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10-year nationwide trends in incidence, treatment patterns, and mortality of patients with myelodysplastic syndromes in Denmark

Tine Bichel Lauritsen [a,1,*], Jan Maxwell Nørgaard [a], Susanne Oksbjerg Dalton [b,c], Kirsten Grønbæk [d,e], Tarec Christoffer El-Galaly [f,g,h], Lene Sofie Granfeldt Østgård [h,i]

[a] Department of Hematology, Aarhus University Hospital, Denmark
[b] Danish Cancer Society Research Center, Denmark
[c] Department of Clinical Oncology and Palliative Care, Zealand University Hospital, Denmark
[d] Department of Hematology, Rigshospitalet, Denmark
[e] Biotech Research and Innovation Centre, BRIC, University of Copenhagen, Denmark
[f] Department of Hematology, Aalborg University Hospital, Aalborgī, Denmark
[g] Department of Clinical Medicine, Aalborg University Hospital, Denmark
[h] Department of Hematology, Odense University Hospital, Denmark
[i] Department of Clinical Epidemiology, Aarhus University Hospital, Denmark

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ABSTRACT

Further temporal data on incidence, treatment patterns, and prognosis for patients with myelodysplastic syndromes (MDS) are needed. This study examined 10-year trends in incidence, treatment patterns, and all-cause mortality in a population-based cohort of 2309 MDS patients using Danish nationwide registries (2010–2019). We computed annual incidence rates overall and according to sex and age-groups. We examined temporal changes in the cumulative incidence of MDS specific treatments initiated within one year from diagnosis and temporal changes in the absolute risk of death and five-year adjusted hazard ratios (aHRs) for death, adjusting for age, sex and comorbidity. The age-standardized incidence rate of MDS per 100,000 person-years increased slightly from 5.3 in 2010 to 6.4 in 2019. Between 2010-2012 to 2016–2017, the use of azacitidine increased overall (8% to 22%), in patients with intermediate risk MDS (12% to 34%), and in patients with high-risk MDS (22% to 50%), while it remained stable (around 5%) for patients with low-risk MDS. The five-year aHR for death in the most recent calendar period compared to the earliest calendar period remained unchanged in patients with low-risk MDS, aHR = 0.90 (95% CI, 0.72–1.12) and in patients with high-risk MDS, aHR = 1.19 (95% CI, 0.89–1.61), while survival improved over time among patients with intermediate risk MDS, aHR = 0.67 (95% CI, 0.48–0.92). In conclusion the incidence of MDS slightly increased during a 10-year period in Denmark. The use of azacitidine increased markedly but five-year overall survival remained unchanged.

1. Introduction

Myelodysplastic syndromes (MDS) represent a group of heterogeneous myeloid neoplasms, characterised by insufficient hematopoiesis and risk of progression to acute myeloid leukemia (AML) [1]. MDS is a rare disease with an age standardized incidence rate around 1.3 and 4.3 per 100,000 person-years, increasing progressively with advancing age [2–10].

Current American and European MDS guidelines recommend treatment options covering best supportive care, hematopoietic growth-factors, disease-modifying agents such as azacitidine or lenalidomide, remission induction chemotherapy, and allogeneic stem cell transplantation (alloHSCT) [11]. Nonetheless, studies indicated that a large proportion of MDS patients are treated solely with supportive care [7, 12–16]. Despite the introduction of azacitidine and lenalidomide during 2004–2009 and an increasing use of alloHSCT, the overall 5-year survival of around 30% for MDS has not changed substantially over time [5, 17–19]. Further data on trends in incidence, treatment, risk of progression to AML and all-cause mortality in an unselected MDS-population are needed. Prior studies were limited by short

* Correspondence to: Department of Hematology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark.
E-mail address: tinelaur@rm.dk (T.B. Lauritsen).
[1] ORCID ID: 0000-0002-1730-8533.

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observation periods [2,3,9], selected study populations (inclusion of patients >66 years, single-centre-studies, claims based data) [5,7,8, 13–18, 20, 21], small sample size [4,6,20], loss to follow-up [2,3,5,18], no data on cytogenetics or comorbidities [5–7,13,15,17–19,21], lacked detailed treatment and transfusion information [7,18], and they were unable to examine subgroup specific trends. Such data are important as trends in prognosis may differ substantially across subgroups of patients. In addition, the studies did not report outcomes from the most recent time period [2–8,13,14,16,18,21], and therefore could not examine contemporary trends. Knowledge on these trends is a cornerstone of public health, as it provides a foundation for effective prevention strategies, resource allocation, and it may inform policy makers, clinicians, and patients. Therefore, we examined 10-year nationwide trends in MDS incidence, treatment patterns and clinical outcomes, overall and in subgroups of patients according to the revised International Prognostic Scoring System (IPSS-R), age, and sex.

2. Methods

2.1. Design, setting and data sources

We conducted a population-based cohort study in Denmark, which covers approximately 6 million inhabitants [22]. The healthcare system is tax-funded providing free access to hospitals and general practitioners for all residents. At birth or upon immigration, all Danish citizens are assigned a 10-digit personal identification-number that enables linkage between Danish healthcare registries and complete longitudinal follow-up [22]. We linked seven Danish nationwide healthcare registries: The Myelodysplastic Syndromes Database [23], the National Acute Leukemia Registry [24,25], The National Patient Registry (DNPR) [26], the Civil Registration System [27], Statistics Denmark [28], the Transfusion Database [29], and the National Prescription Registry [30]. All these registries are described in Supplementary Table S1.

2.2. Study population

Using the Danish Myelodysplastic Syndromes Database, we identified all patients diagnosed with MDS in Denmark between 1 January 2010 and 31 December 2019. It is mandatory for all Danish hospitals to report incident MDS cases to this registry, using criteria as defined by the World Health Organization (WHO) [1,31]. The registry captures 98% of all MDS cases, and the positive predictive value of the diagnosis is around 92% [23]. To ensure patients had incident MDS, we excluded patients with a history of immigration within five years prior to the MDS diagnosis and patients who had MDS diagnosed upon autopsy.

2.3. Patient characteristics

Data on age, sex, type of MDS (de novo or therapy-related), bone marrow blast count, laboratory values (hemoglobin g/dL, platelet count x 10^9/L and white blood cell count x 10^9/L), WHO subtype according to the 2016 classification, IPSS and IPSS-R prognostic risk groups were retrieved from the Danish Myelodysplastic Syndromes Database. Using patients' medical histories, available in the DNPR since 1977, we retrieved data on selected comorbidities and comorbidities included in a modified Charlson Comorbidity Index score (CCI), excluding myeloid diseases from the index [26,32]. We furthermore obtained information from the Danish National Prescription Registry on redeemed prescriptions for antihypertensives, antidiabetics, antiplatelets, anticoagulants, drugs against osteoporosis, and drugs against chronic obstructive pulmonary disease, within 180 days prior to the date of MDS diagnosis. From the DNPR, we also obtained information on number of patients with a history of any bleeding leading to hospitalization or an arterial or venous thromboembolic event (myocardial infarction, ischemic stroke, deep venous thrombosis and pulmonary embolism), within five years prior to MDS diagnosis. *International Classification of Diseases codes, 10th edition* (ICD-10 codes) and *Anatomical Therapeutically Classification codes* (ATC-codes) used to define comorbidities and medication use in this study, are provided in Supplementary Table S2.

2.4. Outcomes

Study outcomes were [1] annual incidence rates of MDS, [2] trends in transfusion use within the first year after diagnosis, 3) trends in MDS specific treatments initiated within one year from diagnosis, 4) trends in the risk of progression to AML, and [5] trends in all-cause mortality. Secondarily, we examined trends in bleeding leading to hospitalization and arterial and venous thromboembolic events within the first year after MDS diagnosis. Further, we compared mortality rates in the MDS population with mortality rates in the entire Danish population aged ≥ 18 years to improve the understanding of the impact of MDS on prognosis.

Information on packed red blood cells (RBC) and platelet transfusions were ascertained from the Danish Transfusion Database [29]. Treatment information was ascertained from the DNPR using first-time treatment codes encompassing erythropoiesis-stimulating agents (ESAS), granulocyte-colony-stimulating-factors (GCSF), the hypomethylating agent azacitidine (decitabine is not approved for MDS in Denmark), remission-induction chemotherapy, and alloHSCT. A recent study showed high validity of hematological treatment codes in the DNPR [33]. We used primary inpatient and outpatient diagnosis codes recorded in the DNPR within the first year after MDS diagnosis to identify any bleeding leading to hospitalization and any thromboembolic event. The discharge date/outpatient visit date was used to define the date of the event. Treatment codes and diagnosis codes are provided in Supplementary Table S2. Information on progression to AML was obtained from the National Acute Leukemia Registry [25], and vital status including date of death was obtained from the Civil Registration System [27].

2.5. Statistics

2.5.1. Annual incidence rates

For each year, annual incidence rates (IR) (age-standardized to the year 2019 when applicable) were computed for all MDS patients and according to sex and age groups (<70, 70–80, >80), as the number of first-time MDS diagnoses divided by the underlying Danish midyear population aged ≥ 18 years.

2.5.2. Treatment, progression to AML and all-cause mortality

Temporal trends in transfusion use, progression to AML and all-cause mortality, were analysed separately according to calendar periods (2010–2012, 2013–2015, 2016–2018). Due to data availability issues, the following calendar periods were applied when examining trends in MDS specific treatments, and adverse events (2010–2012, 2013–2014, 2015–2017). We tabulated the distribution of baseline patient characteristics for all MDS patients and according to calendar periods. We followed patients from date of MDS diagnosis until the outcome of interest, emigration, death, one year of follow-up (transfusion use, treatment, adverse events), two years of follow-up (risk of progression to AML), five years of follow-up (all-cause mortality) or 31 December 2021, whichever came first. The median follow-up time was calculated as the median of follow-up times for each individual.

To examine transfusion burden within the first year after diagnosis, we defined 3 categories of transfusion burden according to definitions by the MDS International Working Group (IWG) 2018 [34]: 1) not transfusion dependent (NTD) including patients who received ≤ 2 RBC units in a period of 16 weeks 2) low transfusion burden (LTB) defined as 3–7 RBC units in a period of 16 weeks, and high transfusion burden (HTB) defined as ≥ 8 RBC units in a 16 weeks period. We also calculated IRs of transfusions within the first year after diagnosis by dividing the number of transfusions by risk time. We used Poisson regression models

Table 1
Characteristics of patients with a first-time diagnosis of myelodysplastic syndromes inDenmark, 2010–2018. Data are shown overall and by calendar period (2010–2012, 2013–2015, 2016–2018).

Calendar period of diagnosis	2010–2018	2010–2012	2013–2015	2016–2018
Total, n (%)	2309	681	746	882
Median age, (25th-75th percentiles)	76 (68–82)	75 (67–81]	76 (69–82)	76 (69–81)
Age groups, years				
< 75	1115 (48)	344 (51]	352 (47)	419 (48)
≥ 75	1194 (52]	337 (49]	394 (53)	463 (52)
Men, n (%)	1444 (62]	420 (62]	468 (63)	556 (63)
Median laboratory values with 25th-75th percentiles				
Bone marrow blast count, (%)	2 (0–6)	2 (0–6)	3 (1–8)	2 (0–6)
Hemoglobin, g/dL	9.8 (8.9–11,1)	9.8 (8.9–11,1)	10 (8.9–11.1)	9.8 (8.7–11.3)
Platelet count x 10^9/L	124 (69–234)	129 (68–236)	117 (68–228)	126 (70–236)
WBC 10^9/L	1.8 (0.9–3.5)	1.9 (1.0–3.5)	1.7 (0.9–3.3)	1.9 (1.0–3.7)
Therapy-related MDS	234 (10)	56 (8)	66 (9)	112 (13)
WHO subtype				
MDS with single lineage dysplasia	236 (10)	104 (15)	65 (9)	67 (8)
MDS with multi lineage dysplasia	674 (29)	206 (30)	218 (29)	250 (28)
MDS with ring sideroblasts	240 (10)	65 (10)	70 (10)	105 (12)
MDS with excess blasts	576 (25)	149 (22)	204(27)	223 (25)
MDS with isolated 5q-	78 (3)	22 (3)	23 (3)	33 (4)
MDS unclassifiable	505 (22)	135 (20)	166(22)	204(23)
IPSS-R prognostic risk group*				
Very low	327 (21)	86 (20)	90 (19)	151 (23)
Low	553 (36)	159 (38)	152 (33)	242 (37)
Intermediate	295 (19)	94 (22)	95 (20)	106 (16)
High	196 (13)	45 (11)	68 (15)	83 (13)
Very High	171 (11)	40 (9)	61 (13)	70 (11)
IPSS prognostic risk group*				
Low risk	456 (25)	115 (21)	142 (23)	229 (29)
Intermediate 1	959 (49)	289 (53)	300 (49)	370 (47)
Intermediate 2	340 (18)	97 (18)	119 (20)	124 (16)
High risk	152 (8)	44 (8)	49 (8)	59 (8)
RBC transfusion within 56 days prior to diagnosis				
Yes	253 (37)	253 (37)	254 (34)	253 (29)
Platelet transfusion within 56 days prior to diagnosis				
Yes	199 (8)	54 (8)	64 (9)	81 ((9)
Charlson comorbidity index score				
0	1363 (59)	398 (58)	462 (602)	503 (57)
1–2	666 (29)	205 (30)	206 (28)	255 (29)
> 2	282 (12)	78 (11)	80 (11)	124 (14)
Main comorbidities				
Ischaemic heart disease	349 (15)	109 (16)	112 (15)	128 (15)
Congestive heart failure	215 (9)	66 (10)	64 (9)	85 (10)
Chronic pulmonary disease	285 (12)	95 (14)	81 (11)	109 (12)
Moderate to severe renal disease	122 (5)	27 (4)	36 (8)	59 (7)
Solid tumour	386 (17)	107 (16)	110 (15)	169 (19)
Alcohol-related disorders	75 (3)	22 (3)	25 (3)	28 (3)
Medication use within 180 days prior to diagnosis				
Antihypertensives	1330 (58)	392 (58)	430 (58)	508 (58)
Antidiabetics	315 (14)	88 (13)	98 (13)	129 (15)
Anti-platelets	643 (28)	211 (31)	209 (28)	223 (25)
Anticoagulants	307 (13)	57 (8)	98 (13)	152 (17)
Drugs against osteoporosis	191 (8)	58 (9)	67 (9)	66 (7)
Drugs against COPD	339 (15)	105 (14)	96 (13)	138 (16)
Adverse event within 5 years prior to diagnosis				
Hospital requiring bleeding	280 (12)	83 (12)	82 (11)	115 (13)
Thromboembolic event	210 (10)	57 (8)	71 (10)	82 (9)
Education				
Long	419 (19)	115 (18)	125 (17)	179(21)
Medium	1098 (49)	296 (46)	361 (50)	441 (51)
Short	716 (32)	235 (37)	234 (33)	247(28)
Cohabitation status				
Living alone	1387 (60)	397 (58)	439 (59)	551 (62)
Living with a partner	922 (40)	284 (42)	307(41)	381 (38)

Abbreviations: CCI; Charlson Comorbidity Index score, IPSS; International Prognostic Scoring System, COPD; Chronic Obstructive Pulmonary Disease, No; number.

* Data on IPSS-R risk group were unavailable for 38% of patients diagnosed during 2010–2012, 38% of patients diagnosed between 2013 and 2015 and 26% of patients diagnosed between 2016 and 2018. Data on IPSS risk group were unavailable for 20% of patients diagnosed in 2010–2012, 18% of patients diagnosed in 2013–2015 and 11% of patients diagnosed during 2016–2018.

to compute crude and age, sex, and comorbidity adjusted 1-year-incidence rate ratios (IRR). Analyses were made overall and by calendar period and level of IPSS-R.

To compute the cumulative incidence of non-fatal outcomes, we used the Aalen Johansen estimator accounting for death as a competing risk and emigration as a censoring event [35]. For all-cause mortality, we applied the one minus Kaplan-Meier estimator. To examine trends in the risk of adverse events, progression to AML and all-cause mortality, we used Cox proportional hazards regression analyses to estimate hazard ratios (HR) by calendar period (reference: 2010–2012) and exposure groups. We accounted for death as a competing risk (non-fatal outcomes). The Cox proportional hazards model assumptions were graphically verified using log minus log plots. Results were presented unadjusted and adjusted for age, sex and CCI. Analyses were made overall and by patient subgroup (sex, age (± 75 years), and IPSS-R (low-risk, intermediate and high-risk prognostic group)). As data were sparse, outcomes regarding trends in adverse events, were only reported according to calendar period.

Using direct standardization, we calculated standardized mortality ratios (SMRs) by comparing mortality rates in the MDS population (2010–2021) with mortality rates in the entire Danish population aged 18 years or older (2010–2021). SMRs were examined overall and in strata of age (18–59,60–69,70–79,80 + years), sex, and level of IPSS-R. We also calculated SMRs within combinations of IPSS-R and age groups. Analyses were performed using STATA version 14.

3. Results

We identified 2330 patients diagnosed with MDS between 1 January 2010 and 31 December 2018. After excluding patients who immigrated within five years prior to the diagnosis of MDS or those who had MDS diagnosed upon autopsy, the study cohort comprised 2309 patients. Median follow-up was 31 months during which 1742 patients died.

Fig. 1. Incidence rates of myelodysplastic syndromes in Denmark, 2010–2019. A) Age standardized to the Danish Midyear population in 2019, B) By age groups (<70, 70–80, 80+ years) and C) By sex and age groups. Note varying axes.

Median age at diagnosis was 76 years and 63% were males (Table 1). The age- and sex distribution remained unchanged during the study period. The proportion of patients diagnosed with therapy-related MDS, the distribution of WHO subtypes, and the proportion of patients in each IPSS and IPSS-R prognostic risk group remained rather stable over time. The prevalence of comorbidity remained steady over time as did the prevalence of patients with a redeemed prescription for drugs against hypertension, diabetes, osteoporosis, and chronic obstructive pulmonary disease. In contrast, the prevalence of patients treated with antiplatelets decreased from 31% in 2010–2012 to 25% in 2016–2017 while the prevalence of patients treated with anticoagulants increased from 8% in 2010–2012–17% to in 2016–2017. The proportion of patients with a history of bleeding leading to hospitalization and arterial and venous thromboembolic events within five years prior to MDS diagnosis were similar across the study period.

3.1. Temporal trends in MDS incidence

The overall age-standardized IR per 100,000 person-years for MDS increased slightly from 5.3 (95% CI: 4.5–6.0) in 2010 to 6.4 (95% CI: 5.7–7.2) in 2019 (Fig. 1A). Age-standardized IRs per 100,000 person-years in 2010 were 6.8 (95% CI: 5.6–8.0) for men and 3.9 (95% CI: 3.0–4.8) for women. In 2019, this increased to 7.3 (95% CI: 6.2–8.5) for men and 5.6 (95% CI: 4.6–6.5) for women per 100,000 person-years. Age-stratified IRs per 100,000 person-years showed stable IRs for patients in the lower age groups (≥18-<70, and 70–80) while it increased slightly for patients aged 80 years or older [2010: IR = 27.8 (95% CI: 21.4–36.1), 2019: IR = 42.4 (95% CI: 34.8–51.6)] (Fig. 1B). Age and sex-stratified IRs per 100,000 person-years showed similar trends, except that men had higher annual IRs than women, which was most pronounced in patients > 80 years. While the IRs were stable among men and women in the younger age groups, it increased among + 80-year-old men [2010: IR = 47.0 (95% CI: 33.4–66.2), 2019: IR = 64.0 (95% CI: 49.5–82.8)] and women [2010: IR: = 17.5 (95% CI: 11.3–26.0), 2019: IR = 28.7 (95% CI: 21.1–39.0)] (Fig. 1C).

3.2. Trends in transfusion use

During the study period, 32% were NTD, 20% had a LTB, and 48% of patients had a HTB with packed RBCs. Use of packed RBCs remained stable around 10 per person-year across the study period (Supplementary Table S3). We observed a decrease in the use of packed RBCs among patients with low-risk and high-risk MDS. For example, there was an increase of low-risk patients who were NTD (65% in 2010–2012 *vs.* 72% in 2016–2018), a decrease in the IR of packed RBCs use from 5.9 per person year in 2010–2012 to 4.5 per person year in 2016–2018 and an adjusted IRR of 0.77 (95% CI: 0.72–0.83) in 2016–2018. Likewise, more patients with intermediate-risk MDS were NTD in 2016–2018 (43%) compared to 2010–2012 (31%), but the adjusted IRR remained stable 1.02 (95% CI: 0.95–1.10) (Supplementary, Table S3).

The use of platelet transfusions within the first year after MDS diagnosis slightly increased from 3.9 per person-year in 2010–2012 to 5.3 per person-year in 2016–2018, with a corresponding adjusted IRR in 2016–2018 of 1.45 (95% CI: 1.41–1.57). This increase was mainly driven among patients with intermediate-risk MDS (IRR = 1.46, 95% CI: 1.29–1.65), whereas platelet use remained stable in low-risk MDS (IRR = 0.99, 95% CI: 0.85–1.15) and high-risk MDS (IRR = 0.95, 95% CI: 0.88–1.03).

3.3. Trends in MDS specific treatments

Temporal changes in the cumulative incidence of MDS specific treatments initiated within one year after MDS diagnosis are graphically illustrated in Fig. 2 and exact numbers are presented in Supplementary Table S4. The cumulative incidence of treatment with ESAS and GCSF decreased between 2010-2012 and 2016–2017 (from 44% to 28% for

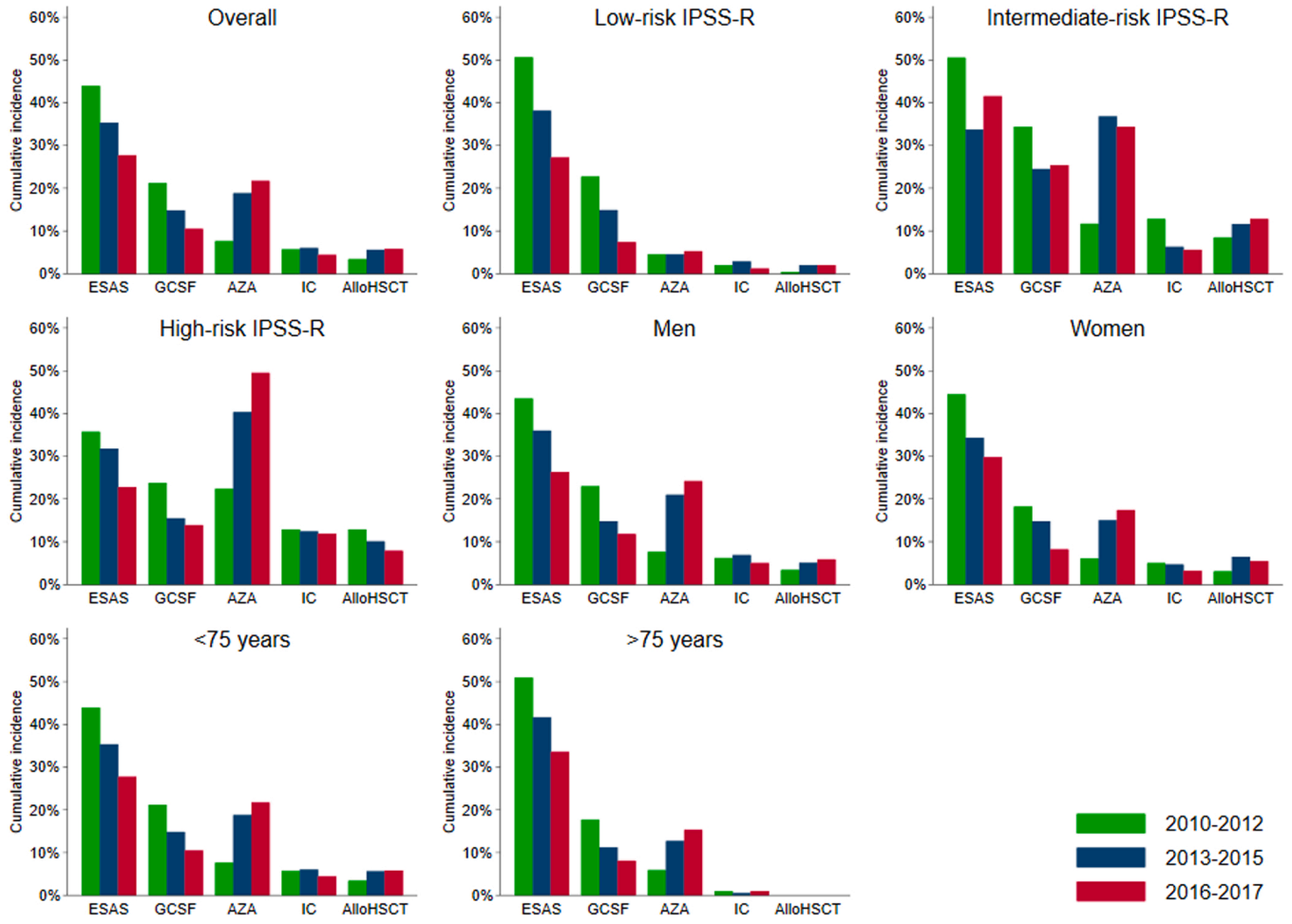

Fig. 2. Temporal changes in the cumulative incidence of treatments for myelodysplastic syndromes initiated within one year after diagnosis in Denmark, 2010–2017, by calendar period. Overall and stratified by IPSS-R prognostic risk group, age group, and sex. Abbreviations: AlloHSCT, allogeneic haematopoietic stem cell transplantation; AZA, azacitidine; ESAS, erythropoiesis stimulating agents; GCSF, granulocyte-colony-stimulating-factors; IC, remission induction chemotherapy.

ESAS and from 21% to 11% for GCSF). Similar trends were seen across IPSS-R prognostic risk groups and age-groups. Azacitidine use remained stable among patients with low-risk MDS (around 5%) whereas the use increased markedly in patients with intermediate-risk (12% to 34%) and high-risk MDS (22% to 50%). The use of azacitidine increased in both age groups, but the increase was more pronounced in the younger age group. The use of remission-induction chemotherapy remained stable overall and in strata of age and IPSS-R risk groups except from in patients with intermediate-risk MDS where it decreased from 13% in 2010–2012 to 6% in 2016–2017. From 2010–2012 to 2016–2017, the use of alloHSCT increased overall (3% to 6%), in strata of low-risk MDS (0.4% to 2.0%), intermediate-risk MDS (9% to 13%) and in the younger age group (7% to 12%). In contrast, the use of alloHSCT decreased in patients with high-risk MDS (12.9% to 7.9%).

3.4. Trends in progression to AML

During a median follow-up of 22.3 months, the cumulative risk of progression to AML was 12% overall, 7% in patients with low-risk MDS, 18% in patients with intermediate-risk MDS, and 13% in patients with high-risk MDS. The two-year cumulative risk of progression to AML was stable during each successive calendar period overall and in strata of low-risk MDS, age and sex (Supplementary Fig. 1 and Supplementary Table S5). In contrast, the cumulative risk of progression to AML decreased for patients with intermediate risk MDS from 17% (95% CI: 0.10–0.25) in 2010–2012 to 5% (95% CI: 0.02–0.11) in 2016–2018. For patients with high-risk MDS it also decreased from 18% (95% CI: 0.11–0.27) in 2010–2012 to 8% (95% CI: 0.05–0.13) in 2016–2018. In adjusted models, the 2-year HR for progression to AML was unaltered overall and in strata of age, sex and low-risk MDS. Noticeably, the adjusted HR (aHR) of progression to AML was markedly lower in 2016–2018 compared to 2010–2012 for patients with intermediate risk MDS (aHR = 0.23, 95% CI: 0.08–0.63) and high-risk MDS (aHR = 0.44 (0.20–0.96) (Supplementary Fig. S2).

3.5. Trends in all-cause mortality

Absolute risks of death are graphically illustrated in Fig. 3 and exact numbers are presented in Supplementary Table S6. Overall and within strata of sex, age-groups and low-risk MDS the 1-year, 3-year, and 5-year absolute risk of death remained unaltered during the study period. The 1-year, 3-year and 5-year absolute risk of death declined from 2010-2012 to 2016-2018 in patients with intermediate-risk MDS. For example, the 3-year absolute risk of death was 69% (95% CI: 0.60–0.78) in 2010–2012 *vs* 59% (95% CI: 0.50–0.68) in 2016–2018. In contrast, the absolute risk of death increased among patients with IPSS-R high-risk MDS during the study periods (*i.e.* 3-year absolute risk of death was 68% (95% CI: 0.58–0.78) in 2010–2012 *vs* 87% (95% CI: 0.81–0.92) in 2016–2018).

The adjusted 5-year HR for death in 2016–2018 was unchanged for all MDS patients (aHR = 0.97, 95% CI: 0.86–1.10) and in strata of low-risk MDS, high-risk MDS, age, and sex (Fig. 4). In contrast, prognosis may have improved from 2010- 2012 to 2016–2018 for patients with intermediate-risk MDS (aHR = 0.67, 95% CI: 0.48–0.92).

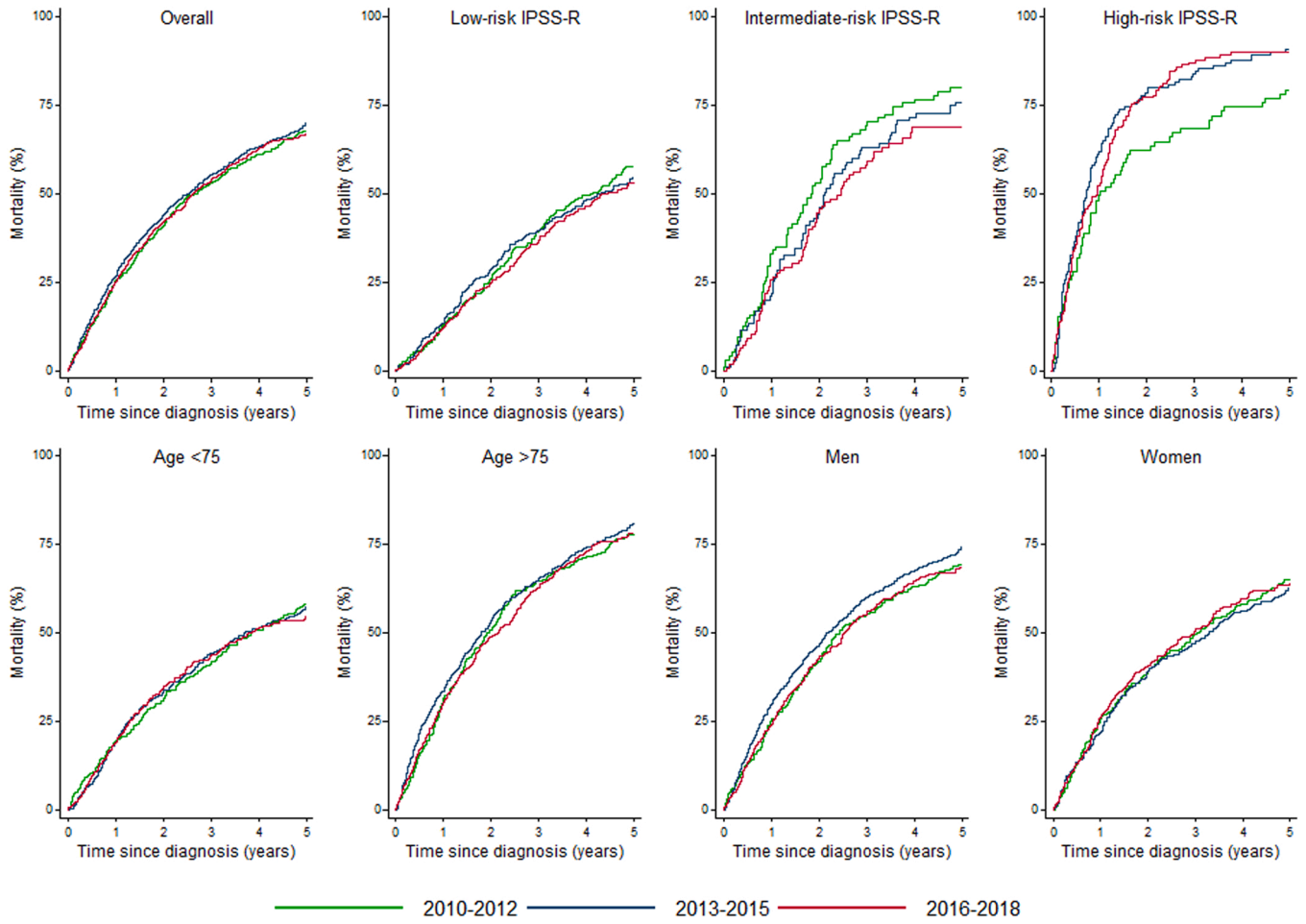

Fig. 3. Absolute risk of death in patients diagnosed with myelodysplastic syndromes in Denmark, 2010–2018, by calendar period. Overall and stratified by IPSS-R risk groups, age (± 75 years) and sex.

The SMRs are shown in Fig. 5. The number of observed deaths in the MDS population were substantially higher than what would be expected if the MDS population had the same risk of dying as the general population. The SMR was 47.8 (95% CI: 37.3–61.3) for MDS patients younger than 60 years. The SMR decreased rapidly with advancing age but was still high (7.93, 95% CI: 7.33–8.58) in patients aged 70–79 years. As expected, the SMR increased with level of IPSS-R but was equivalent across sex. SMRs in combinations of IPSS-R and age groups are given in Supplementary Table S7.

3.6. Trends in bleedings leading to hospitalization and arterial and venous thromboembolic events

The cumulative risk of any bleeding leading to hospitalization within the first year after MDS diagnosis was unaltered around 8% during the study period. This finding was confirmed in adjusted analyses [aHR= 1.25 (95% CI: 0.83–1.88)]. In contrast, the 1-year cumulative risk of a thromboembolic event decreased from 6.9% (95% CI: 0.05–0.09) in 2010-2012 to 4.5% (95% CI: 0.03–0.06) in 2016-2017 which was confirmed in adjusted analyses [aHR = 0.62 (95% CI: 0.39–1.00)] (Supplementary Table S8).

4. Discussion

Our study provided new insights into MDS and its incidence, prevalence of comorbidity, treatment patterns, and prognosis in a population-based cohort of Danish patients with MDS.

4.1. Comparison with other studies

We found a slightly higher overall age-standardized MDS incidence in 2019 than reported in prior US (4.0) [9], German (4.2) [4], Dutch (2.3) [7], Finnish (3.9) [10], Swiss (2.5) [5], Korean (1.1) [36] and Japanese studies (0.8–1.6) [8],while one study reported a substantial higher incidence rate of MDS in the US than we observed in a Danish setting [37]. This discrepancy reflects the complexity of the MDS diagnosis, and the use of different algorithms to record the MDS diagnosis. Further it could be attributed to different age distributions, environmental, and ethnic differences in the study populations [9]. In line with the prior reports, we found a male predominance and an increasing male/female ratio with advancing age [5,9]. Our study expands the literature by examining temporal trends in MDS incidence during 2010–2019. The increase in MDS incidence in those aged + 80 years may be explained by improved diagnostic work-up and/or increased surveillance for chronic diseases. Other contributory features could be environmental factors or improved cancer survival as the risk of MDS increases after chemo- and radiotherapy [38,39].

Our descriptive data on the Danish MDS population corroborate findings in prior studies [17,40]. For example, the median age in our study was 76 years, which is similar to that reported in cohorts from SEER data [2,9], Sweden [40], and Switzerland [5], but slightly higher than in cohorts from Netherlands Cancer Registry [7] and Düsseldorf MDS Registry [4]. Regarding transfusion burden, a recent single centre Dutch study of MDS patients during 2005–2017 (n = 292) [41], which defined transfusion burden according to the IWIG 2018 guidelines, found that 45% of patients were NTD, 6% had a LTB, and 47% of patients had a HTB during follow-up. We found the same level of patients

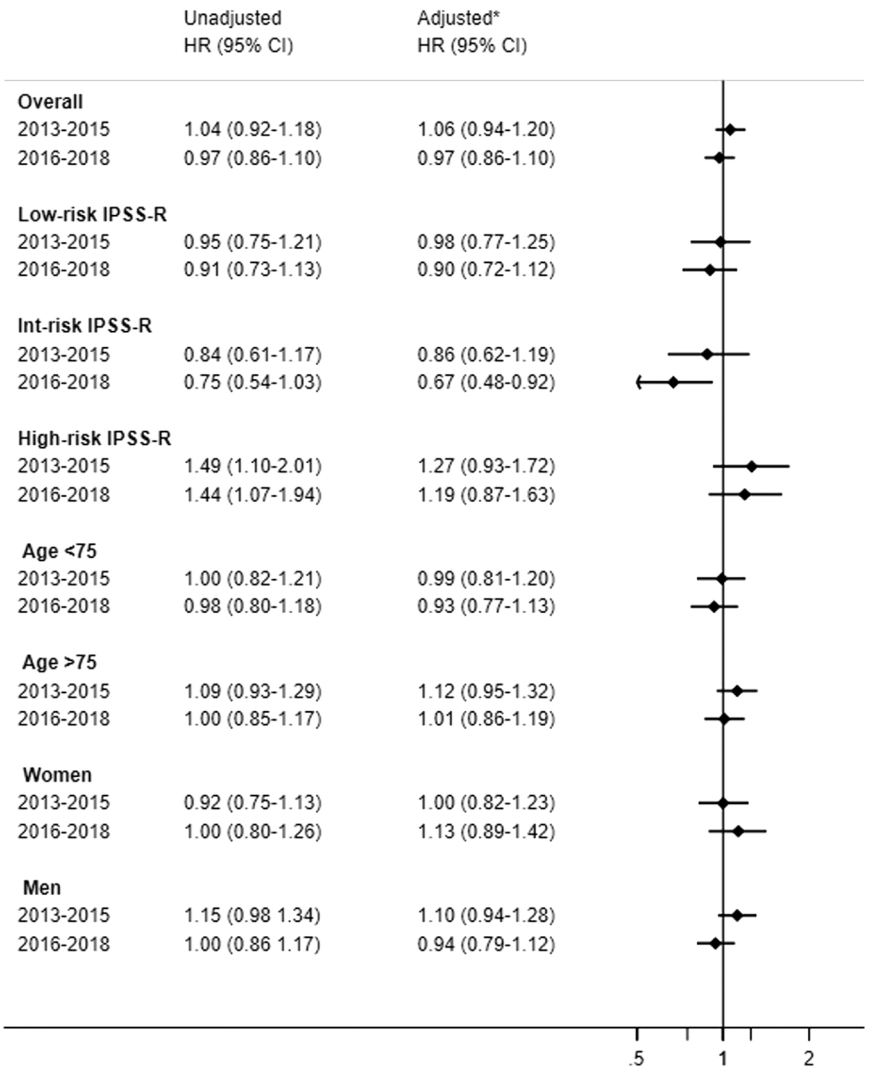

Fig. 4. Unadjusted and age, sex and comorbidity adjusted five-year hazard ratios of death in patients diagnosed with myelodysplastic syndromes in Denmark, 2010–2018, by calendar period using 2010–2012 as the reference. Overall and by IPSS-R prognostic risk group, age (± 75 years) and sex. Abbreviations: CI; confidence interval; HR; hazard ratio; IPSS-R; revised International Prognostic Scoring System.

with a HTB (48%), but a higher proportion of patients with a LTB (20%) and accordingly less patients who were NTD (32%). Reasons for the discrepancy are unclear, but may at least partly be explained by the small sample size in the Dutch study or varying national transfusion policies. Interestingly, we observed a noteworthy decline in the use of ESAS across each successive calendar period and in all strata but despite this, we found no increase in the overall use of packed RBCs. In 2014, the Danish Health Authorities changed the recommended transfusion threshold from 9.7 to 9.0 g/dL for hematological patients not undergoing curative intended treatment [42]. This likely explains the decline in packed RBC use observed in low- and high risk patients, and it may to some extent explain the decreased use of ESAS as it could be argued that the lowered transfusion threshold have led to a greater acceptance, among clinicians, of a lower level of hemoglobin before initiating treatment. Another potential explanation could be earlier diagnosis due to improved diagnostic work-up rendering less pronounced anemia at diagnosis, but the stable median hemoglobin level within each successive calendar period opposes this hypothesis. Interestingly, in patients with intermediate risk MDS, the use of packed RBCs remained stable and the use of platelet transfusions increased over time. It can be speculated that this may be linked to an increased use of azacitidine and alloHSCT.

Compared to the general population without MDS, it is well recognized that MDS patients have a 5-fold increased risk of bleeding leading to hospitalization, a 1.6-fold increased risk of myocardial infarction, a 1.2-fold increased risk of ischemic stroke, and a 2.2-fold higher risk of venous thromboembolic events [43]. Given the high and increasing proportion of patients receiving anticoagulants at time of MDS diagnosis and the increasing use of azacitidine and alloHSCT, we examined trends in these outcomes within one year from MDS diagnosis. Of note, the risk of bleeding was unchanged over time, while the risk of thromboembolic events decreased. This may be rooted in an increased use of platelet transfusions observed in our study and/or increased use of anticoagulant treatment.

As done previously, we also investigated trends in the risk of AML following MDS [15,16]. It was encouraging to observe a decreasing trend in the risk of progression to AML in both intermediate and high-risk patients although it seemed somewhat unintuitive that the risk of progression to AML was similar in patients with intermediate and high-risk MDS within one and two years from MDS diagnosis, and highest in patients with intermediate-risk MDS when examining the risk during the entire follow-up period. This discrepancy should be interpreted in light of the higher mortality risk associated with high-risk MDS (1-year all-cause mortality 52% *vs.* 26%). Further, confidence intervals were wide, and therefore results should be interpreted with caution. Another explanation for the observed difference could be surveillance bias as *e.g.* renewed bone marrow examination and flow cytometry may

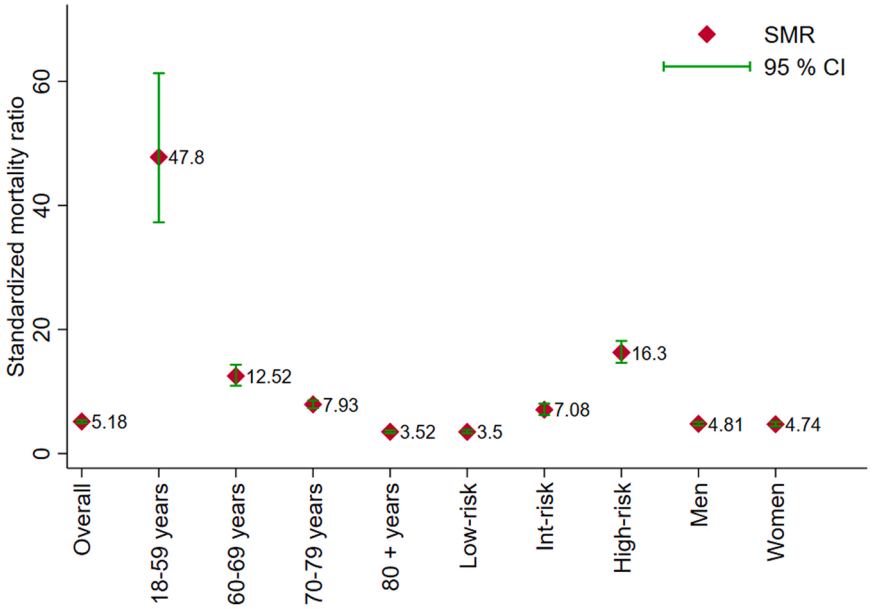

Fig. 5. Standardized mortality ratios (SMR) between mortality rates in the MDS population (2010–2021) and mortality rates in the general population aged ≥ 18 years (2010–2021).

be performed less often in elderly high-risk patients, where it will have no therapeutic consequences whether progression to AML was confirmed, but this assumption is only speculative. Contrasting our results, a US single centre study (1989–2014) and a German study from the Düsseldorf MDS registry (1982–2014) reported unaltered trends in the risk of progression to AML. Reasons for this discrepancy is unclear, but neither the German nor the US study examined trends in strata of IPSS/IPSS-R, and they did not report on any adjusted effect estimates. Reasons for the decreased risk of progression to AML in intermediate- and high-risk patients in our study is unclear but it may be related to the increased use of azacitidine or alloHSCT during the study period. A recent study from the Hellenic National Registry of Myelodysplastic and Hypoplastic Syndromes (1986–2016) including 486 patients with intermediate risk MDS, however, found no difference in the risk of progression to AML between patients treated with or without azacitidine [44]. Although a multivariable adjusted analysis was performed, the effect estimate was not reported in the study. In contrast, two randomized clinical trials demonstrated that azacitidine delayed progression to AML and improved overall survival compared to conventional treatment [45,46]. As such, one would expect a correspondingly improved prognosis in intermediate and high-risk MDS patients – a pattern that was only observed in intermediate-risk patients and not apparent among high-risk patients in our analyses.

The unchanged survival in high-risk MDS patients despite increased use of azacitidine is consistent with results from the Spanish MDS registry comparing overall survival between high-risk patients treated with azacitidine *vs* conventional treatment [HR = 1.08 (95% CI: 0.86–1.35]. Moreover, few other population-based studies examining overall survival in the pre and post hypometylating era also failed to demonstrate any survival benefit after the introduction of azacitidine [5,17–19].

While the mortality of MDS remain high, it is less understood how the mortality relates to the risk of death expected in the general population with a similar age distribution as the MDS cohort. Importantly, we found that the risk of dying was substantially higher among patients with MDS across all age strata than in the general population, underscoring the urgent need for improved treatment options for MDS.

4.1.1. Strengths, limitations and generalizability. Our study has several strengths. We conducted a population-based study including virtually all Danish patients with MDS with complete follow-up. We used high-quality and validated collected data from Danish nationwide registries. This design minimizes the risk of selection bias and misclassification bias. Limitations should also be addressed. We had missing data on IPSS-R prognostic risk group as not all patients had extensive cytogenetic work-up performed and unfortunately molecular data are currently not available to researchers in Denmark. We also had some missing data on performance status, tobacco use, and alcohol consumption, which could have led to residual confounding and have affected our adjusted effect estimates. We did, however, adjust for comorbidities, which may have captured some of these effects indirectly. Additionally, any unmeasured confounding is unlikely to be major as we only observed small differences between our adjusted and unadjusted effect estimates. We lacked data on ethnicity, but the vast majority of patients included in our study were Danish in origin. Our results generalize to other Nordic countries with a healthcare system similar to the Danish. Although it is likely that our findings apply to some other Western countries, there may be important disparities in population composition (*e.g.* related to ethnicity and socioeconomic position) across countries, which limits the generalizability of our results to other settings. Last, we were unable to provide data on long-term thromboembolic outcomes, and we lacked data on cardiovascular risk factors *e.g.* smoking.

5. Conclusion

In conclusion, we found a slight increase in MDS incidence, primarily driven by an increasing incidence among men and women aged + 80 years. We found a stable use of packed RBCs, a decrease in the use of ESAS and GCSF, a substantial increase in the use of azacitidine in intermediate and high-risk patients, and a slight increase in the use of alloHSCT. Survival improved in patients with intermediate risk MDS over time. Most importantly five-year overall survival remained poor and unaltered yielding a need for new and better treatment opportunities in MDS.

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CRediT authorship contribution statement

TBL, LSGØ, KG, JMN, TEG, and SOD conceived of and designed the study. TBL conducted the analyses. TBL, LSGØ, KG, JMN, TEG, and SOD interpreted the data and wrote the manuscript.

Conflict of interest

Authors have no conflicts of interest to declare.

Data availability

Our institutional approval to use the data sources for the current study do not allow us to distribute or make patient data directly available to other parties. Interested researchers may apply for data access through the Research Service at the Danish Health Data Authority (e-mail: forskerservice@sundhedsdata.dk; phone: +45 3268 5116). Up-to-date information on data access is available online (http://sundhedsdatastyrelsen.dk/da/forskerservice). Access to data from the Danish Health Data Authority requires approval from the Danish Data Protection Agency (https://www.datatilsynet.dk/english/the-danish-data-protection-agency/introduction-to-the-danish[1]data-protection-agency/).

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.leukres.2023.107056.

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