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Comorbidities and malignancies negatively affect survival in myelodysplastic syndromes: a population-based study

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Key Points

- A substantial part of the MDS population had a prior malignancy; both therapy-related and secondary MDS patients had significantly shorter OS.
- A combination of comorbidities was associated with significantly worse OS.

Population-based studies that contain detailed clinical data on patients with myelodysplastic syndrome (MDS) are scarce. This study focused on the real-world overall survival (OS) of MDS patients in association with comorbidities, specifically malignancies. An observational population-based study using the HemoBase registry was performed, including all patients with MDS diagnosed between 2005 and 2017 in Friesland, a Dutch province. Detailed information about diagnosis, patient characteristics, previous treatment of malignancies, and comorbidities according to the Charlson Comorbidity Index (CCI) was collected from electronic health records. Patients were followed up until June 2019. Kaplan-Meier plots and Cox regression analyses were used to study survival differences. In the 291 patients diagnosed with MDS, the median OS was 25.3 months (95% confidence interval [CI], 20.3-30.2). OS was significantly better for patients with CCI score <4, age <65 years, female sex, and low-risk MDS. Fifty-seven patients (20%) had encountered a prior malignancy (excluding nonmelanoma skin cancer), and a majority (38 patients; 67%) were therapy related. Both therapy-related and secondary MDSs were associated with worse OS (hazard ratio, 1.51; 95% CI, 1.02-2.23 and 1.58; 95% CI, 0.95-2.65, respectively), as compared with de novo MDS patients ($P = .04$). Patients in remission at time of MDS diagnosis had a similar median OS compared with patients with de novo MDS (25.5 vs 28.3 months). This population-based study involving all newly diagnosed MDS patients over a 13-year period in Friesland showed that multiple comorbidities, including previous malignancies, are associated with shorter OS. OS was not related to the use of radiotherapy or chemotherapy.

Introduction

Myelodysplastic syndromes (MDSs) comprise a group of hematological malignancies characterized by inefficient hematopoiesis, leading to cytopenias and dysplasias in the blood.[1,2] MDS is a clinically heterogeneous disease, and prognosis can vary from months to years among patients. Causes of MDS and driving mutations for MDS are not yet fully understood, but exposure to radiotherapy and chemotherapeutic agents is considered a risk factor for the development of MDS.[1-4] These therapy-related neoplasms constitute a distinct category from de novo MDS in the 2016 revision of the World Health Organization (WHO) classification and are listed under acute myeloid leukemia (AML) and related neoplasms. Therapy-related neoplasms can be further categorized into therapy-related MDS

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(t-MDS) and t-AML, depending on blast count.[1] In studies, patients with t-MDS tend to have worse overall survival (OS) than de novo MDS patients, but only limited population-based data are available.[4-7]

MDS predominantly manifests in the elderly, with a median age at diagnosis of 70 to 75 years.[8-10] Elderly patients often have multiple chronic diseases, such as diabetes mellitus, cardiovascular disease, and chronic pulmonary disease. These comorbidities each have an impact on survival.[3,11-13] In addition, cancer as a comorbidity is increasingly seen in older patients.[12,14,15] Given the median age of MDS patients, a substantial number will encounter a malignancy before or sometimes concurrently with the diagnosis of MDS.

Population-based studies of MDS containing detailed clinical information on patient characteristics, treatment, and comorbidities are scarce, and real-world data on previous or concurrent malignancies and t-MDS are rare.[8-10,12,16-20] The impact of comorbidities at diagnosis and the WHO 2016 diagnosis of t-MDS on treatment approach and outcome is therefore unclear. To address these aspects, an observational population-based study was performed with the HemoBase registry, including detailed clinical data on diagnosis and follow-up over a prolonged period of time. Since January 2005, all patients diagnosed with hematological malignancies in Friesland, a northern province of The Netherlands with ~650 000 inhabitants, have been prospectively registered and followed by their clinicians in this population-based registry. The HemoBase registry is a multidisciplinary electronic patient file and includes data from all Frisian hospitals, pathology and clinical laboratories, and the regional radiotherapy institute.[21-23] The HemoBase registry provides insights into day-to-day practice involving MDS patients. This report presents the findings of the observational population-based study using the HemoBase registry. It focuses on the OS of MDS patients in the real world, with particular attention to the effect of comorbidities, specifically of malignancies, on the OS of MDS patients.

Methods

An observational population-based study was performed. The Medical Ethics Committee in Leeuwarden confirmed the conduct of the retrospective study without the need for ethical review, and the institutional boards approved the execution of the study without the need for consent in accordance with Dutch regulations. The study was conducted in accordance with the Declaration of Helsinki.

A query in the HemoBase population registry identified and selected all patients with the (possible) diagnosis of MDS.[21] Subsequently, the diagnosis of each patient was blindly revised, without knowledge of clinical outcome; the bone marrow biopsies and aspirates and the genetics and cytogenetics of all MDS patients were independently reviewed according to the WHO 2016 classification[1] by an expert panel consisting of a hematologist, hematopathologist, bone marrow cytologist, and clinical laboratory geneticist. Additional information about patient characteristics and treatment regimens was collected from electronic health records. Patient characteristics included, but were not limited to, age, sex, MDS subtype, Revised International Prognostic Scoring System (IPSS-R) category, comorbidities, prior malignancies, type of malignancy, anticancer therapy, supportive care, referrals to specialized medical centers, and transplantation. All patients newly diagnosed with MDS in Frisian hospitals between 1 January 2005 and 31 December 2017 were included in this study; exclusion criteria were not applicable. Patients were followed through June 2019. Patients were followed from date of diagnosis to date of death or end of follow-up.

Comorbidities were scored according to the Charlson Comorbidity Index (CCI; without age adjustment).[24] A CCI score of 0 indicated no relevant comorbidities. Patients with t-MDS were defined as patients who received radiotherapy or chemotherapy for a malignancy before their MDS diagnosis.[5] Patients with a malignancy in their medical history who did not receive radiotherapy or chemotherapy before their MDS diagnosis were considered to have secondary MDS (s-MDS). Low-risk MDS was defined as IPSS-R (very) low or intermediate, and high-risk MDS as IPSS-R (very) high.[25,26] Because of missing cytogenetic data or unsuccessful bone marrow biopsy, IPSS-R category could not be determined for all MDS patients. These patients were analyzed as a separate IPSS-R group. Descriptive statistics were used to describe patient characteristics. Mann-Whitney *U* and Fisher's exact tests were used to determine differences between variables. We performed a Kaplan-Meier survival analysis to estimate OS. Cox regression analyses were used to determine differences in survival between groups, using hazard ratios (HRs) with 95% confidence intervals (CIs). A multivariable analysis was performed to study the effect of age, sex, IPSS-R category, CCI score, and individual comorbidities. Variables were included in the multivariable analysis when their *P* value in univariate analysis was $<.15$. Two models were used, the first including all individual comorbidities and the other using CCI score as the composite of comorbidities, to prevent collinearity between CCI and its underlying components in a single multivariable model. Statistical analyses were performed using IBM SPSS (version 24).

Results

A total of 291 MDS patients were identified and included in this study. Sixty-seven percent of the population had a relevant comorbidity; 47% had a CCI score of ≥2 (Table 1). The most common comorbidities at the time of diagnosis were cardiovascular disease (30.9%), (previous) malignancy (24.4%), chronic lung disease (17.2%), and diabetes mellitus (17.2%). The median OS of the study population was 25.3 months (95% CI, 20.3-30.2 months), and the 3-year survival rate was 42.2%. The median OS was significantly different between strata for the following factors: CCI, age, sex, and IPSS-R (Table 2; Figure 1). Patients with CCI score of 0, 1, 2 to 3, and ≥4 had a median OS of 40.3, 31.2, 25.2, and 15.0 months, respectively, corresponding to HRs of 1.01 (95% CI, 0.68-1.52) for CCI of 1, 1.31 (95% CI, 0.91-1.90) for CCI of 2 to 3 (Table 2; Figure 1A), and 2.32 (95% CI, 1.60-3.37) for CCI of ≥4. Survival of patients with CCI of ≥4 was significantly impaired compared with patients with a lower CCI score ($P < .01$). The median OS of patients age ≥85, 75 to 84, 65 to 74, and <65 years was 12.9, 24.0, 26.0, and 61.7 months, respectively, corresponding with HRs of 3.87 (95% CI, 2.27-6.61), 1.95 (95% CI, 1.29-2.9), and 1.58 (95% CI, 1.01-2.45) compared with patients age <65 years. Women had a better median OS compared with men (22.5 vs 42.2 months; HR for men, 1.48; 95% CI, 1.09-2.01; Figure 1B). The median OS was 44.9 months for low-risk MDS patients in comparison with 9.8 months for high-risk MDS patients (HR, 3.66; 95% CI, 2.49-5.38) and 15.0 months for patients with unknown IPSS-R category (HR, 2.55; 95% CI, 1.89-3.45).

Multivariable analyses showed that CCI score of ≥4 ($P = .03$), age ≥65 years ($P < .01$), sex ($P = .02$), and IPSS-R category ($P < .01$) were independent variables significantly influencing survival in MDS patients (Table 3).

Patients with a prior malignancy (t-MDS and s-MDS) had a statistically significantly shorter median OS compared with patients without a malignancy (16.1 and 13.9 vs 28.3 months; $P = .04$; Table 2; Figure 1C). Except for renal disease ($P = .03$), other comorbidities did not have a statistically significant effect on OS. No differences in IPSS-R category, sex, transformation to AML, or treatment were observed in patients with or without the comorbidity malignancy. However, patients with a prior malignancy were older (median age, 79.2 vs 73.9 years; $P < .01$) compared with patients without a malignancy. In addition, the karyotype of many patients with a prior malignancy was unknown (43.7% vs 25.9%).

In 71 patients, 115 cases of malignancy were found. The most common malignancies were nonmelanoma skin cancer (29 cases), hematological malignancies (22 cases), breast cancer (13 cases), and prostate cancer (13 cases; Table 4). At time of MDS diagnosis, 49 patients (69.0%) were in remission. The malignancy was present at time of MDS diagnosis in 22 patients (31.0%), 6 of whom were diagnosed with a malignancy and MDS simultaneously. Patients who were in remission at time of MDS diagnosis had a similar median OS compared with patients with de novo MDS (25.5 vs 28.3 months), whereas patients with active disease had a significantly shorter median OS (12.4 months; $P < .01$). One patient with s-MDS died as a result of a malignancy other than MDS. A majority (n = 67; 94.4%) of patients with a malignancy received some form of intervention: radiotherapy, chemotherapy, hormonal therapy, or surgery. Radiotherapy or chemotherapy was administered in 38 patients (13.1% of total population). Nonmelanoma skin cancer was treated with surgery only, and these cases (14 patients) were not counted as a malignancy in the analyses. The median time between first malignancy and MDS diagnosis was 6.7 years (range, 0.1-42.1 years). The median time between last malignancy (before MDS) and MDS diagnosis was 4.2 years (range, 0.1-36.1 years). The time between first malignancy and MDS diagnosis varied greatly but showed a peak after 3 to 6 years. The time to MDS diagnosis was shortest for patients treated with hormone therapy (5.4 years; range, 0.9-38.5 years; n = 10), followed by chemotherapy (9.5 years; range, 3.0-42.1 years; n = 17 [2 cases were diagnosed with MDS simultaneously]), and longest for patients treated with radiotherapy (12.1 years; range, 0.1-42.1 years; n = 28).

Patients with s-MDS had a similar OS compared with patients with t-MDS, but both groups had a significantly higher risk of death compared with de novo MDS patients (HR, 1.51; 95% CI, 1.02-2.23 and 1.58; 95% CI, 0.95-2.65, respectively; $P = .04$; Table 2; Figure 1C). Multivariable analysis did not identify t-MDS (ie, previous treatment with radiotherapy or chemotherapy) or s-MDS as an independent prognostic factor for OS (Table 3). Because there was no significant difference in median OS between s-MDS and t-MDS patients, the multivariable analysis was subsequently performed for both groups combined. This analysis identified prior malignancy as a borderline significant independent prognostic factor (HR, 1.41; 95% CI, 1.00-1.99; $P = .05$).

Discussion

In this population-based study including all newly diagnosed MDS patients over a 13-year period, we observed that higher CCI score

Table 1. Characteristics of Frisian MDS patients

	n (%)
Total	291 (100)
Male sex	203 (69.8)
Age, y	
Median	75.2
Range	18.2-92.0
Hospital	
Peripheral	148 (50.9)
Teaching	143 (49.1)
MDS subtype	
SLD	42 (14.4)
MLD	41 (14.1)
RS SLD	44 (15.1)
RS MLD	30 (10.3)
Del 5q	6 (2.1)
EB-1	54 (18.6)
EB-2	39 (13.4)
U	6 (2.0)
NOS	29 (10.0)
IPSS-R risk	
Low	150 (51.5)
Very	19 (6.5)
Low	88 (30.2)
Intermediate	43 (14.8)
High	39 (13.4)
High	22 (7.6)
Very High	17 (5.8)
Unknown	102 (35.1)
CCI	
0	91 (31.3)
1	60 (20.6)
2-3	72 (24.7)
≥4	64 (22.0)
Unknown	4 (1.4)
Type of comorbidity	
Cardiovascular disease	90 (30.9)
Cerebrovascular disease	37 (12.7)
Chronic lung disease	50 (17.2)
Diabetes mellitus	50 (17.2)
Malignancy	71 (24.4)
Renal disease	20 (6.9)
Other	46 (15.8)
Treatment for MDS	
BSC	136 (46.7)
ESA	81 (27.8)
DMT	90 (30.9)
Transplantation	23 (7.9)
Transformation to AML	41 (14.1)

BSC, best supportive care; Del 5q, deletion of 5q chromosome; DMT, disease-modifying treatment; EB, excess blasts; ESA, erythropoiesis stimulating agent; MLD, multiline dysplasia; NOS, not otherwise specified; RS, ring sideroblasts; SLD, single-line dysplasia; U, unclassifiable.

Table 2. OS and crude HRs of Frisian MDS patients

Factor	n	Median OS, mo	95% CI	*P*	Crude HR	95% CI	*P*
Total	291	25.3	20.3-30.2				
Age, y				<.01			<.01
<65	55	61.7	49.2-74.2		Ref		
65-74	87	26.0	17.9-34.0		1.58	1.01-2.45)	
75-84	120	24.0	19.2-28.9		1.95	1.29-2.94	
≥85	29	12.9	5.5-20.4		3.87	2.27-6.61	
Sex				.01			.01
Male	203	22.5	18.1-26.8		1.48	1.09-2.01	
Female	88	42.2	28.4-55.9		Ref		
IPSS-R risk				<.01			<.01
Low	150	44.9	38.6-51.2)		Ref		
High	39	9.8	4.3-15.3		3.66	2.49-5.38	
Unknown	102	15.0	12.2-17.9		2.55	1.89-3.45	
Cardiovascular disease				.21			.21
Yes	90	24.0	20.7-27.4		1.20	0.90-1.61	
No	197	29.1	18.0-40.2		Ref		
Cerebrovascular disease				.61			.61
Yes	37	24.3	14.2-34.5		1.11	0.74-1.67	
No	250	25.8	20.5-31.1		Ref		
Chronic lung disease				.11			.11
Yes	50	20.9	14.6-27.1		1.33	0.94-1.88	
No	237	26.8	19.2-34.4		Ref		
Diabetes mellitus				.11			.11
Yes	50	19.7	15.5-24.0		1.33	0.94-1.88	
No	237	28.6	20.8-36.4		Ref		
Malignancy*				.04			.04
t-MDS	38	16.1	8.2-23.9		1.51	1.02-2.23	
s-MDS	19	13.9	10.6-17.2		1.58	0.95-2.65	
De novo	231	28.3	21.3-35.3		Ref		
Renal disease				.03			.04
Yes	20	11.7	0-31.0		1.71	1.04-2.81	
No	267	27.2	21.8-32.5		Ref		
Other comorbidity				.70			.70
Yes	46	25.3	19.5-31.0		1.07	0.75-1.55	
No	241	26.0	20.2-31.7		Ref		
CCI score†				<.01			<.01
0	91	40.3	30.5-50.2		Ref		
1	60	31.2	8.1-54.3		1.01	0.68-1.52)	
2-3	72	25.2	16.2-34.2		1.31	0.91-1.90	
≥4	64	15.0	11.8-18.2		2.32	1.60-3.37	

*Nonmelanoma skin cancer was not considered malignancy in this analysis.
†Four patients excluded from analysis because of missing data.

(≥4), older age (≥65 years), male sex, and high-risk MDS negatively affected OS. A quarter of the population had another malignancy in their medical history, and of these patients, two-thirds were considered to have t-MDS according to the WHO 2016 classification. Prior malignancy had a negative effect on OS; patients with active disease had a significantly shorter median OS, whereas patients who were in remission at time of MDS diagnosis had a similar median OS, compared with patients with de novo MDS.

Sixty-seven percent of patients had at least 1 relevant comorbidity, which is comparable to percentages reported in literature.[12,15,19,20]

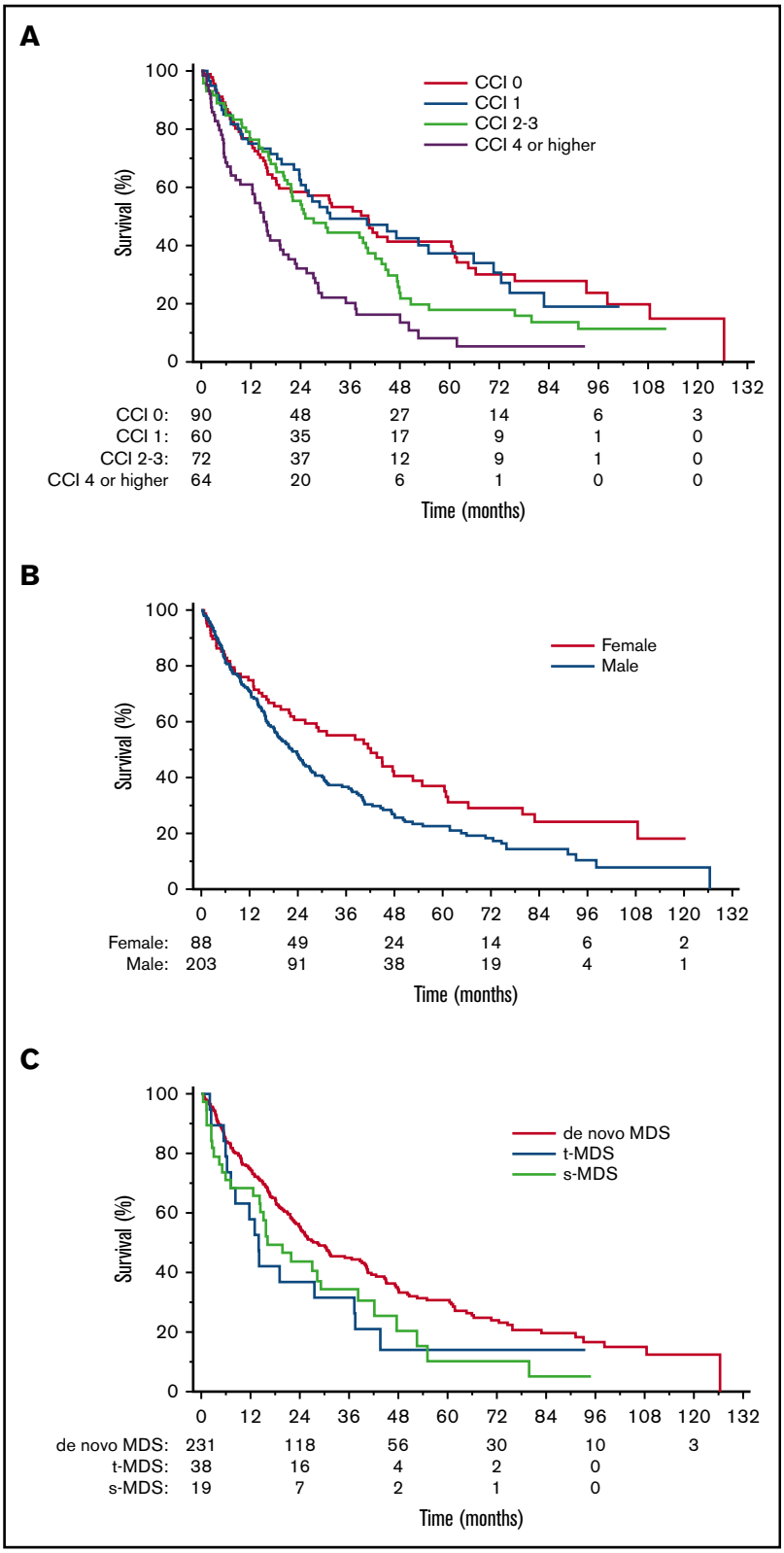

Figure 1. OS of MDS patients and the effect of different variables presented in Kaplan-Meier plots. Effects of CCI score (A), sex (B), and t-MDS and s-MDS (C) on OS.

Most of the patients with comorbidities might not have been included in randomized clinical trials, which highlights the importance of population-based research.[27-29] Comorbidities, previous malignancies, and their effect on median OS have not been studied in depth before in MDS patients in a population-based setting. Our long-term population-based data show that a combination of comorbidities (reflected by increasing CCI score), malignancy, or renal disease was associated with worse OS. Furthermore, patients

Table 3. Multivariable analysis of OS in MDS patients

Model	Adjusted HR	95% CI	*P*
1			
Age, y			<.01
65-74	1.69	1.07-2.68	
75-84	2.12	1.37-3.28	
≥85	3.31	1.81-6.04	
Male sex	1.68	1.21-2.33	<.01
IPSS-R risk			<.01
High	4.25	2.84-6.37	
Unknown	2.33	1.69-3.22	
Chronic lung disease	1.06	0.74-1.52	.75
Diabetes mellitus	1.34	0.93-1.94	.12
Malignancy			.15
t-MDS	1.42	0.93-2.16	
s-MDS	1.40	0.83-2.35	
Renal disease	0.79	0.46-1.37	.40
2			
Age, y			<.01
65-74	1.65	1.04-2.60	
75-84	2.00	1.29-3.10	
≥85	2.85	1.58-5.13	
Male sex	1.50	1.08-2.09	.02
IPSS-R risk			<.01
High Risk	4.09	2.75-6.10	
Unknown	2.20	1.59-3.04	
CCI			.03
1	1.19	0.78-1.79	
2-3	1.28	0.88-1.85	
≥4	1.80	1.21-2.67	

Table 4. Detailed information on prior malignancies in MDS patients

	Patients	Cases
Total	71 (100)	
Present at time of MDS diagnosis	22 (31.0)	
Type of malignancy*		
Total	71 (100)	115 (100)
Nonmelanoma skin cancer	24 (33.8)	29 (25.2)
Melanoma	2 (2.8)	4 (3.5)
Breast	10 (14.1)	13 (11.3)
Prostate	11 (15.5)	13 (11.3)
Hemato-oncological	14 (19.7)	22 (19.1)
Urinary	7 (9.9)	13 (11.3)
Lung	5 (7.0)	5 (4.3)
Endocrine	3 (4.2)	3 (2.6)
Colorectal	6 (8.5)	6 (5.2)
Endometrial	3 (4.2)	3 (2.6)
Other	4 (5.6)	4 (3.5)
Treatment*		
Chemotherapy	19 (26.8)	
Radiotherapy	28 (39.4)	
Hormone therapy	10 (14.1)	
Surgery	54 (76.1)	
No intervention	4 (5.6)	
Time to onset MDS, median (range), y†		
First malignancy	6.7 (0.1-42.1)	
Radiotherapy	12.1 (0.1-42.1)	
Chemotherapy	9.5 (3.0-42.1)	
Hormone therapy	5.4 (0.9-38.5)	
Last malignancy	4.2 (0.1-36.1)	
Radiotherapy	3.4 (0.1-22.2)	
Chemotherapy	4.3 (0.4-17.0)	
Hormone therapy	4.3 (0.9-22.2)	

*Single patient can have multiple malignancies and multiple treatments.
†Excluding nonmelanoma skin cancer cases and malignancies diagnosed simultaneously with MDS.

with a prior malignancy who were not in remission by the time of MDS diagnosis had a significantly shorter median OS. Consistent with previous studies, patients with a prior malignancy were older compared with patients without a malignancy.[6] Individual comorbidities by themselves were not a prognostic variable in multivariable analysis. Despite the age difference, CCI score remained a significant factor in multivariable analysis. Therefore, it is appropriate to take into account an individual MDS patient's medical history when discussing prognosis and treatment options. Falantes et al[11] have already suggested this for low-risk MDS patients. It is possible that CCI score indirectly reflects the likelihood of death resulting from MDS or comorbidity-related factors.[11]

Thirty-eight MDS patients (13.1%) with a prior malignancy received radiotherapy or chemotherapy and were considered to have t-MDS; the other patients with a prior malignancy (s-MDS) received a different kind of intervention (ie, hormone therapy or surgery). In accordance with the present results, previous studies have demonstrated that roughly 2% to 20% of MDS cases are therapy related.[4,9,30,31] As expected, patients with t-MDS had worse OS compared with de novo MDS patients, but it did not reach statistical significance in multivariable analysis. The worse OS of t-MDS patients cannot be solely explained by previous treatment with radiotherapy or chemotherapy, because the OS and HRs for t-MDS patients were comparable to those of s-MDS patients. The adjusted HRs failed to meet statistical significance in multivariable analysis, but it is notable that s-MDS patients had outcomes just as poor as t-MDS patients. Death resulting from a second malignancy was rare (supplemental Data), suggesting further research is needed to identify the effect of prior treatment with radiotherapy or chemotherapy when studying OS.[6,9]

The observed median OS in this population of MDS patients is similar to findings in other population-based studies.[8,9,12,17,30,31] As expected, the median OS was dependent on IPSS-R risk category. Low-risk MDS patients had a median OS of 44.9 months, whereas high-risk MDS patients had a median OS of only 9.8 months. This outcome reflects the severity of the disease. The number of patients undergoing transplantation was 8%, which is in line with other

population-based studies.[7,8] Transplantation was considered part of treatment during follow-up and was not included in the multivariable analysis. OS was also dependent on sex. Multivariable analyses showed that sex was an independent prognostic factor for OS, where women had a significantly better OS compared with men after the first year. It is difficult to pinpoint the reason for this difference. Individual MDS subtypes ($P = .97$) and IPSS-R risk groups ($P = .65$) were similar for men and women; none of our parameters could explain the difference in OS between men and women. Other population-based studies have also reported a better median OS for female patients, but a clear explanation is missing.[8,12,31,32] Perhaps the differences in survival in this study might be related to a better OS for women in general.

The strengths of this study lie in its population-based setting with real-world data over a 13-year period. In contrast to randomized clinical trials, there were no inclusion or exclusion criteria, thus minimizing selection bias and ensuring external validity. The diagnosis of each patient was carefully assessed and reviewed by an expert panel, and the complete study population was categorized according to the WHO 2016 classification. In addition, this study included more detailed clinical data on patient characteristics and treatments than previous population-based studies.[6,8,32]

The most important limitation lies in the fact that this was a retrospective observational study. The causality of the relationship between (treatment of) a previous malignancy and onset of MDS still needs to be determined. Secondly, we only documented cytotoxic treatment that was administered for a previous malignancy. Cytotoxic agents for a different indication (eg, methotrexate for rheumatoid arthritis) were not considered in this study. Therefore, the number of t-MDS patients may have been higher than reported in this study. In addition, it is difficult to attribute differences in OS to specific treatment types, because malignancies are often treated with a combination of therapies.

In conclusion, this population-based study showed that a majority of MDS patients had comorbidities. A combination of comorbidities, reflected by increasing CCI score, was associated with significantly worse OS. A substantial part of the MDS population had a prior malignancy, and these patients had a significantly shorter OS. OS was not related to the use of radiotherapy or chemotherapy. OS was similar between patients with a prior malignancy that was in remission and patients with de novo MDS, but significantly shorter in patients with an active malignancy. Future clinical trials should more often include MDS patients with at least 1 comorbidity, so new therapeutic agents and treatment options are tested in the population in which they will eventually be used.

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Authorship

Contribution: J.R. collected the data and wrote the manuscript; J.R., E.v.R., M.H., and R.K. designed the project; J.R. and N.V. analyzed the data; E.v.R., M.H., R.K., E.v.d.B., and N.V. provided input for data analysis; and all authors contributed to critical revision and gave final approval of the manuscript.

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A complete list of the members of the HemoBase Population Registry Consortium appears in the supplemental appendix.

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