Age-related disparities in treatment and outcomes for newly diagnosed multiple myeloma: a population-based study

Multiple myeloma (MM) predominantly impacts older individuals, with a median age at diagnosis of 69 years, and approximately one-third of patients being over 75.[1] Less intensive treatment options are frequently offered to older patients due to frailty.[1] We sought to determine whether frontline treatment patterns impact clinical outcomes of the elderly myeloma population by examining outcomes in patients aged ≥75 from the Multiple Myeloma Research Foundation (MMRF) CoMMpass Study. Our study found that proteasome inhibitors (PI) and immunomodulatory drugs (IMiD) combination therapies lead to better overall survival (OS) and progression-free survival (PFS) compared to either agent alone even after adjusting for frailty and other confounding variables. In addition, we did not find a difference in the baseline disease risk profile using cytogenetics and SKY92, highlighting that undertreatment is a major contributor to the outcome gap between older and younger patients.

The MMRF CoMMpass Study is a longitudinal international prospective study that enrolled 1,143 newly diagnosed multiple myeloma (NDMM) patients from 2011 to 2015.[2] The interim analysis 19 was used for all analyses, except for the Charlson Comorbidity Index (CCI), calculated from interim analysis 16. Patients were stratified into three age groups for analysis - those who are ≥75, 65-74 and <65 years old.. Survival analysis was conducted using the Kaplan-Meier method to compare OS and PFS across different subgroups. The Cox proportional hazards regression model was employed to estimate hazard ratios (HR) and 95% confidence intervals (CI) for various predictors of survival. We measured frailty with the simplified frailty scale.[3] This scoring system evaluates patients based on age, CCI, and Eastern Cooperative Oncology Group performance status (ECOG PS), with each factor contributing to a total score. The SKY92 score was calculated based on gene expression data.[4] All analyses were performed in R (version 4.4.0). The MMRF CoMMpass dataset is a de-identified dataset made available for research purposes, and all data accessed were anonymized to protect patient privacy. The research was conducted in compliance with the principles outlined in the Declaration of Helsinki and adhered to ethical guidelines for secondary data analysis. We identified 146 (12.8%) patients aged ≥75. Their median OS was 47 months, compared with unreached in patients aged <65 and 80 months in patients aged 65-74 (Figure 1A). A similar pattern emerged for PFS: the median PFS

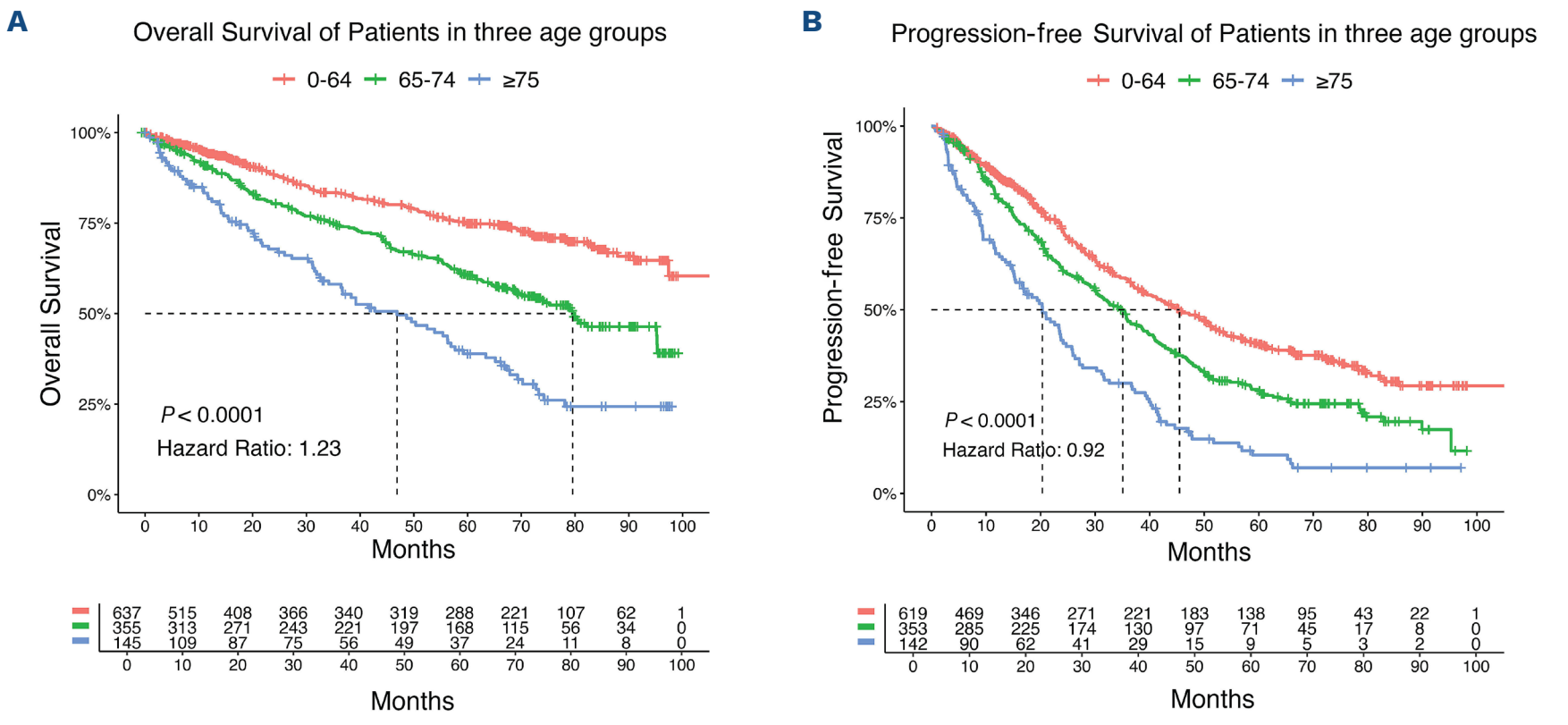


Figure 1. Overall survival and progression-free survival in three age groups. Kaplan-Meier survival curves representing (A) overall survival (OS) and (B) progression-free survival (PFS) for patients stratified by age group: under 65 years (red), 65-74 years (green), and ≥75 years old (blue). The median survival times are indicated by the dashed lines. Statistical significance was assessed with log-rank tests, and hazard ratios are presented.

was 20.3 months for patients aged ≥75, compared with 45.5 months and 35.1 months for those <65 and 65-74, respectively (Figure 1B).

Baseline characteristics of patients ≥75 were compared with other age groups (*Online Supplementary Table S1*). They tend to have higher rates of ISS stage III disease (43.1% *vs.* 22.8%; *P*<0.001), anemia (64.9% *vs*. 52.6%; *P*<0.001), and renal insufficiency (9.2% *vs*. 6.9%; *P*=0.049). Notably, 84.9% of these older patients were classified as frail. No difference in the prevalence of high-risk cytogenetics (t(4;14), t(14;16), t(14;20), del(17p) and amp(1q)) was observed among the three age groups. SKY92 scores were calculated for 754 patients with baseline gene expression data: 430 were <65, 226 were 65-74, and 98 were ≥75. High-risk patients comprised 12.8%, 12.9%, and 8.2% in each group, respectively, with no significant differences (ANOVA; *P*=0.711), and the overall SKY92 score distribution was also consistent (Figure 2).

Comparing with patients < 65, older patients aged ≥75 were less likely to receive combination regimens of PI and IMiD (30.5% *vs*. 80%; *P*<0.001) or undergo high-dose melphalan and autologous stem cell transplantation (ASCT) (9.8% *vs*. 62%; *P*<0.001). Within patients ≥75, receiving frontline PI-IMiD combination treatment is associated with improved survival in (OS: 70.2 *vs*. 36.7 months; *P*<0.001; PFS: 23.7 *vs*. 19.8 months; *P*=0.012; Figure 3A, B). In comparison, PI-IMiD combination treatment does not portend better OS in younger patients (*Online Supplementary Figure S1*). PI-IMiD combination therapy also resulted in a significantly longer time to next treatment for older patients (28.8 *vs*. 11.2 months; *P*<0.001).

Among the 131 transplant-ineligible older patients, the median OS for the PI-IMiD combination group was significantly longer than the other group (70.2 *vs*. 36.5 months; *P*<0.001; *Online Supplementary Figure S2A*), and the PFS difference also remained significant (25.9 *vs*. 15.4 months; *P*<0.001; *Online Supplementary Figure S2B*). We then matched the two treatment groups using IPW to adjust for confounding variables - simplified frailty scale, sex and International Staging System (ISS) stage. The OS and PFS remained different (*P*=0.0015 and P=0.037, respectively; *Online Supplementary Figure S2C, D*). A 6-month landmark analysis was performed to assess the impact of early mortality on differences between the two groups. The difference in OS was still significant (*P* 0.042), whereas PFS was not (*Online Supplementary Figure S2E, F*). In the PI- or IMiD-based group, 25 patients died within the first 6 months - five from disease progression and nine from complications in other organ systems. In contrast, no patients in the PI-IMiD combination group died within the first 6 months. We evaluated attrition rates across age groups and found that patients ≥75 had a higher rate than younger groups. Death was the main cause of attrition in older patients, with 45 (30.8%) dying after the first line of therapy (LOT) - ten in the PI-IMiD combination group and 35 in the other groups (*P*<0.001). In the PI-IMiD group, 50% proceeded to second-line treatments, while only 39.1% did so in the PI or IMiD group. Death also remained the leading cause of treatment discontinuation in the second and third LOT, accounting for 29.0% and 41.9% of attrition, respectively. Our findings indicate that inferior outcomes in older patients are not solely driven by increased frailty or advanced age but are also influenced by suboptimal treatment selection. Although older patients have naturally shorter life expectancy, we observed significant differences in OS and PFS between treatment groups of similar median age, suggesting that optimized therapy could meaningfully improve outcomes. While patients receiving more intensive regimens were somewhat fitter - as reflected by a lower median simplified frailty score in the PI-IMiD group

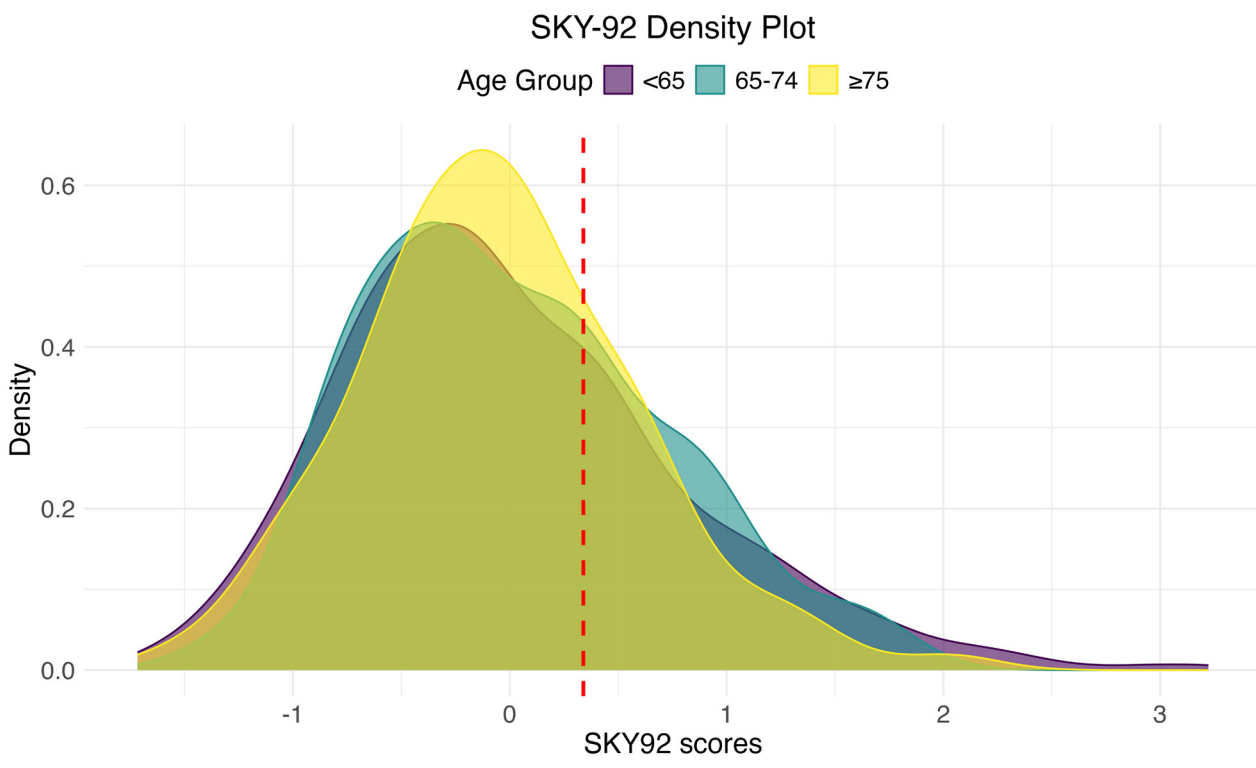
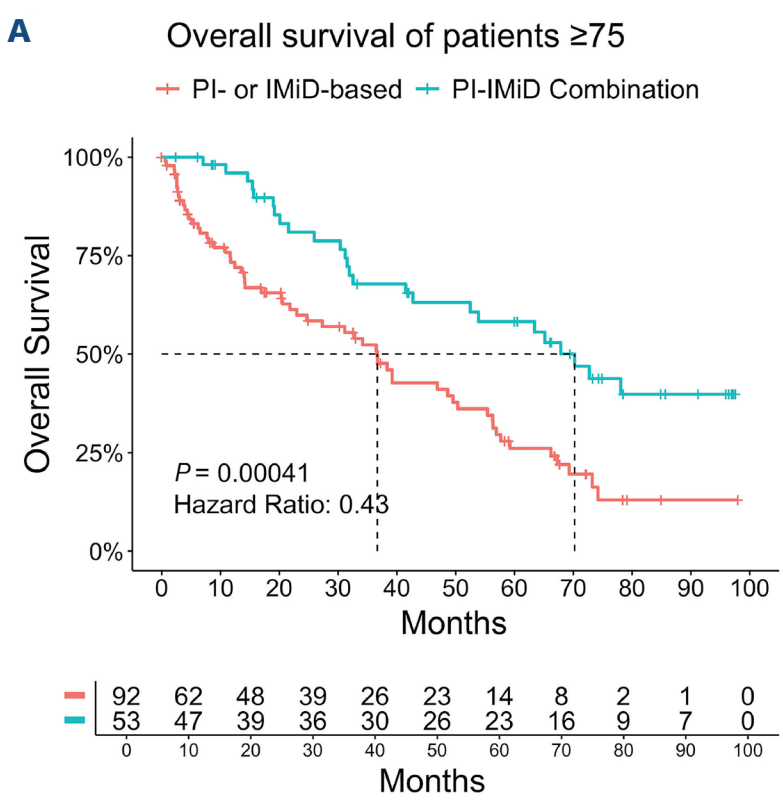


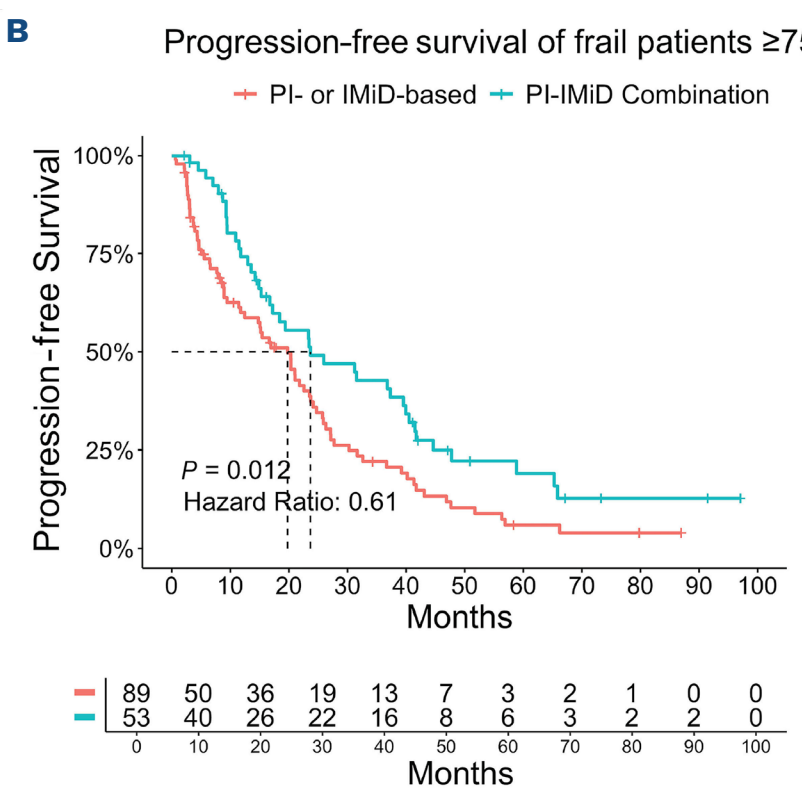
Figure 2. Distribution of SKY92 scores by age group. Density plot of SKY92 scores by age group, illustrating the distribution of risk scores across 3 age categories: under 65 years (purple), 65-74 years (green), and equal and above 75 years (yellow). The dotted vertical line represents the cutoff score that indicates high-risk status, separating low-risk from high-risk groups.

compared to the PI- or IMiD-alone group (2 *vs.* 3; *P*=0.023) - PI-IMiD combination therapy remained the strongest predictor of prolonged OS after adjusting for frailty and other covariates (Figure 3C). Notably, patients ≥75 years treated with combination therapy achieved a median OS comparable to that of patients aged 65-74 years (70.2 *vs.* 80 months), despite greater frailty (median frailty score 2 *vs.* 1; *P*<0.001), suggesting that combination therapy can mitigate the adverse effects of age and frailty.

Importantly, the benefit of PI-IMiD combination therapy was seen only among patients aged ≥75, underscoring the critical need to use the most effective frontline regimen in this population. Higher attrition rates observed among elderly myeloma patients compared to younger limit opportunities for successful salvage therapies, making initial treatment choice particularly consequential.[5]

Our results strongly discourage the use of PI or IMiD single agent in treating older MM patients. Prior data show declining efficacy of PI and IMiD with age, while anti-CD38 antibodies maintain benefit.[6] In the MAIA trial,





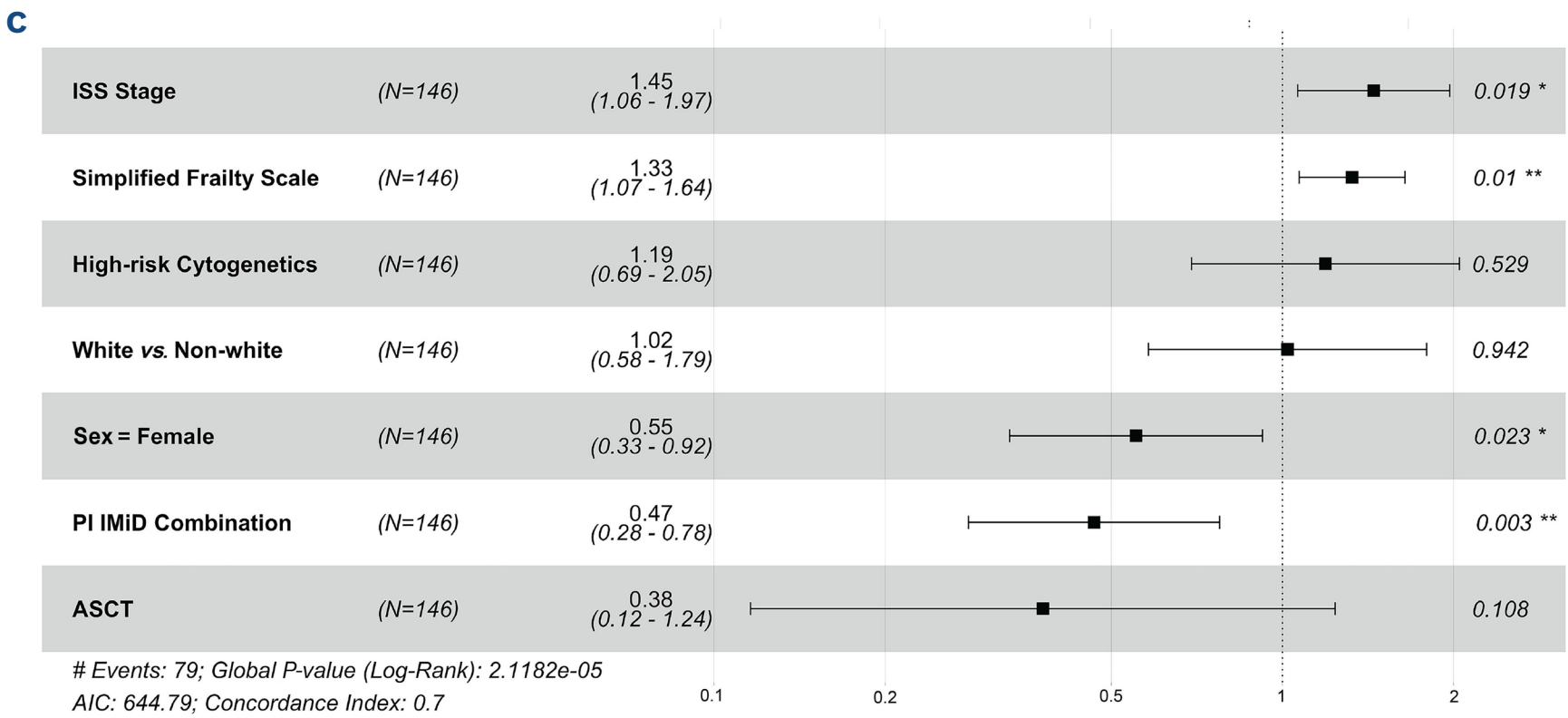


Figure 3. Survival outcomes and prognostic factors in patients aged ≥75 treated with either proteasome inhibitor-immunomodulatory drug (PI–IMiD) combination therapy or PI- or IMiD-based monotherapy. (A) Kaplan-Meier curve for overall survival (OS) comparing patients aged ≥75 who received either PI- or IMiD-based therapy (red) or a PI-IMiD combination therapy (blue) as first-line treatment. Median survival times are indicated by the dashed lines.(B) Kaplan-Meier curve for progression-free survival (PFS) in the same patient groups. (C) Forest plot of hazard ratios for various prognostic factors associated with likelihood of death in patients aged ≥75 years. ISS: International Staging System; ASCT: autologous stem cell transplantation; AIC: Akaike information criterion.

the daratumumab-lenalidomide-dexamethasone (DRd) triplet extended PFS even in frail, transplant-ineligible subjects.[7] However, adding isatuximab tobortezomib-lenalidomide-dexamethasone (VRd) failed to improve PFS in patients >75 years. In our real-world cohort of frail patients ≥75, PI-IMiD doublet therapy produced a median PFS of just 23.4 months - less than half of the 54.3 months achieved with DRd in MAIA. Although real-world outcomes are typically tempered by greater clinical heterogeneity, comorbidities, and adherence barriers,[8] the magnitude of this difference supports the notion that DRd may offer superior efficacy in this population, as recently reported.[9] Importantly, the underlying disease biology in older patients does not appear to differ significantly from that of younger individuals. We found no significant differences in the prevalence of high-risk cytogenetic abnormalities across age groups. Furthermore, our use of the SKY92 score to assess genetic risk across age groups revealed a consistent distribution, suggesting that disease biology does not vary substantially with age. These observations further support the notion that disparities in survival may stem predominantly from differences in treatment, rather than fundamental biological distinctions in the myeloma itself. An interesting observation is that female sex is associated with better survival. Mixed results have been reported in prior studies.[10,11] Further studies are needed to confirm the validity of this sex-based survival advantage and elucidate the underlying biological or treatment-related mechanisms.

Our study has several limitations. The difference in OS is more significant than PFS for patients aged ≥75. This finding is somewhat atypical, as significant improvements in PFS often do not fully translate into similarly large OS gains in some myeloma studies. Despite our best effort to adjust for frailty, there might be other unaccounted factors contributing to the better OS of the group receiving combination therapy. Limited daratumumab use (1 patient) may affect generalizability to current practice. Lastly, the SKY92 model, adapted from microarray data for RNA sequencing, has not been fully validated in its current form.

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RK is an employee and option holder at SkylineDx. All other authors have no conflicts of interest to disclose.

Contributions

XS performed data analysis and wrote the manuscript. RK and CD helped with SKY92 score calculation. PM and ES edited the manuscript. SSA supervised the study.

Data-sharing statement

The data supporting the findings of this study was obtained from Interim Analysis 19 and 16 of the MMRF CoMMpass study. These data can be accessed upon request via the MMRF's Researcher Gateway, at https://research.themmrf.org/.

References

1. Facon T, Leleu X, Manier S. How I treat multiple myeloma in geriatric patients? Blood. 2024;143(3):224-232.
2. Steiger H. MMRF Research update: key study looks to CoMMpass to inform a new prognostic model. MMRF. January 23, 2024. https://themmrf.org/scientific-research-publications/mmrf-research-update-key-study-looks-to-commpass-to-inform-a-new-prognostic-model. Accessed June 24, 2024.
3. Facon T, Dimopoulos MA, Meuleman N, et al. A simplified frailty scale predicts outcomes in transplant-ineligible patients with newly diagnosed multiple myeloma treated in the FIRST (MM-020) trial. Leukemia. 2020;34(1):224-233.
4. Kuiper R, Zweegman S, van Duin M, et al. Prognostic and predictive performance of R-ISS with SKY92 in older patients with multiple myeloma: the HOVON-87/NMSG-18 trial. Blood Advances. 2020;4(24):6298-6309.
5. Benda MA, Ulmer H, Weger R, et al. Attrition rates in multiple myeloma treatment under real world conditions - an analysis from the Austrian Myeloma Registry (AMR). Cancers (Basel). 2023;15(3):962.
6. Pawlyn C, Schjesvold FH, Cairns DA, et al. Progression-free survival as a surrogate endpoint in myeloma clinical trials: an evolving paradigm. Blood Cancer J. 2024;14(1):134.
7. Facon T, Cook G, Usmani SZ, et al. Daratumumab plus lenalidomide and dexamethasone in transplant-ineligible newly

diagnosed multiple myeloma: frailty subgroup analysis of MAIA. Leukemia. 2022;36(4):1066-1077.
8. Richardson PG, San Miguel JF, Moreau P, et al. Interpreting clinical trial data in multiple myeloma: translating findings to the real-world setting. Blood Cancer Journal. 2018;8(11):109.
9. Hansen DK, Gautam S, Lafeuille M, et al. Comparison of time to next treatment or death between front‐line daratumumab, lenalidomide, and dexamethasone (DRd) versus bortezomib, lenalidomide, and dexamethasone (VRd) among transplant‐ineligible patients with multiple myeloma. Cancer Med. 2024;13(21):e70308.
10. Bird S, Cairns D, Menzies T, et al. Sex differences in multiple myeloma biology but not clinical outcomes: results from 3894 patients in the Myeloma XI trial. Clin Lymphoma Myeloma Leuk. 2021;21(10):667-675.
11. Derman BA, Langerman SS, Maric M, Jakubowiak A, Zhang W, Chiu BCH. Sex differences in outcomes in multiple myeloma. Br J Haematol. 2021;192(3):e66-e69.