Multiple myeloma in the young: insights on prognosis, clinical features and treatment outcome derived from nationwide German registry data and a nested multicenter sample

Multiple myeloma (MM) is commonly associated with elderly individuals, typically diagnosed at a median age of 72 to 74 years.[1] However, there is a subset of patients diagnosed with MM at a particular age of under 40 years, accounting for less than 1% of all myeloma patients.[1] In the era of novel plasma cell-directed therapies, the definition of unfavorable prognostic factors and the survival of exceptionally young MM patients is a controversial topic.[2-4] In the absence of specific recommendations for induction and consolidation therapies, including the frequently discussed role of allogeneic stem cell transplantation (SCT) for exceptionally young MM patients and the current prevalence of heterogeneous treatment approaches, we aimed to scrutinize the specific clinical features and prognosis of MM patients diagnosed ≤40 years of age.

In this study, we combined a 20-year retrospective, nationwide population-based dataset from Germany with a specialized dataset of MM patients up to the age of 40 years. The nationwide dataset, derived from the German Center for Cancer Registry Data, includes diagnoses from 2000-2019 with mortality follow-up until December 31, 2020, with MM cases identified using the ICD-10 code "C90.0". Additionally, we included data from four German Cancer Centers (University Medical Center Hamburg-Eppendorf, University Hospital Essen, University Hospital Münster, and University Hospital Lübeck) covering the years 2000-2023. The overall response rate (ORR) was defined as achieving a partial response (PR) or better. The ethics committee of the Medical Council of Hamburg, Duisburg-Essen, Westphalen-Lippe, and Lübeck reviewed and approved the data collection for the clinical cohort (approval no.2022-100775-BO-ff). For the nationwide sample, an assessment of the ethics committee and informed consent were not required, as scientific use without informed patient consent is granted by federal law. The primary objective of this study was to compare long-term overall survival (OS) among transplant-eligible MM patients diagnosed ≤40 years to patients aged 41-65. A secondary objective was to describe the clinical features and treatment practices of MM patients ≤40 years of age. Unadjusted survival disparities and median survival among study groups concerning OS were evaluated via Kaplan-Meier functions, accompanied by 95% confidence intervals (CI) and log-rank tests. Differences in OS concerning age group, sex, and calendar year were quantified using multivariate Cox proportional hazard models and expressed as hazard ratios with 95% CI, including interaction terms for age group and sex, and age group and calendar year.

After applying the primary filter criteria, we identified 24,905 patients in the German nationwide sample (*Online Supplementary Figure S1*). The selected center's cohort included 79 newly diagnosed MM patients aged 18-40 (Table 1). The most frequently utilized induction regimes were triplet therapies, consisting of a proteasome inhibitor combined with conventional chemotherapy and steroids (35.4%), followed by quadruplet therapies (21.5%) and conventional chemotherapy combined with steroids (13.9%) (Table 2). Seventy-six patients (96.2%) underwent a melphalan-based high-dose therapy with subsequent autologous SCT. The ORR to first-line therapy, including high-dose therapy, was 90.4% in 52 evaluable patients. A total of 36 patients (47.4%) relapsed after first-line therapy after a median time of 29.5 months. Twenty-four patients (30.4%) underwent allogeneic SCT. Of those, 13 received subsequent consolidating allogeneic SCT after consolidating melphalan-based high-dose therapy followed by an autologous SCT. Nine of 13 during first-line treatment allogeneic transplanted patients achieved a very good partial remission or better. Seven and ten patients received BCMA-directed therapies (including 4 who received BCMA-directed chimeric antigen receptor [CAR] T-cell therapy) or intensive salvage chemotherapy, respectively. The adjusted OS of younger myeloma patients, according to the nationwide population-based dataset, was generally more favorable compared to older patients (Figure 1). Five-year OS was about 9% higher in younger *versus* older patients (83% *vs.* 64%), and 10-year OS was about 26% higher in younger *versus* older patients (69% *vs.* 43%). For patients ≤40 years, the age distribution (*Online Supplementary Table S1*) and survival (5-year OS 0.83, 95% CI: 0.74-0.94; 10-year OS 0.69, 95% CI: 0.56-0.85; median survival 18.4 years) in the selected centers seemed to be largely similar to the values in the nationwide sample. In the adjusted model, death risk was about 2.32 higher (95% CI: 2.04-2.64) in older patients as compared to younger patients, about 15% lower in females than in males (95% CI: 11%-18%) and decreased approximately 3% annually

Table 1. Patient characteristics at the time of first diagnosis of the selected center's cohort (2000-2023).

Characteristics	Total of patients N=79
Age at diagnosis in years, median (IQR)	37.00 (34.00-39.00)
Female sex, N (%)	30 (38.0)
Isotype, N (%)	
IgG	31 (39.2)
IgA	19 (24.1)
Light chain	22 (27.2)
Other#	6 (7.7)
Unknown	1 (1.3)
Derived from MGUS or smoldering MM, N (%)	11 (13.9)
CNS involvement, N (%)	2 (2.5)
ISS, N (%)	
I*	24 (30.4)
II*	17 (21.5)
III*	14 (17.7)
Not evaluable	24 (30.4)
R-ISS stages, N (%)	
I	18 (22.8)
II	17 (21.5)
III	9 (11.4)
Not evaluable	35 (44.3)
High-risk cytogenetics, N (%)	
Total	26 (40.6)
del(17p)[a]	10 (15.6)
t(4;14)[a]	4 (6.3)
t(14;16)[b]	0 (0)
Amplification 1q (>3 copies)[b]	15 (23.8)
>1 high risk aberration[b]	12 (19)
EMD, N (%)	30 (38.0)
At initial diagnosis	22 (27.8)
Extraosseous EMD	13 (16.5)
LDH >upper limit of normal, N (%)[c]	10 (23.3)
Thrombocytopenia at diagnosis, N (%)[c]	0 (0)
Renal impairment at diagnosis, N (%)[c]	14 (32.6)

Disease staging (International Staging System [ISS] and revised ISS [R-ISS]) was performed according to International Myeloma Working Group criteria[8,12] when the necessary data were available. ISS distribution was as follows: 43.6%, 30.9%, and 25.5% for stages I, II, and III, respectively. R-ISS stratification showed high-risk MM with R-ISS stage III in 9 of 44 evaluable patients (11.4%, R-ISS was not assessable in 35 patients) with high-risk cytogenetic aberrations in 26 of 64 evaluable patients (40.6%). The most frequent cytogenetic aberration was the amplification of 1q in 15 patients (23.8%), followed by del(17p) in 10 patients (15.6%) and t(4;14) in 4 (6.3%). None of the 64 evaluable patients had t(14;16), but 12 patients (19%) showed more than 1 high-risk aberration. The presence of any of del(17p), 1q amplification with >3 copies, t(4;14), or t(14;16) was considered a high-risk cytogenetic feature.[12-14] Extramedullary multiple myeloma (MM) was defined according to Bhutani et al.[15] Extramedullary myeloma was observed in 30 patients (38%). Of those, an extraosseous extramedullary myeloma occurred in 13 patients (16.5%). #Including immunglobulin (Ig) D and asecretory multiple myeloma (MM); *43.6%, 30.9%, and 25.5% if calculated with 55 evaluable patients; [a]evaluable in 64 of 79 patients; [b]evaluable in 63 of 79 patients; [c]evaluable in 43 of 79 patients. IQR: interquartile range; MGUS: monoclonal gammopathy of undetermined significance; EMD: extramedullary myeloma; CNS: central nervous system; LDH: lactate dehydrogenase.

(95% CI: 3-4). The improvement over time did not significantly differ between younger and older patients (P=0.76) and between males and females (P=0.26).

The finding of a much greater death risk among older as compared to younger transplant-eligible MM patients aligns with previous studies (*Online Supplementary Table S2*).[2,5] Interestingly, beyond these general survival differences, our study revealed that younger and older MM cohorts exhibited a similar survival disadvantage of male compared to female patients and a similar improvement in survival over time. Regarding the clinical features of MM patients diagnosed at the age of maximal 40 years, the distribution of International Staging System (ISS) stages I,

Table 2. Overview of treatment features of the selected center's cohort (2000-2023).

Treatment features	Total of patients N=79
No treatment, N (%)	2 (2.53)
Induction regime, N (%)	
Chemotherapy and steroid	11 (13.9)
Chemotherapy, PI and steroid	28 (35.4)
PI and steroid	4 (5.1)
PI, IMiD and steroid	10 (12.7)
Quadruplet	17 (21.5)
Other	2 (2.5)
Participants of clinical trials	17 (21.5)
Response to induction therapy, N (%)	
Complete response	9 (11.4)
Very good partial response	20 (25.3)
Partial response	18 (22.8)
Minor response	2 (2.5)
Stable disease	5 (6.3)
Refractory	4 (5.1)
Not evaluable	21 (26.6)
Melphalan-based high-dose therapy followed by autologous stem cell transplantation, N (%)	76 (96.2)
Tandem therapy	8 (10.5)
Response to high-dose therapy, N (%)	
Complete response	19 (25)
Very good partial response	22 (28.9)
Partial response	6 (7.9)
Stable disease	1 (1.3)
Refractory	4 (5.3)
Not evaluable	27 (35.5)
Maintenance therapy, N (%)	40 (50.6)
Lenalidomide-containing	33 (41.8)
Number of therapy lines, median (range)[a]	2 (0-15)
Tripleclass-refractory, N (%)	14 (18.4)
Pentaclass-refractory, N (%)	12 (15.8)
Allogeneic stem cell transplantation, N (%)	24 (30.4)

The remission status of multiple myeloma (MM) was evaluated according to the valid remission criteria. [a]Until the last follow-up time point. PI: proteasome inhibitor; IMiD: immunomodulatory drug.

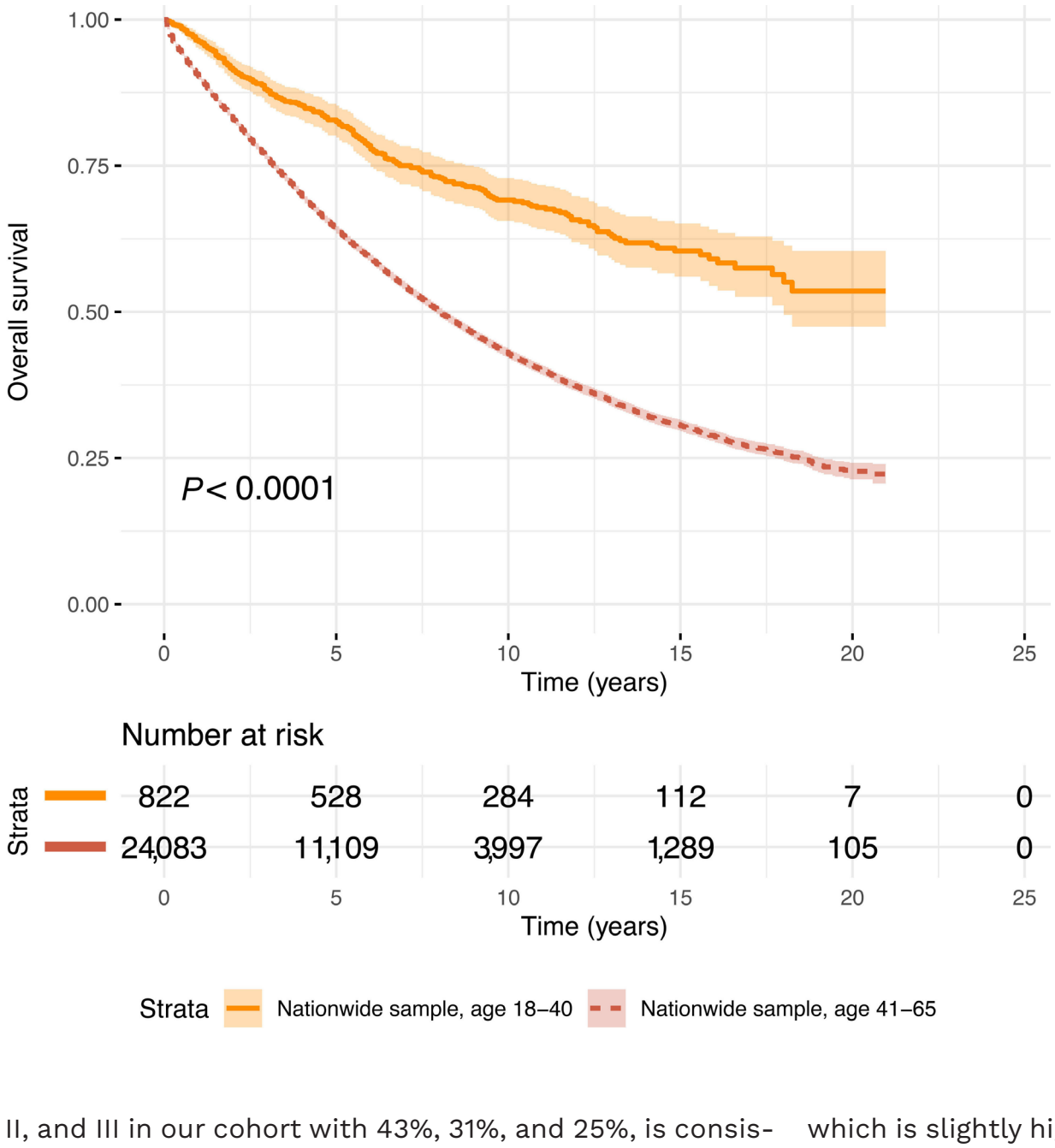

Figure 1. Overall survival of young multiple myeloma patients. Total number of patients' (N=822) 5-year overall survival (OS) 0.83, 95% confidence interval (CI): 0.80-0.86, and 10-year OS 0.69, 95% CI: 0.66-0.73, median survival not reached; compared with older MM patients (N=24,083), 5-year OS 0.64, 95% CI: 0.64-0.65, and 10-year OS 0.43, 95% CI: 0.42-0.44, median survival 8.0 years from the German nationwide sample (2000-2019).

II, and III in our cohort with 43%, 31%, and 25%, is consistent with previously reported rates of 47-52%, 28-33%, and 20%, respectively in young myeloma patients.[2,5-7] However, compared to the study population of the initial validation of the ISS with a median age of 60 years, the favorable ISS stage I appears to occur more frequently in young MM patients than in the general myeloma population, with 28% based on the majority of study results.[8] Furthermore, we observed extramedullary myeloma (EDM) in 38% of patients, mostly being already present at the time of initial myeloma diagnosis (27.8%). This rate is significantly higher than in the general myeloma population, with reported EDM rates of 18.2%.[9] In addition, extraosseous EDM occurred almost 4-fold more frequently (16.5%) than reported in the general myeloma population with 3.7%.[9] In our cohort, high-risk genetic aberrations were detectable in 40.6% of all evaluable patients, with amplification of 1q (>3 copies) being the most frequent one (23.8%), followed by del(17p) (15.6%) and t(4;14) (6.3%). With an amplification 1q rate of approximately 24%, our results are consistent with those previously reported with 27-30%.[2,3] However, compared to a 35-40% rate in the general myeloma population, amplification 1q seems less frequent in the younger subset of myeloma patients.[10,11] Contrary, we observed del(17p) in approximately 16% of patients, which is slightly higher than previously described with 11-12%,[2,3] but markedly higher than in the general myeloma population (7-8%).[10,11] Regarding t(4;14), our results are lower than previously described not only in younger MM patients (10-12%) but in the general MM population as well (15%).[2,3,10,11] Nevertheless, the interpretation of cytogenetic abnormalities between heterogeneous study populations remains limited based on the detection method. In our selected center's cohort, patients received heterogeneous first-line induction regimes followed by melphalan-based high-dose therapy and subsequent SCT, leading to an ORR of 90.4%, with an additional approximately 30% of patients receiving an allogeneic SCT during the first or subsequent treatment lines. Our ORR, as well as rates of autologous and allogeneic SCT, are consistent with previously reported rates in surpassing young myeloma patients.[2] In our cohort, all first-line allogeneic SCT was performed before 2016, and 12 of 13 patients received a non-immunomodulatory-drug-based induction regime. After the approval of daratumumab and particularly in recent years, no allogeneic SCT was performed during first-line treatment. The apparent decrease in tandem transplantation consisting of autologous and subsequent allogeneic SCT reflects the development of new promising agents in the treatment landscape of MM.

Despite all efforts to account for confounding factors in the analysis, data on genetic aberrations and ISS were not available for all patients included in the selected center's cohort. Because of a comparable low number of survival events in the selected center's cohort, a statistical analysis of prognostic factors was not possible. Moreover, since the ICD-10 code "C90.0" does not differ between smoldering MM and MM, the portion of smoldering MM patients in the nationwide sample remains unknown. However, more detailed analyses of the entire nationwide sample will be feasible in the future since the regional cancer registries started collecting additional clinical data around 2014, which are currently harmonized at the German Center for Cancer Registry Data.

In conclusion, our findings reveal significantly higher 10-year OS rates in particularly young MM patients diagnosed ≤40 years compared to patients aged 41-65. Moreover, based on higher rates of favorable ISS stage I but more frequent occurrence of EMD, and particularly extraosseous myeloma, young myeloma patients seem to contain clinical features suggesting a unique biological habit compared to the common myeloma population. Further research is needed to better understand the complex biological characteristics of MM in exceptionally young patients to convey specific recommendations and optimize myeloma therapy for patients diagnosed with MM ≤40 years.

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Contributions

Study design, data collection, writing - original draft, writing - review and editing was performed by AK. Data collection, writing - review and editing was performed by PA. Writing - review and editing was performed by LL, CS, RC, and CB. Literature search and writing of the original draft was done by FM. Figures, study design, data collection, data analysis, data interpretation, writing of the original draft, and writing - review and editing, conceptualization, data curation, formal analysis, and methodology was performed by FP. Figures, study design, data collection, data analysis, data interpretation, writing – original draft, and writing–review & editing, conceptualization, data curation, formal analysis, and methodology was performed by HK. TZ, CH, MS, ES, TL, and CK were responsible for data collection and writing – review and editing. Supervision and writing - review and editing was provided by KW. Literature search, figures, study design, data collection, data analysis, data interpretation, writing – original draft, and writing – review and editing, methodology, and project administration by SG.

Data-sharing statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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