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Prognostic scoring systems for myelodysplastic syndromes (MDS) in a population-based setting: a report from the Swedish MDS register

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Summary

The myelodysplastic syndromes (MDS) have highly variable outcomes and prognostic scoring systems are important tools for risk assessment and to guide therapeutic decisions. However, few population-based studies have compared the value of the different scoring systems. With data from the nationwide Swedish population-based MDS register we validated the International Prognostic Scoring System (IPSS), revised IPSS (IPSS-R) and the World Health Organization (WHO) Classification-based Prognostic Scoring System (WPSS). We also present population-based data on incidence, clinical characteristics including detailed cytogenetics and outcome from the register. The study encompassed 1329 patients reported to the register between 2009 and 2013, 14% of these had therapy-related MDS (t-MDS). Based on the MDS register, the yearly crude incidence of MDS in Sweden was 2·9 per 100 000 inhabitants. IPSS-R had a significantly better prognostic power than IPSS ($P < 0{\cdot}001$). There was a trend for better prognostic power of IPSS-R compared to WPSS ($P = 0{\cdot}05$) and for WPSS compared to IPSS ($P = 0{\cdot}07$). IPSS-R was superior to both IPSS and WPSS for patients aged ≤70 years. Patients with t-MDS had a worse outcome compared to *de novo* MDS (d-MDS), however, the validity of the prognostic scoring systems was comparable for d-MDS and t-MDS. In conclusion, population-based studies are important to validate prognostic scores in a 'real-world' setting. In our nationwide cohort, the IPSS-R showed the best predictive power.

Keywords: myelodysplastic syndrome, International Prognostic Scoring System, revised International Prognostic Scoring System, WHO Classification-based Prognostic Scoring System, therapy-related myelodysplastic syndrome.

The myelodysplastic syndromes (MDS) constitute a heterogeneous group of clonal haematopoietic stem cell disorders, characterized by dysplastic and ineffective haematopoiesis leading to cytopenias and risk of transformation to acute myeloid leukaemia (AML). The yearly incidence of MDS is reported to be approximately 3–5 per 100 000 inhabitants (Rollison *et al*, 2008; Cogle *et al*, 2011; Rodger & Morison, 2012) with a sharp increase in incidence with age. The prognosis varies considerably for individual patients, with survival ranging from months to decades. In conditions with such diverse outcome, prognostic models are important tools for estimating life expectancy and optimizing therapy-related decisions.

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The International Prognostic Scoring System (IPSS), the standard risk stratification tool for patients with primary MDS both in clinical practice and clinical trials since 1997 (Greenberg *et al*, 1997), includes four risk groups based on the percentage of bone marrow blasts, number of cytopenias and cytogenetic abnormalities. In 2012 the Revised IPSS (IPSS-R) was introduced (Greenberg *et al*, 2012). The updates were the integration of the 'New Comprehensive Cytogenetic Scoring System' (Schanz *et al*, 2012), a higher scoring weight given to cytogenetic abnormalities, a decreased weight to elevated bone marrow blasts, new cut-off limits for marrow blast percentage values and a replacement of the number of cytopenias with the depth of cytopenias. The number of risk groups increased from four to five. Another prognostic model, the World Health Organization (WHO) Classification-based Prognostic Scoring System (WPSS) incorporates the WHO morphological categorization of MDS (Swerdlow *et al*, 2008) and red blood cell (RBC) transfusion dependency together with the IPSS cytogenetic classification (Malcovati *et al*, 2007). Based on criticism for using a subjective variable, such as transfusion dependency as a measure of severe anaemia (Bowen *et al*, 2008), a revised WPSS with sex-specific haemoglobin (Hb) levels was introduced (Malcovati *et al*, 2011). The original cohorts for IPSS, IPSS-R and WPSS were newly diagnosed patients excluding t-MDS and patients receiving disease-modifying treatments. There are now several reports indicating that IPSS-R can adequately risk stratify patients with various treatments, including stem cell transplantation (Mishra *et al*, 2013; Neukirchen *et al*, 2014; Sekeres *et al*, 2014).

Prognostic scoring systems for MDS are mainly based on collaborative efforts between international MDS-registries (Greenberg *et al*, 1997, 2012). Since these registries are not population-based and, in some cases, initiated by a tertiary referral centre there might be a selection bias of patients. A population-based register offers an excellent opportunity to evaluate the relevance of the scoring systems in all groups of MDS patients in a 'real-world' setting.

Using the Swedish nationwide MDS register we are, for the first time, able to validate and compare the prognostic power of the IPSS, IPSS-R and WPSS in a large population-based cohort. We also investigate if the scoring systems are valid for therapy-related MDS (t-MDS), and present population-based data on incidence of MDS, clinical characteristics, including detailed cytogenetics, and survival.

Patients and methods

The Swedish MDS-register

The Swedish MDS register was founded in 2009 by the Swedish section of the Nordic MDS group and the Swedish Society of Haematology. It is nationwide for a population of 9·5 million people and includes patients aged 16 years or above diagnosed with MDS or myelodysplastic/myeloproliferative neoplasms (MDS/MPN). It is supported by the Swedish Association of Local Authorities and Regions and managed in collaboration with six Regional Cancer Centres (RCCs) in Sweden. The coverage against the Swedish Cancer Register was 95% for the study period (2009–2013). The Swedish Cancer Register is based on mandated reporting by both pathologists and clinicians. If a patient is reported to the Cancer Register with a diagnosis of MDS but not to the MDS register, the RCCs actively request clinicians to report the case to the MDS register. All hospitals in Sweden diagnosing patients with MDS report to the register.

Inclusion criteria and variables

Swedish residents diagnosed with MDS according to the WHO 2008 classification (Swerdlow *et al*, 2008) between 2009 and 2013 and reported to the Swedish MDS register were included in this study. Patients with MDS/MPN were excluded. Given that no other restriction of inclusion was made, the study also encompasses t-MDS and patients receiving all types of disease-modifying treatment after registration in the register. Data, submitted electronically to a central database, included date of diagnosis, age, gender, WHO category, laboratory parameters, transfusions dependency, diagnostic procedures including data on bone marrow morphology and cytogenetics, information on antecedent haematological disease and previous treatment with chemotherapy or irradiation. By means of record linkage, information was obtained from the Swedish Population Register, Swedish Cause of Death Register and the Swedish AML Register up to 31 December 2014 to calculate overall survival (OS) and transformation to AML. End of follow-up was defined as the earliest of the date of death, emigration or 31 December 2014. This study was approved by the ethics committee of Uppsala University (2014/176).

Cytogenetics

The cytogenetic data in the Swedish MDS register was incomplete for patients diagnosed before 2015. The karyotypes were therefore retrospectively retrieved from the six laboratories that analyse cytogenetics and data for all patients with an evaluable karyotype was gathered. Cytogenetic analyses were performed at the regional clinical genetic laboratories according to local standards and clinical routines at the time of diagnosis. Abnormalities reported only by fluorescent *in situ* hybridization (FISH) were not included. Karyotypes were documented according to the International System for Human Cytogenetic Nomenclature (ISCN) (Schaffer *et al*, 2009). All ISCN classifications were reviewed centrally by a clinical laboratory geneticist. The IPSS and IPSS-R cytogenetic scores were assigned by one of the investigators and verified by a clinical laboratory geneticist.

Statistics

To assess the distribution of baseline patient characteristics, standard descriptive techniques were used, including chi-

squared test and Wilcoxon rank sum test. OS was defined as the time from diagnosis to end of follow-up. We analysed OS and leukaemia-free survival (LFS) using the Kaplan–Meier approach. Log-rank test were used to compare OS and LFS. In multivariate analyses including IPSS-R scores, the separate impacts of age, sex, bone marrow fibrosis, lactate dehydrogenase (LDH) and t-MDS were analysed with Cox regression models (Cox, 1972). The proportional hazard assumption was formally tested for each model using Schoenfeld residuals (Grambsch & Therneau, 1994). *P*-values less than 0·05 were considered to indicate statistical significance.

To evaluate the prognostic discrimination of IPSS, IPSS-R and WPSS in predicting clinical outcome, the Harrell concordance (C) index was used (Harrell *et al*, 1982). The C-index ranges between 0·5 and 1, where 1 stands for perfect discrimination and 0·5 for no discrimination at all. Indices were internally validated by bootstrapping using 1000 samples. The approach described by Kang *et al* (2015) was used when comparing C indices. This method estimates C indices for a pair of scoring systems using a U-statistic approach and then compares them using a *z*-score test and their estimated variances. All analyses were performed using R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS Statistics for Windows, Version 24 (IBM, Armonk, NY, USA).

Results

Study population and incidence

During the 5-year study period (2009–2013) a total of 1345 patients diagnosed with MDS were reported to the Swedish MDS register. The seven university hospitals reported 44% of the patients while 56% were reported by 57 regional or local hospitals. A total of 16 patients were excluded, nine were diagnosed with AML less than 2 months from the diagnosis of MDS, five had acute leukaemia at the date of diagnosis and two had died before the reported date of diagnosis. The final study population encompassed 1329 subjects, corresponding to a crude annual incidence of 2·9 per 100 000 inhabitants.

Patient characteristics at diagnosis

Baseline characteristics and their impact on survival are described in Table I. Of the 1329 patients, 183 (14%) had a history of treatment with irradiation or chemotherapy prior to the diagnosis of MDS and were considered to have t-MDS. Of the patients with t-MDS, 55% were exposed to chemotherapy, 25% to irradiation and 20% to both chemotherapy and irradiation.

There was a 58% male predominance, and the median age at diagnosis was 75 years; only 10% were younger than 60 years. According to WHO 2008 category, refractory cytopenia with multilineage dysplasia (RCMD)/RCMD and ringed sideroblasts (RCMD-RS) was the most common diagnosis (30%), followed by refractory anaemia with excess blasts, type II (RAEB-II) and type I (RAEB-I). We observed that 49% of patients were RBC transfusion-dependent at diagnosis and 5% needed platelet transfusions. In comparison with *de novo* MDS (d-MDS), patients with t-MDS were younger, had a higher medullary blast count, a poorer cytogenetic score, more advanced cytopenias and were more often dependent on RBC and platelet transfusions. For a complete comparison of the basic characteristics between t-MDS and d-MDS see Table SI.

Cytogenetics

Karyotype was available for 995 patients (75%). Lack of cytogenetics was correlated with age; the median age among patients with and without an available karyotype was 73 (range 17–93) and 81 years (range 40–96), respectively. The median number of metaphases analysed was 24 (range 2–38). Clonal abnormalities were observed in 512 (51%) of the patients with an evaluable karyotype. Univariate analysis for the risk of death and AML of each distinct cytogenetic aberration included in the IPSS-R is presented in Fig 1. Loss of chromosome Y, the most common single cytogenetic aberration ($n = 53$), was not associated with a better OS than a normal karyotype (hazard ratio [HR] 1·03, 95% confidence interval [CI] 0·66–1·62). Complex karyotype with >3 aberrations, observed in 145 patients (15%), was associated with the highest risk of death (HR 7·06, 95% CI 5·63–8·85) in comparison with a normal karyotype. As expected, loss of chromosome 7 was associated with a reduced OS. For t-MDS there was a higher proportion of complex karyotype with >3 aberrations compared to d-MDS (27% vs. 13%), and aberrations involving chromosome 7 were more frequently found. A normal karyotype was observed in 37% of patients with t-MDS. See Table SII for details on cytogenetic aberrations for t-MDS and d-MDS.

The risk of progression to AML was increased in patients with isolated trisomy 8, double aberrations including monosomy 7 or del(7q) and particularly in patients with a complex karyotype with >3 aberrations. Isolated trisomy 8 was observed in 45 patients, only two of whom had t-MDS. The distribution of the IPSS- and IPSS-R-based cytogenetic stratification is presented in Table I.

Prognostic scoring systems: impact of separate components

For 973 (73%) of the total population there was complete data to calculate the IPSS and IPSS-R and 854 (64%) had complete data to calculate the WPSS. Missing data was attributed to the lack of karyotyping in 334 patients (25%). Given that the WPSS does not incorporate the category 'MDS unclassifiable', fewer patients could be assigned a WPSS classification than IPSS and IPSS-R classifications.

Table I. Characteristics and median overall survival (OS) in months.

	N (%)	Median OS (95% CI)*
Total patients	1329 (100)	27·8 (24·1–31·1)
d-MDS	1146 (86)	31·7 (28·0–35·0)
t-MDS	183 (14)	14·9 (11·1–19·1)
Sex		
Male	776 (58)	27·2 (23·0–32·0)
Female	553 (42)	28·9 (24·0–34·8)
Age at diagnosis, years		
Median (range)	75 (17–96)	
<60	136 (10)	NR
60–74	530 (40)	33·5 (30·2–38·3)
≥75	663 (50)	20·6 (18·6–23·0)
WHO category		
RCUD (RA/RN/RT)	119 (9)	46·6 (45·5–Inf)
RCMD/RCMD-RS	399 (30)	35·5 (29·8–43·1)
RARS	148 (11)	NR
RAEB-I	225 (17)	18·4 (15·8–21·0)
RAEB-II	243 (18)	11·6 (9·9–14·8)
5q-syndrome	52 (4)	44·4 (38·2–Inf)
MDS-U	143 (11)	24·1 (21·5–32·5)
Haemoglobin, g/l		
<80	146 (11)	13·3 (10·3–17·2)
80–100	561 (42)	19·8 (17·8–21·7)
≥100	622 (47)	45·5 (42·2–51·1)
ANC, $\times 10^9$/l		
<0·8	279 (21)	15·7 (12·9–19·3)
≥0·8	1030 (78)	32·5 (28·9–36·3)
Missing data	20 (2)	18·6 (7·8–NR)
Platelet count, $\times 10^9$/l		
<50	190 (14)	11·3 (9·0–14·7)
50–100	338 (25)	19·1 (16·7–22·1)
≥100	799 (60)	40·0 (35·2–44·3)
Missing data	2 (0)	–
Platelet transfusion dependency at diagnosis		
No	1259 (95)	29·3 (26·3–32·5)
Yes	61 (5)	8·3 (5·1–13·4)
Missing data	9 (1)	–
RBC transfusion dependency at diagnosis		
No	675 (51)	45·9 (42·9–51·1)
Yes	650 (49)	16·1 (14·0–18·4)
Missing data	4 (0)	–
Medullary blast count, %		
<2	400 (30)	46·6 (40·7–57·7)
2–4·9	405 (30)	38·8 (33·1–45·6)
5–9·9	297 (22)	17·1 (14·4–19·8)
≥10	211 (16)	11·7 (10·0–14·9)
Missing data	16 (1)	–
Bone marrow fibrosis		
0–1	1203 (91)	28·8 (25·3–32·2)
2–3	57 (4)	15·6 (11·7–27·5)
Missing data	69 (5)	21·9 (16·0–Inf)
LDH, μ/l		
<240	738 (56)	36·3 (31·9–41·9)
≥240	358 (27)	16·9 (14·7–19·1)
Missing data	233 (18)	31·1 (23·6–36·8)
IPSS: Cytogenetic score		
Low	599 (45)	47·2 (44·0–56·5)
Intermediate	167 (13)	26·8 (22·0–38·8)
High	229 (17)	11·1 (9·5–12·1)
Missing data	334 (25)	18·6 (14·6–22·1)
IPSS-R: Cytogenetic score		
Very good	57 (4)	45·2 (32·8–NR)
Good	561 (42)	47·3 (44·0–56·5)
Intermediate	152 (11)	24·1 (21·5–33·5)
Poor	81 (6)	17·0 (14·6–23·1)
Very poor	144 (11)	8·3 (6·9–10·3)
Missing data	334 (25)	18·6 (14·6–22·1)

5q-syndrome, myelodysplastic syndrome associated with isolated del (5q); ANC, absolute neutrophil count; CI, confidence interval; d-MDS, *de novo* MDS; IPSS, International Prognostic Scoring System; IPSS-R, revised International Prognostic Scoring System; LDH, lactate dehydrogenase; MDS-U, myelodysplastic syndrome unclassified; NR, not reached; OS, overall survival; RA, refractory anaemia; RAEB-I/-II, refractory anaemia with excess blasts type I/II; RARS, refractory anaemia with ringed sideroblasts; RBC, red blood cell; RCMD (-RS), refractory cytopenia with multilineage dysplasia (and ringed sideroblasts); RCUD, refractory cytopenia with unilineage dysplasia; RN, refractory neutropenia; RT, refractory thrombocytopenia; t-MDS, therapy-related MDS.

*Not shown if not reached (NR) or if fewer than 20 patients were included.

The impact on OS and AML risk of the different components included in IPSS, IPSS-R and WPSS is presented in Table II. Most separate components show good prognostic discrimination for both OS and progression to AML. However, a blast count of less than 2% in comparison with a blast count between 2% and less than 5% did not alter the OS in IPSS-R. In all scoring systems, karyotype had a major impact on survival and leukaemic transformation, although patients with a very good cytogenetic score according to IPSS-R had a similar outcome to patients with a good cytogenetic score. RBC transfusion dependency or low haemoglobin levels were associated with a substantially reduced survival. For WPSS both the original definition of severe anaemia and the alternative version defined by Hb <90 g/l in males and <80 g/l in females are presented. The median haemoglobin level at diagnosis for patients reported to be transfusion-dependent was 88 g/l for both males and females.

Prognostic scoring systems; distribution in risk groups and redistribution between different scores

The distribution of risk groups in IPSS, IPSS-R and WPSS is shown in Table III. More patients were placed in the high- or very high-risk groups of WPSS compared to IPSS-R, 45% and 33% of the patients, respectively. As expected,

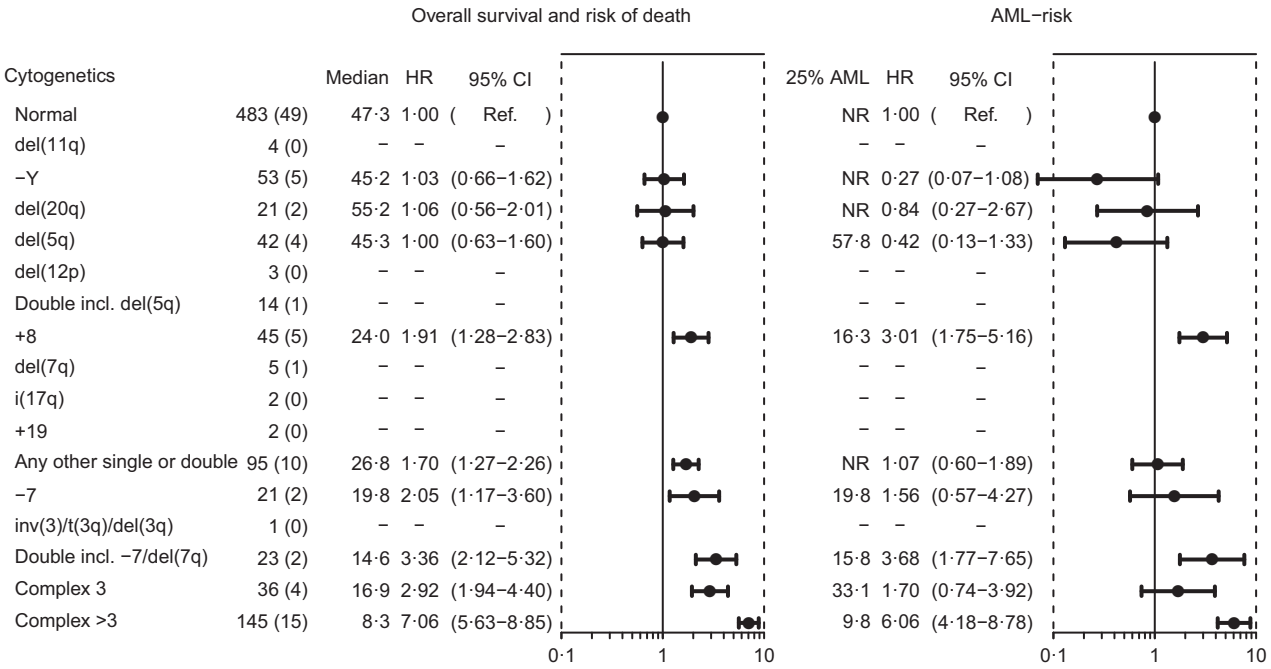

Fig 1. Distribution of IPSS-R cytogenetics, survival and AML-risk in months for patients with data on cytogenetics. AML = acute myeloid leukaemia, 25% AML = time (months) when 25% of patients had developed AML. CI = confidence interval, complex 3 = three abnormalities, complex >3 = four or more abnormalities, HR = crude hazard ratio, Ref. = reference.

when analysing t-MDS separately, we found that this group of patients more often had a higher risk score; 54% of t-MDS patients were in the IPSS-R high- or very high-risk group compared to 29% of patients with d-MDS (see Table SIII for details).

The redistribution of patients between IPSS and IPPS-R is shown in Figure S1. In general, the two systems correlate well with each other. However, patients with IPSS intermediate-1 were found in all five IPSS-R groups, and 15% of these were redistributed to the IPSS-R high- or very high-risk group. When comparing the redistribution of IPSS-R to WPSS, as many as 47% of patients in IPSS-R intermediate risk group were redistributed to WPSS high risk or very high risk (Figure S2). Also, 4% of patients classified as IPSS-R very low risk and 8% classified as low risk were assigned to the high-risk group by the WPSS. In comparison, only 7% of patients with WPSS intermediate risk group were redistributed to IPSS-R high risk or very high-risk group; there was no redistribution from WPSS very low or low risk to IPSS-R high risk (Figure S3).

Prognostic scoring system: survival

The median follow-up for surviving patients at the end of the study was 34 months. The 2-year OS was 53% and, at the end of the study, 41% of the patients still were alive. Progression to AML occurred in 221 cases (17%): 25% of patients with t-MDS and 15% of patients with d-MDS developed AML. The median OS for the whole population was 28 months; patients with t-MDS had a worse outcome than patients with d-MDS (median survival 15 months vs. 32 months).

The median OS in patients according to IPSS group ranged from 11 to 67 months, for the IPSS-R it was 9–58 months (not reached in very low risk) and for WPSS the median OS varied between 10 and 66 months (Table III). All three scoring systems were able to discriminate between the risk groups for both OS and evolution to AML (Table III).

The Kaplan–Meier curves for OS and LFS for the three scoring systems are shown in Fig 2. Patients with missing data for score calculations were also analysed; these patients were older (median 81 years) and were more often RBC transfusion-dependent, see Table SIV for more details.

Comparison of the prognostic scoring systems

We compared the prognostic power of IPSS, IPSS-R and WPSS for both OS and risk of AML (Table III). There were no large differences in the C-index, but the IPSS-R had the highest C-index of 0·74 and the prognostic power for OS was statistically significantly better than for IPSS (C-index 0·71, $P < 0·001$) and borderline significantly better than WPSS (C-index 0·73, $P = 0·05$), the difference in C-index between WPSS and IPSS was statistically not significant ($P = 0·07$). For AML risk the C-index was higher (0·78–0·79) than for OS, but the differences between the scoring systems were not significant.

When t-MDS was analysed separately, we found similar results; the C-index for IPSS, WPSS and IPSS-R was 0·71,

Table II. Components of the different scoring systems, median OS and risk of AML. Only patients with complete data for classification in each system are included.

		Overall survival and risk of death			AML-risk		
	N (%)	Median	HR	95% CI	25% AML*	HR	95% CI
WPSS: WHO type							
RA/RARS/5q-syndrome	227 (27)	67·1	1·00	Ref.	NR	1·00	Ref.
RCMD/RCMD-RS	281 (33)	35·5	1·83	1·39–2·43	NR	3·63	1·74–7·57
RAEB I	164 (19)	19·8	3·55	2·67–4·73	20·8	10·61	5·18–21·73
RAEB II	182 (21)	14·9	4·05	3·05–5·39	9·6	20·00	9·97–40·12
WPSS: Karyotype risk							
Low	515 (60)	45·6	1·00	Ref.	NR	1·00	Ref.
Intermediate	143 (17)	29·2	1·51	1·17–1·94	42·4	1·54	0·99–2·40
High	196 (23)	10·9	4·59	3·74–5·64	11·9	4·84	3·42–6·84
WPSS: RBC transfusion req.							
No	445 (52)	45·9	1·00	Ref.	NR	1·00	Ref.
Yes	409 (48)	18·9	2·22	1·85–2·66	19·1	2·11	1·54–2·89
WPSS: Severe anaemia†							
No	695 (81)	35·5	1·00	Ref.	45·7	1·00	Ref.
Yes	159 (19)	17·9	1·66	1·34–2·05	16·9	1·78	1·25–2·53
IPSS: Cytogenetic group							
Low	583 (60)	48·6	1·00	Ref.	NR	1·00	Ref.
Intermediate	164 (17)	26·8	1·68	1·33–2·13	42·4	1·64	1·09–2·47
High	226 (23)	10·9	4·84	3·99–5·88	12·0	4·53	3·25–6·30
IPSS: Medullary blasts							
<5	600 (62)	47·3	1·00	Ref.	NR	1·00	Ref.
5–10	182 (19)	18·8	2·29	1·85–2·82	22·0	3·34	2·26–4·91
11–20	191 (20)	15·3	2·83	2·31–3·48	9·7	6·83	4·85–9·61
21–30	0 (0)	–	–	–	–	–	–
IPSS: Number of cytopenias							
0–1	533 (55)	54·7	1·00	Ref.	NR	1·00	Ref.
2–3	440 (45)	18·3	2·58	2·17–3·06	16·4	3·76	2·75–5·15
IPSS-R: Cytogenetic score							
Good	547 (56)	50·8	1·00	Ref.	NR	1·00	Ref.
Very good	54 (6)	45·6	0·88	0·55–1·41	NR	0·27	0·07–1·08
Intermediate	150 (15)	24·1	1·85	1·45–2·35	38·5	1·78	1·18–2·68
Poor	79 (8)	17·0	2·91	2·18–3·87	20·5	2·29	1·35–3·87
Very poor	143 (15)	8·3	7·05	5·64–8·80	9·8	6·45	4·46–9·33
IPSS-R: Medullary blasts							
<2	298 (31)	55·9	1·00	Ref.	NR	1·00	Ref.
2–4·9	302 (31)	44·3	1·14	0·90–1·46	NR	1·62	0·96–2·73
5–9·9	218 (22)	18·8	2·46	1·95–3·12	20·5	4·85	2·99–7·87
10	155 (16)	14·9	3·18	2·47–4·10	9·7	9·22	5·70–14·90
IPSS-R: Haemoglobin (g/l)							
≥100	480 (49)	48·6	1·00	Ref.	NR	1·00	Ref.
80–100	393 (40)	20·9	2·21	1·84–2·65	22·0	1·96	1·43–2·68
<80	100 (10)	17·0	2·71	2·08–3·54	19·3	2·32	1·46–3·69
IPSS-R: Platelet count ($\times 10^9$/l)							
≥100	589 (61)	45·3	1·00	Ref.	NR	1·00	Ref.
50–100	251 (26)	22·1	1·84	1·52–2·24	19·1	2·56	1·84–3·57
<50	133 (14)	14·1	2·74	2·19–3·43	11·3	3·80	2·59–5·56
IPSS-R: ANC ($\times 10^9$/l)							
≥0·8	758 (78)	37·3	1·00	Ref.	57·8	1·00	Ref.
<0·8	215 (22)	17·7	1·79	1·49–2·16	13·5	2·75	2·04–3·72

5q-syndrome, myelodysplastic syndrome associated with isolated del(5q); ANC, absolute neutrophil count; CI, confidence interval; HR, hazard ratio; IPSS, International Prognostic Scoring System; IPSS-R, revised International Prognostic Scoring System; NR, not reached; RA, refractory anaemia; RAEB-I/-II, refractory anaemia with excess blasts type I/II; RARS, refractory anaemia with ringed sideroblasts; RBC, red blood cell; WPSS, World Health Organization classification-based Prognostic Scoring System.

*Number of months after diagnosis when 25% of patients had developed AML.

†Severe anaemia was defined as a haemoglobin <90 g/l for men and <80 g/l for women.

0·73 and 0·74, respectively (Table SV). We also stratified patients according to age (≤70 years, >70 years; Table SVIa, b). For patients ≤70 years of age, the IPSS-R was superior for prediction of OS in comparison with both IPSS ($P < 0·001$) and WPSS ($P = 0·01$) with a C-index of 0·76. The results for patients >70 years showed that IPSS-R was better than IPSS ($P = 0·002$), but there was no difference between IPSS-R and WPSS or WPSS and IPSS. All three scoring systems had an especially good prognostic power for patients with d-MDS younger than 70 years; the C-index for IPSS, WPSS and IPSS-R was 0·77, 0·78 and 0·80, respectively (data not shown). For t-MDS the C-index was not higher for younger patients than for older patients.

In our calculation of WPSS, we used the original variable transfusion dependency, as recorded by the reporting clinicians. When WPSS was recalculated using severe anaemia with sex-specific haemoglobin levels instead of transfusion dependency, the C-index was reduced to 0·71.

Additional prognostic factors

The prognostic effect of additional clinical parameters beside IPSS-R risk group was analysed (Fig 3). In multiple Cox-regression analyses, age group, gender, LDH, bone marrow fibrosis and type of MDS (t- or d-MDS) was added to IPSS-R risk group in the model. As expected, age was associated with a worse outcome, patients ≥75 years had a more than 3-fold risk of death compared to patients <60 years of age (HR 3·15, 95% CI 2·31–4·30). An elevated LDH was independently associated with reduced survival (HR 1·48, 95% CI 1·21–1·80) whereas bone marrow fibrosis did not influence survival in multivariate analyses. Female gender was associated with a better OS compared to male gender (HR 0·79, 95% CI 0·66–0·94). Compared with d-MDS patients, those with t-MDS had a worse OS independent of IPSS-R risk group and other known risk factors adjusted for in the model (HR 1·52, CI 1·21–1·90).

Discussion

Because of the heterogeneous nature and the wide range of clinical courses, prognostic scoring systems are of crucial importance for the management of MDS. The IPSS, IPSS-R and WPSS have been validated in previous studies (Voso *et al*, 2013; Della Porta *et al*, 2015; de Swart *et al*, 2015), but, to our knowledge, this is the first validation in a nationwide population-based register. Our findings, based on 1329 patients from the Swedish MDS register, confirm the validity of all three scoring systems in a population-based setting without selection of patients. When comparing the prognostic systems we found that IPSS-R had better prognostic power for survival than IPSS and a trend towards better prognostic power for OS than WPSS. IPSS-R was a more powerful prognostic instrument than both IPSS and WPSS for patients younger than 70 years. When analysing t-MDS separately, the prognostic power of the three systems did not significantly change.

The different scoring systems for MDS have advantages and disadvantages: IPSS-R and WPSS have five risk groups enabling a more refined risk classification compared to IPSS. It is possible to risk-classify more patients with IPSS and IPSS-R because MDS-unclassified is excluded from WPSS. Several previous studies have observed an advantage for IPSS-R in comparison to IPSS and WPSS (Voso *et al*, 2013; Neukirchen *et al*, 2014), but equal prognostic power of IPSS-R and WPSS has also been reported (Della Porta *et al*, 2015). WPSS is suggested to mainly improve risk assessment of patients with early-stage disease (Della Porta *et al*, 2015). Another study concluded that the IPSS-R was the best scoring system to identify high-risk patients within the lower risk groups in IPSS (Valcarcel *et al*, 2015). In our study, 15% of patients with IPSS intermediate-1 were redistributed to IPSS-R high risk or very high-risk group. We noticed a difference in redistribution of patients within the intermediate risk group of WPSS and IPSS-R; substantially more patients with intermediate IPSS-R were redistributed to the high-risk groups of WPSS than the proportion of patients moving from intermediate WPSS to high-risk groups in IPSS-R. This illustrates that a decision of disease-modifying treatment in patients with IPSS-R/WPSS intermediate risk must be taken individually for each patient, also incorporating other factors, such as need for transfusions, comorbidity and mutations.

The IPSS, IPSS-R and WPSS were developed and validated using cohorts from collaborating academic centres (Greenberg *et al*, 1997, 2012; Malcovati *et al*, 2007). In comparison with the original studies, our population was older, though the median age of 75 years is well in line with other studies with a more population-based setting (Cogle *et al*, 2011; de Swart *et al*, 2015). In terms of the distribution of risk groups, the most striking difference was a larger proportion of patients in the high- and very high-risk groups in our study (33% vs. 23% observed in the original cohort for IPSS-R). This was also true for WPSS, with 45% of our patients in the two highest risk groups in comparison to 30% in the original WPSS study (Malcovati *et al*, 2007). In contrast, the distribution of patients in risk groups according to IPSS was similar in our study and in the original IPSS cohort. Hence the outcome is worse than concluded from existing registries and this should be taken into account when designing therapeutic guidelines.

In recent years several attempts have been made to improve and refine existing prognostic scoring systems for MDS. It is clear that there are other important factors to consider for prognostication beside the components included in the classical scoring systems, e.g. chronic comorbidity conditions, performance status and mutations. Studies have shown that the MDS-specific comorbidity index (MDS-CI) remains an independent factor for OS when controlling for IPSS and IPSS-R (van Spronsen *et al*, 2014; Balleari *et al*, 2015). One limitation in our study is the lack of information

Table III. Risk score classification, survival in months and discriminative power between the scoring systems.

		Overall survival						
						P-value		
	N	Median	HR	95% CI	C-index†	vs. WPSS	vs. IPSS	vs. IPSS-R
WPSS					0·73		0·07	0·05
Very low risk	109	NR	0·49	0·30–0·79				
Low risk	207	65·6	1·00	Ref.				
Intermediate risk	158	36·0	1·84	1·35–2·50				
High risk	247	19·9	3·20	2·44–4·20				
Very high risk	133	9·8	6·61	4·90–8·92				
IPSS					0·71	0·07		<0·001
Low risk	301	67·2	1·00	Ref.				
Interm. risk I	370	31·1	2·91	2·25–3·77				
Interm. risk II	223	13·4	6·38	4·88–8·34				
High risk	79	10·8	10·22	7·34–14·25				
IPSS-R					0·74	0·05	<0·001	
Low risk	330	57·7	1·00	Ref.				
Very low risk	130	NR	0·58	0·39–0·87				
Intermediate risk	196	29·8	2·14	1·66–2·75				
High risk	153	17·0	3·96	3·08–5·10				
Very high risk	164	9·3	7·23	5·65–9·25				

		AML-risk						
						P-value		
	N	AML 25%*	HR	95% CI	C-index†	vs. WPSS	vs. IPSS	vs. IPSS-R
WPSS					0·79		0·4	0·7
Very low risk	109	–	–	–				
Low risk	207	NR	1·00	Ref.				
Intermediate risk	158	NR	3·35	1·64–6·85				
High risk	247	16·3	10·26	5·44–19·37				
Very high risk	133	9·7	17·73	9·09–34·59				
IPSS					0·78	0·4		0·1
Low risk	301	NR	1·00	Ref.				
Interm. risk I	370	42·4	6·63	3·50–12·55				
Interm. risk II	223	13·3	16·93	8·92–32·14				
High risk	79	7·4	35·83	18·04–71·18				
IPSS-R					0·79	0·7	0·1	
Low risk	330	NR	1·00	Ref.				
Very low risk	130	NR	0·36	0·13–1·03				
Intermediate risk	196	31·7	3·78	2·34–6·10				
High risk	153	15·9	6·60	4·08–10·67				
Very high risk	164	9·0	12·30	7·72–19·58				

AML, acute myeloid leukaemia; CI, confidence interval; HR, hazard ratio; IPSS, International Prognostic Scoring System; IPSS-R, revised International Prognostic Scoring System; NR, not reached; Ref., reference; WPSS, World Health Organization classification-based Prognostic Scoring System.

*Number of months after diagnosis when 25% of patients had developed AML.

†The C-index measures the discriminative power of a score, ranging between 0·5 (no discriminative power) and 1 (perfect discrimination).

on comorbidities besides history of previous cancer or haematological disease. Several somatic mutations have been shown to play an important role in the pathobiology of MDS (Bejar *et al*, 2011; Papaemmanuil *et al*, 2013) and approximately 80% of patients with MDS have at least one known somatic pathogenic variant. Pathogenic mutations in genes such as *TP53*, *EZH2*, *ETV6*, *RUNX1* and *ASXL1* negatively influence survival (Bejar *et al*, 2011; Jadersten *et al*, 2011) and prognostic scores including mutational status have been proposed. Nazha *et al* (2016) suggested a prognostic score adding *SF3B1*, *EZH2* and *TP53* to IPSS-R and age. This model also appears to be valid for t-MDS and chronic

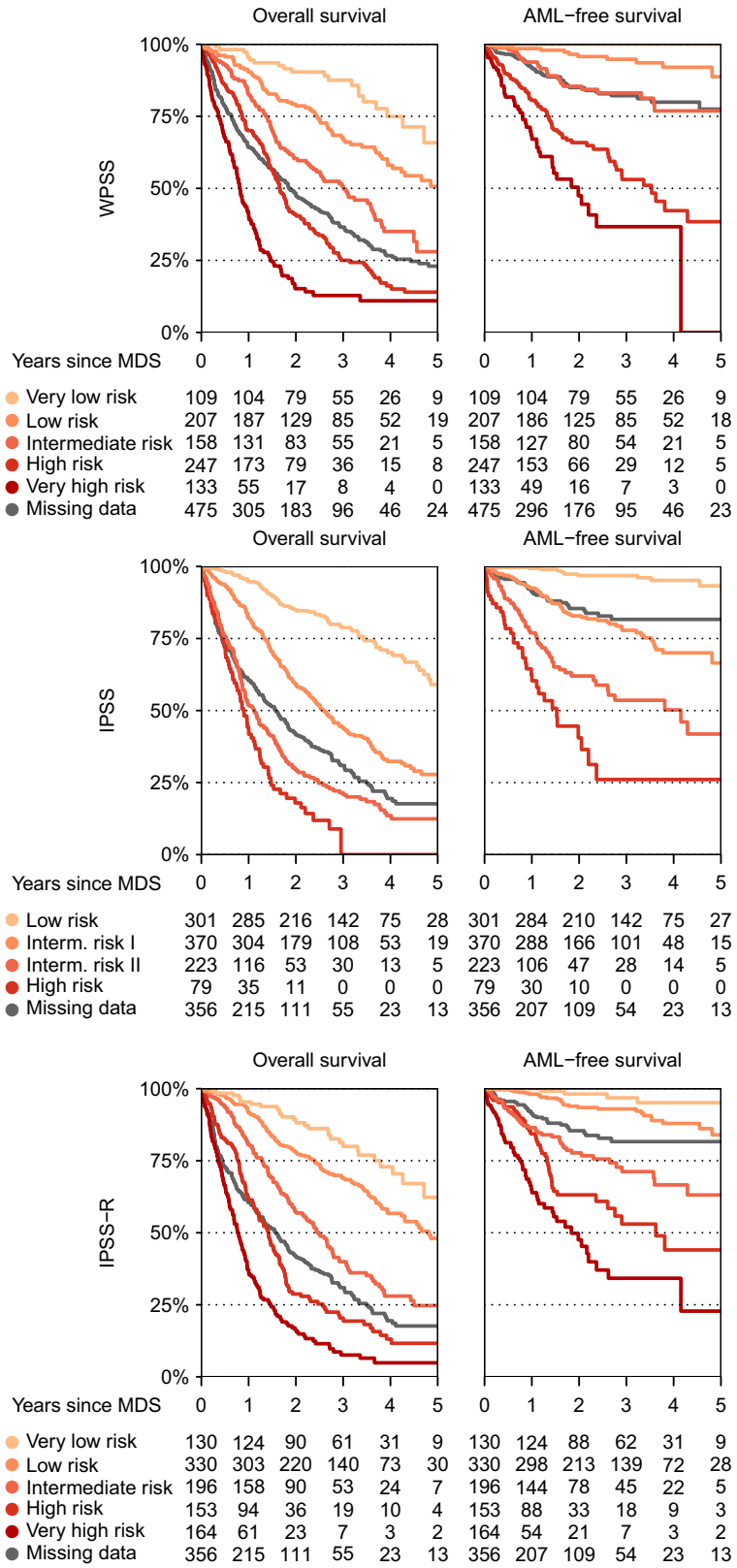

Fig 2. Overall and AML-free survival, categorized according to different scoring systems. AML = acute myeloid leukaemia, Interm. = intermediate, IPSS = International Prognostic Scoring System, IPSS-R = revised International Prognostic Scoring System, MDS = myelodysplastic syndrome, WPSS = World Health Organization classification-based Prognostic Scoring System.

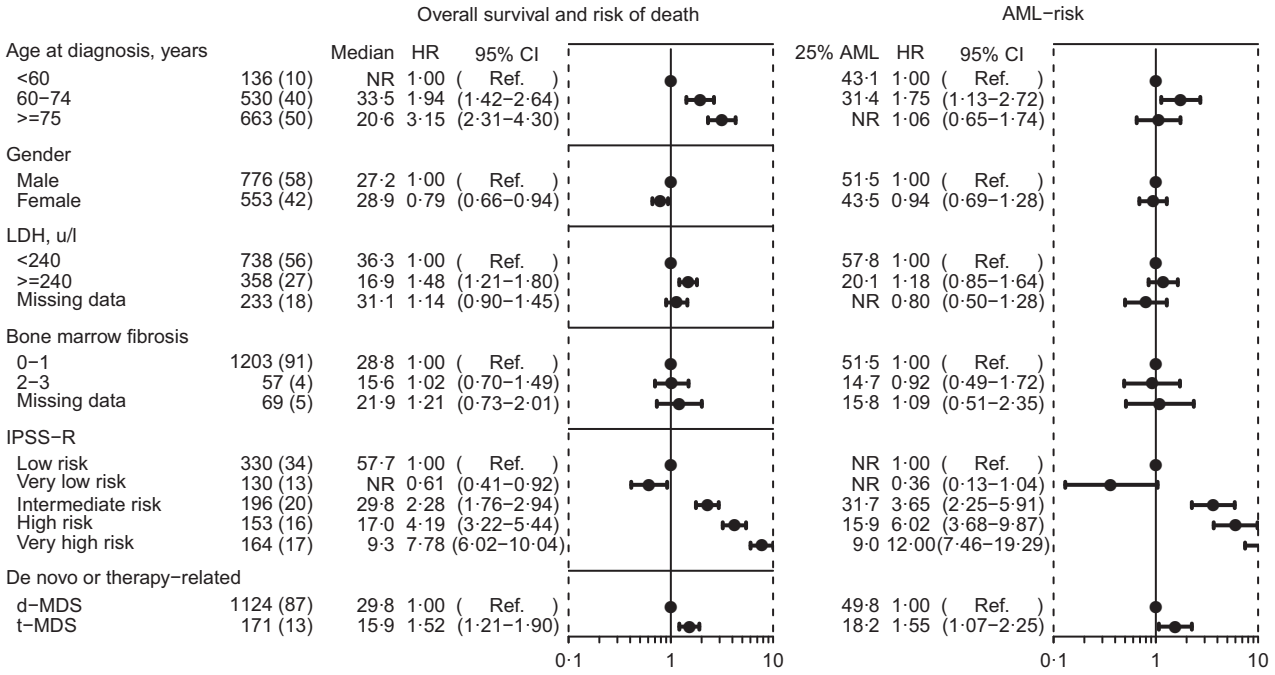

Fig 3. Multivariate analyses of additional characteristics and IPSS-R risk group, OS and AML-risk. AML = acute myeloid leukaemia, 25% AML = time (months) when 25% of patients had developed AML, CI = confidence interval, d-MDS = *de novo* MDS, HR = crude hazard ratio, IPSS-R = revised International Prognostic Scoring System, LDH = Lactate dehydrogenase, NR = not reached, OS = overall survival, Ref. = reference, t-MDS = therapy-related MDS.

myelomonocytic leukaemia and can be used during the course of the disease regardless of treatment.

The yearly crude incidence of MDS in Sweden based on the Swedish MDS register was 2·9 per 100 000 inhabitants. There is a variation in the incidence rate reported from population-based registries. In Unites States the yearly incidence was estimated to be 4·9/100 000 inhabitants based on reports to registries (Cogle *et al*, 2011), in Switzerland this was 3·98 per 100 000 (Bonadies *et al*, 2017), and in Poland it was 1·95 per 100 000 (Drozd-Sokolowska *et al*, 2017). The variation in incidence might reflect underreporting of MDS to registries (McQuilten *et al*, 2014; Cogle, 2015). The Swedish register had a high completeness (95%) as compared to the Swedish Cancer Register to which reporting is mandated by law. However, underreporting may exist; if the pathologist considers the bone marrow sample non-conclusive but a diagnosis of MDS is made anyway, e.g. taking cytogenetics into consideration, it is up to the clinician to report to the Cancer and MDS register. The accurate incidence of MDS may also be hindered by under-diagnosis (Cogle, 2015), e.g. older patients with moderate cytopenias might not always be referred for a proper medical investigation.

Cytogenetic data was missing for a substantial fraction (25%) of the patients. This reflects clinical reality; although it is emphasized in the Nordic guidelines for MDS that cytogenetic analysis should be undertaken in all patients (Nordic MDS Group, 2017). One reason that clinicians do not always perform a full diagnostic work-up might be that the treatment options are restricted to supportive care, regardless of risk group, in older patients with co-morbidities. The patients with missing karyotypes in our data set were older and more commonly had transfusion-dependency and a shorter OS.

The karyotype is a strong independent prognostic factor in MDS (Haase *et al*, 2007). In the original IPSS-R cohort, complex karyotype with >3 aberrations was observed in 7% of the patients (Greenberg *et al*, 2012) compared to 15% in our study, and the proportion of patients with high- and very high-risk cytogenetics was 12% vs. 22%. Higher median age and the inclusion of t-MDS might explain more patients with high-risk cytogenetics (Haase *et al*, 2007; Nazha *et al*, 2015) in our study. We could confirm that patients with aberrations involving chromosome 7, isolated trisomy 8 and, in particular, complex karyotype have an adverse outcome. Loss of chromosome Y is associated with a 'very good' cytogenetic risk group in IPSS-R but is also a normal age-related event (Ganster *et al*, 2015). In our study loss of chromosome Y was not associated with a better survival in comparison with a normal karyotype. Since the median age was high in our study, a loss of chromosome Y could, to a greater extent than in other MDS-cohorts with younger patients, be related to 'normal' ageing instead of being a clonal aberration associated with MDS. It has been proposed that a cut-off point of loss in >75% metaphases of chromosome Y can discriminate between a disease-related and an age-related event (Wiktor *et al*, 2000). Although we reanalysed our data using this cut-off point, this did not significantly

alter the result (HR 0·8, 95% CI 0·41–1·55 in comparison with a normal karyotype).

Red blood cell transfusion dependency had a major impact on survival; the median OS in patients with and without transfusion dependency was 16 and 46 months, respectively. In the original WPSS study, the pre-transfusion median Hb was 79 g/l in the learning cohort (Malcovati *et al*, 2007). In our population the pre-transfusion median Hb was 88 g/l reflecting current Swedish clinical transfusion practice. Sex-specific Hb levels have shown to be as effective as transfusion dependency in the WPSS (Malcovati *et al*, 2011), but in our cohort WPSS loses some of its prognostic power when using Hb levels compared to the original severe anaemia variable. A hypothesis explaining this could be that transfusion dependency in some part reflects comorbidities. A patient with significant cardiac or pulmonary comorbidities will be transfused at a higher Hb level, and these comorbidities could influence survival.

The proportion of t-MDS in different MDS cohorts has been reported to vary between 10% and 20% (Churpek & Larson, 2013). In our study, 14% of the patients were previously exposed to chemotherapy or irradiation. As expected, they had an inferior median survival compared to d-MDS, 15 months vs. 32 months. Patients with t-MDS had a significantly higher blast count and were more often dependent on transfusion of both erythrocytes and platelets. The t-MDS group had more than twice the percentage of patients in the highest cytogenetic risk group for both IPSS and IPSS-R. These known risk factors highly contribute to the worse outcome for t-MDS as compared with d-MDS. In general, patients with t-MDS have high-risk disease, however, there are indications that subgroups of patients classified as t-MDS have a more indolent disease course (Quintas-Cardama *et al*, 2014). Therefore, useful prognostic tools are important to identify patients with t-MDS that do not necessarily benefit from aggressive disease-modifying treatments. The value of prognostic scores for t-MDS was not addressed in the original cohorts of IPSS, IPSS-R and WPSS because these patients were excluded. Prognostic scores in t-MDS have recently been validated; Zeidan *et al* (2017) concluded that patients with t-MDS with varying clinical outcomes could be identified using conventional risk stratification models. Similarly, we found that the value of IPSS, IPSS-R and WPSS was comparable for t-MDS and d-MDS with exception of patients aged ≤70 years, where we observed a better prognostic power for d-MDS than for t-MDS; however, the number of younger patients with t-MDS was limited.

In adjusted analysis including IPSS-R we could conclude that age, male gender, elevated LDH and t-MDS independently reduced OS. Elevated LDH is a disease feature previously reported to be associated with poor survival in MDS (Greenberg *et al*, 2012). A negative prognostic value of bone marrow fibrosis has been observed in some (van Spronsen *et al*, 2014; Ramos *et al*, 2016) but not in all studies (Greenberg *et al*, 2012). In unadjusted analyses, patients with fibrosis ≥ grade 2 had a shorter median OS in our study but not in adjusted analyses. It is well known that older age has a negative impact on survival in MDS (Greenberg *et al*, 1997, 2012) and the age-adjusted IPSS-R can easily be calculated by using the IPSS-RA (the age-adjusted formula for calculation of risk). We observed a moderate increased risk of death for patients with t-MDS independent of IPSS-R and other known risk factors adjusted for in the analyses. t-MDS has a higher risk disease with higher blast count, worse cytogenetics and a higher degree of transfusion dependency, but there must be other factors contributing to the worse outcome. This could be partly explained by the mortality related to the previous cancer itself. Differences in the mutational spectrum between t- and d-MDS can also be one explanation. *TP53* has been reported to be more frequently mutated in t-MDS and is associated with shorter survival (Lindsley *et al*, 2017). Studies with future prognostication tools, such as the molecular IPSS-R, should investigate if t-MDS is retained as an independent prognostic factor independent of mutations.

In Sweden, diagnosing and treatment of MDS is decentralized, as shown by the fact that MDS patients were registered by 65 hospitals. Under such circumstances it is of particular importance to provide and adhere to nationwide guidelines to establish equal health care for all patients. Since 2004 the Nordic MDS group has published widely used guidelines for MDS and MDS/MPN (Nordic MDS Group, 2017). We believe that, besides being a valuable resource for research, well-established quality-of-care registries are also of key importance for performing a continuous evaluation of adherence to MDS guidelines in a decentralized health-care system.

In summary, the IPSS, IPSS-R and WPSS all represent valid and useful tools in predicting OS and progression to AML in MDS. In this large, prospectively collected nationwide population-based cohort, IPSS-R was the best prognostic tool. We also conclude that existing scoring systems for MDS appears to be valid for t-MDS. In our view, population-based registers can be useful sources of data when developing and validating systems for prognostication of survival. Linking these registers to BioBank data on mutations will provide even more useful information, as the mutational status of patients will be incorporated in the clinical prognostication.

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Author contributions

DMB preformed the research, analysed the data and wrote the paper. YF conducted the statistical analyses. ME reviewed

and analysed the cytogenetic data. JS collected the cytogenetic data and constructed the database. SL and ML helped designing the study. PA, HG, MJ, FF, LN and BR are local coordinators of the Swedish MDS register; they provided data. EHL analysed and provided data. EE designed the study, analysed the data and wrote the paper. All authors critically reviewed the manuscript and approved the final version.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Fig S1. Distribution (percentage) of IPSS in different categories of IPSS-R.

Fig S2. Distribution (percentage) of IPSS-R in different categories of WPSS.

Fig S3. Distribution (percentage) of WPSS in different categories of IPSS-R.

Table SI. Characteristics and median overall survival (OS) in months presented separately for t-MDS and d-MDS.

Table SII. Distribution of cytogenetic aberrations for t-MDS and d-MDS.

Table SIII. Distribution of risk groups for the whole cohort, d-MDS and t-MDS.

Table SIV. Characteristics and median overall survival (OS) in months for patients with insufficient data for categorization of WPSS or IPSS/IPSS-R.

Table SV. Risk score classification for patients with t-MDS, survival in months and discriminative power between the scoring systems.

Table SVI. Patients aged (a) ≤70 years, (b) >70 years – risk score classification, survival in months and discriminative power between the scoring systems.

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