	150	190	310	318	501	317
Number of events	9	106	42	20	54	83	90	67
OS, proportion (95% CI), months	0.90 (0.82–0.95)	0.82 (0.78–0.85)	0.72 (0.64–0.78)	0.89 (0.84–0.93)	0.83 (0.78–0.86)	0.74 (0.69–0.78)	0.82 (0.78–0.85)	0.79 (0.74–0.83)

CA: chromosomal abnormalities; CI: confidence interval; ISS: International Staging System; mPFS: modified progression-free survival; NDMM: newly diagnosed multiple myeloma; NE: not estimable; OS: overall survival; R-ISS: revised ISS.
[a]Cohort 2 for survival analyses included patients diagnosed from 1 January 2015 to 31 December 2018, with a follow-up through 31 December 2020.

in cohort 2 stratified in R-ISS III ($n = 248$), R-ISS II ($n = 988$), and R-ISS I ($n = 146$), 44 (17.7%), 212 (21.5%), and 42 (28.8%) patients, respectively, received SCT. This trend was consistent in patients stratified according to the ISS risk stratification criteria, wherein 98 (17.3%), 117 (22.9%), and 83 (27.1%) patients stratified in ISS III, II, and I, respectively, received SCT. A similar proportion of patients stratified in standard-risk CA (190 [21.7%]) and high-risk CA (108 [21.3%]) received SCT. Across all the treatment regimens in cohort 2, 6–12% of patients treated with doublets and 20–36% of patients treated with triplets received SCT (Table 4).

Discussion

This retrospective study evaluated the ability to implement three different risk stratification systems, namely ISS, R-ISS, and CA, to characterize treatment patterns and survival outcomes, including mPFS and two-year OS, among patients with NDMM in the US community practice. Key findings from this study demonstrated that the median mPFS and two-year OS proportion gradually decreased with increasing risk severity in patients with NDMM. Across all risk stratification criteria, triplets were the most frequently administered treatment regimens, with most patients being treated with a combination of PIs, IMiDs, and dexamethasone. Among patients treated with triplets, approximately one-third received SCT.

Multiple myeloma is mostly diagnosed in patients aged >65 years [18,19], and most patients included in this study were aged ≥60 years and a larger proportion of patients aged ≥75 years was high-risk according to the R-ISS and ISS criteria. This observation was consistent with other reports describing patients with MM [20–22]. An analysis of the patients in the Connect MM registry, the first observational and prospective registry of patients with NDMM in the US, indicated that 57% of patients were >65 years old [23]. Hypercalcemia, anemia, and renal failure are frequently observed in patients with MM, and a greater proportion of high-risk patients are associated with these clinical manifestations [24–28]. These observations were consistent with those in the current study, wherein higher rates of hypercalcemia and anemia were observed in high-risk patients. Additionally, poor renal function was more frequently observed in high-risk categories. Hence, a lower proportion of high-risk patients in this study received BTAs, which are contraindicated in patients with poor renal function [29,30].

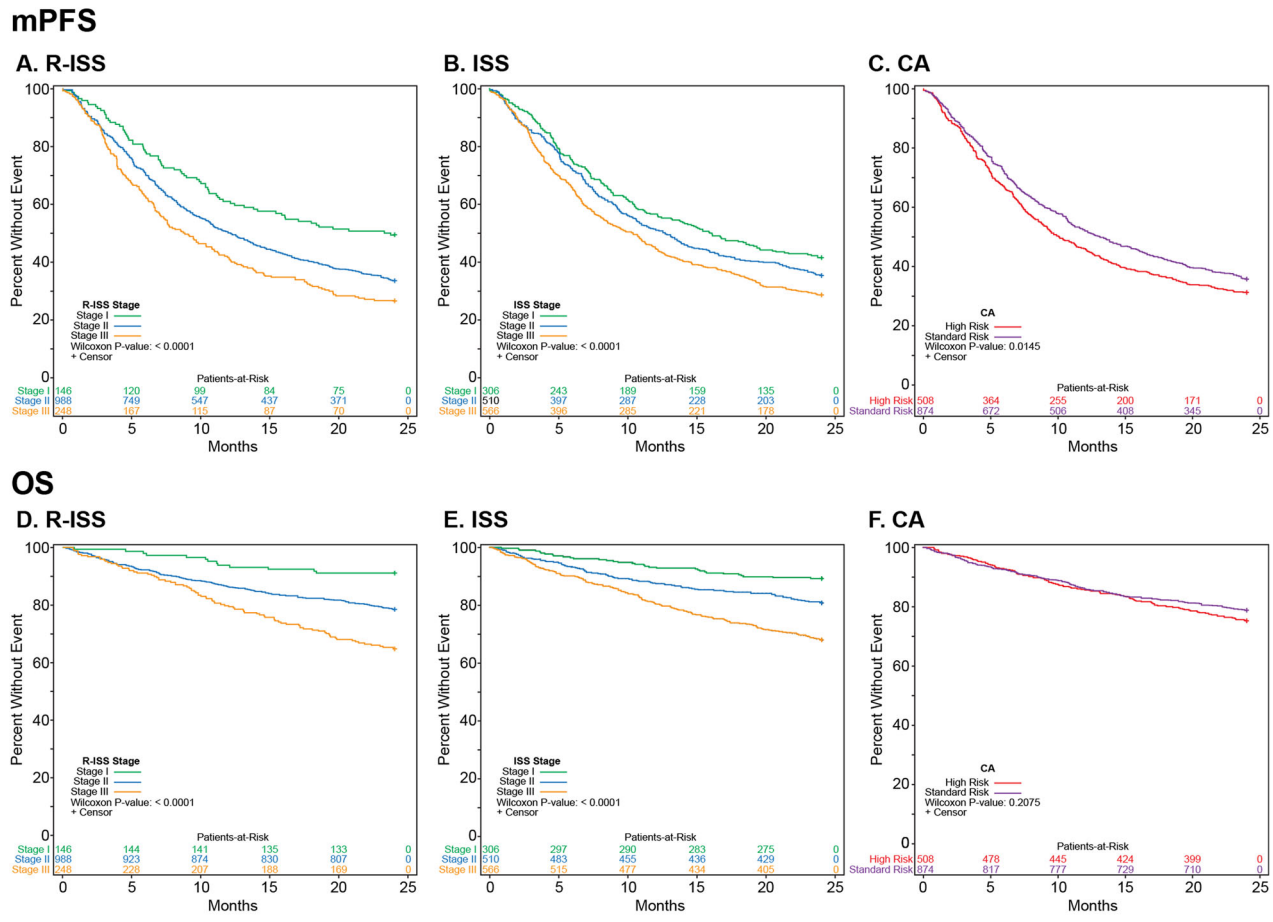

Figure 2. Modified progression-free survival and two-year overall survival. CA: chromosomal abnormalities; ISS: International Staging System; mPFS: modified progression-free survival; OS: overall survival; R-ISS: revised ISS.

Table 4. Transplant distribution among patients with NDMM after LOT1 and before LOT2 initiation (cohort 2).

	R-ISS			ISS			CA	
Therapy type, *n*/*N* (%)[a]	I	II	III	I	II	III	Standard risk	High risk
Monotherapy	3/17 (17.6)	9/83 (10.8)	1/20 (5.0)	5/32 (15.6)	6/43 (14.0)	2/45 (4.4)	8/77 (10.4)	5/43 (11.6)
Doublets	3/33 (9.1)	28/302 (9.3)	5/67 (7.5)	8/79 (10.1)	17/147 (11.6)	11/176 (6.3)	22/266 (8.3)	14/136 (10.3)
Triplets	33/92 (35.9)	162/576 (28.1)	30/150 (20.0)	66/190 (34.7)	91/310 (29.4)	68/318 (21.4)	145/501 (28.9)	80/317 (25.2)
Quadruplets	3/4 (75.0)	13/27 (48.1)	8/11 (72.7)	4/5 (80.0)	3/10 (30.0)	17/27 (63.0)	15/30 (50.0)	9/12 (75.0)

CA: chromosomal abnormalities; ISS: International Staging System; LOT1: first line of therapy; LOT2: second line of therapy; *N*: patient count per therapy type; *n*: transplant count per therapy type; NDMM: newly diagnosed multiple myeloma; R-ISS: revised ISS.
[a]Cohort 2 for survival analyses included patients diagnosed from 1 January 2015 to 31 December 2018, with a follow-up through 31 December 2020.

Triplets were the most frequently used regimens in this study across all R-ISS and ISS risk stratification categories in patients with NDMM. Further, a greater proportion of patients were treated with the triplet combination of PIs, IMiDs, and dexamethasone than with other triplet combinations. According to the European Society of Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment, and follow-up of patients with MM, the standard treatment of transplant-eligible patients with MM consisted of induction therapy followed by high-dose chemotherapy and SCT, and maintenance therapy [18]. For induction therapy, a triplet regimen consisting of four to six cycles of a PI, an IMiD, and dexamethasone before SCT was recommended [18,19]. According to the National Comprehensive Cancer Network (NCCN) and ESMO guidelines, the triplet combinations of thalidomide, lenalidomide, doxorubicin, or cyclophosphamide added to the bortezomib-dexamethasone backbone are currently the standard of care before SCT [18,19]. PIs play an important role in these regimens in increasing survival rates and

achieving a deeper response, particularly in patients with poor prognosis [31]. Overall, the proportion of patients treated with quadruplets was higher in the high-risk categories of R-ISS and ISS criteria than in the low-risk categories. This suggests that there may be a trend for risk-adapted therapy developing over the study period, which is becoming a recommended practice [32].

Among patients who underwent SCT in this study across all risk categories, a greater proportion of patients were treated with triplet and quadruplet regimens before SCT. Similar outcomes were reported in a retrospective study conducted in patients at the Mayo Clinic in Arizona and the University Hospital of Salamanca in Spain, wherein 65% of patients treated with a triplet drug combination underwent SCT [13]. Further, treatment with a triplet combination of carfilzomib, lenalidomide, and dexamethasone evaluated in the FORTE study displayed a greater benefit in high-risk and transplant-eligible patients with NDMM [33]. This was in accordance with the international guidelines on the preferred use of triplet drug combination as LOT1 in transplant-eligible patients [18,19].

High-risk features of MM are associated with poor survival outcomes [21,22,34,35]. A univariate analysis of survival outcomes in Korean patients with MM demonstrated that patients stratified in ISS III had significantly lower median OS than those in ISS II (30.8 vs. 53.8 months) [21]. Similar results were observed in an Asian Myeloma Network Study [22]. In accordance with these reports, a gradual decline in mPFS and two-year OS with an increase in risk severity was observed in the current study. Overall, mPFS and OS in this study were shorter than those reported in the studies conducted in academic settings. This could be attributed to the selection of patients enrolled in trials conducted at academic centers, presence of specialized teams for the treatment of cancer, and access to various clinical trials. NCCN guidelines recommend triplet regimens as the primary treatment for SCT eligible and ineligible patients, with a combination of bortezomib, lenalidomide, and dexamethasone as the preferred treatment regimen [19]. Consistent with these guidelines, patients treated with triplets in this study had a higher two-year OS, especially in the high-risk categories. In contrast to the treatment guidelines, the observed SCT rate was perhaps lower than expected (18–28% across risk stratification groups), reflecting that not all patients in the community setting receive the most intensive therapeutic options.

In this study, the difference in mPFS and two-year OS between high-risk and low-risk patients was more pronounced when R-ISS risk stratification criteria were used instead of ISS or CA. These observations were comparable to the findings of a real-world, multicenter, retrospective study conducted in Japanese patients with MM, which demonstrated that R-ISS discriminated the differences in OS between stages more distinctly than ISS ($p = 2.4 \times 10^{-12}$ and $p = 1.4 \times 10^{-8}$, respectively) [35]. The discriminatory power of R-ISS over ISS was further corroborated by the results obtained in a retrospective study conducted in patients with NDMM from 17 hospitals in Korea [36]. It can be noted that a majority of real-world and retrospective studies were conducted in patients with MM regardless of the diagnosis status. Since the discriminative power of R-ISS has been demonstrated in the current study in patients with NDMM, we believe that an informed decision on potential treatments can be taken by the physicians at an earlier stage if R-ISS is routinely employed, which would subsequently improve disease prognosis and treatment outcomes. Although only one-third of the patients had the required data points to be classified by R-ISS criteria (including laboratory values of LDH and cytogenetics) in this study, an observation which is also valid in real-world settings, R-ISS was still able to distinguish between survival outcomes even in the nonacademic setting. Accordingly, a more risk-adapted approach can be more feasible, with a greater population-level impact. Further, it is also recommended that all patients should be assessed thoroughly to be classified by the R-ISS criteria.

The study had a few limitations. First, this study was subject to the shortcomings of the accuracy and completeness of the Flatiron data. Data limitations prevent complete ascertainment of treatment that occurred outside of the outpatient clinic setting, including a LOT that began in the inpatient clinic, laboratory tests that were conducted before the treatment began in outpatient clinics, or SCTs that occurred in a hospital. Second, the results of this study are generalizable to patients who were treated in the US outpatient oncology clinics and may not be generalizable to patients who are being treated in the inpatient setting of countries outside the US. As data from these outpatient oncology clinics were collected with a focus on disease management, it may have led to incomplete data entry and misclassification. Finally, although the clinics that have contributed data to Flatiron were geographically diverse and the large size of the underlying population provided diversity

regarding patient demographics, these data were most reflective of patients treated in community-based clinics and may not be representative of care provided in academic settings or in other centers of excellence, possibly resulting in a selection bias among patients. Notwithstanding these limitations, to the best of our knowledge, this is one of the first real-world studies on treatment patterns and outcomes across different risk stratification systems using an EHR database conducted in a large number of patients.

In conclusion, this retrospective study demonstrated that R-ISS has a greater discriminatory power than ISS or high-risk CA alone, because a distinct difference in median mPFS and the proportion of two-year OS was observed when R-ISS was used. In addition, the study demonstrated that the median mPFS and the proportion of two-year OS were consistently lower in high-risk patients than in low-risk patients.

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Motiur Rahman was an employee of Amgen Inc. at the time this study was conducted. Christopher Kim and Alissa Keegan are employees and stockholders of Amgen Inc. Jazmine Mateus is an employee of Simulstat Inc., which consults for Amgen Inc.

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Data availability statement

Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: http://www.amgen.com/datasharing

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