

ARTICLE OPEN



Myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T): Mayo-Moffitt collaborative study of 158 patients

Abhishek A. Mangaonkar^{1,4}, Terra L. Lasho¹, Rhett P. Ketterling², Kaaren K. Reichard², Naseema Gangat¹, Aref Al-Kali¹, Kebede H. Begna¹, Animesh Pardanan¹, Najla H. Al Ali³, Chetasi Talati³, David Sallman³, Eric Padron³, Mrinal M. Patnaik¹, Ayalew Tefferi^{1,4} and Rami Komrokji^{3,4}

© The Author(s) 2022

The current World Health Organization (WHO) classification of myeloid malignancies includes myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) as a distinct entity. Previous literature on predictors of survival was based on the provisional category of refractory anemia with ring sideroblast and thrombocytosis (RARS-T), which was not subject to MDS/MPN-RS-T exclusionary criteria such as PB blast% ≥ 1 , BM blast% ≥ 5 or cytogenetic abnormalities such as t(3;3)(q21.2;q26.2), inv(3)(q21.23q26.2) or isolated del(5q). We examined overall (OS) and leukemia-free (LFS) survival and its predictors, among 158 patients with WHO-defined MDS/MPN-RS-T. In univariate analysis, age ≥ 70 years ($P = 0.006$), hemoglobin (Hb) ≤ 10 g/dL ($P = 0.03$) and abnormal karyotype (excluding -Y, $P = 0.008$) were associated with shortened OS, which was otherwise not affected by either *ASXL1* ($P = 0.7$), *SF3B1* ($P = 0.4$) or *JAK2* V617F ($P = 0.7$) mutations; in multivariable analysis, Hb ≤ 10 g/dL ($P = 0.03$) and abnormal karyotype ($P = 0.001$) remained significant, and thus allowed the development of an operational survival model with low (0 risk factors, median OS 10.5 years), intermediate (1 risk factor, median OS 4.8 years) and high risk (2 risk factors, median OS 1.4 years) categories ($P = 0.0009$). Comparison of MDS/MPN-RS-T ($n = 158$) and MDS/MPN-U with BM RS $\geq 15\%$ (MDS/MPN-U-RS; $n = 25$) did not reveal significant differences in frequency of thrombosis, OS, or LFS, although *SF3B1* mutation frequency was higher in the former (93% versus 59%; $P = 0.0005$). These data suggest limited survival impact for molecular abnormalities and the morphological distinction between MDS/MPN-RS-T and MDS/MPN-U-RS.

Blood Cancer Journal (2022)12:26; <https://doi.org/10.1038/s41408-022-00622-8>

INTRODUCTION

The 2016 World Health Organization (WHO) revision of myeloid malignancies and its recent iteration included patients with myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) as a distinct entity, under the MDS/MPN category [1, 2]. Previously, these patients were included under the provisional MDS/MPN category of refractory anemia with ring sideroblasts and thrombocytosis (RARS-T) [3, 4]. MDS/MPN-RS-T is distinguished from myelodysplastic syndrome with ring sideroblasts (MDS-RS) by the presence of thrombocytosis (platelet count $\geq 450 \times 10^9/L$) and bone marrow (BM) megakaryocyte morphology similar to that seen in MPN. MDS/MPN-RS-T is in addition characterized by presence of *SF3B1* mutations in 60–90% of patients and *JAK2* V617F in a smaller percentage [1, 5–10]. In order to be classified under the MDS/MPN-RS-T category, patients should also meet certain exclusionary criteria such as BM blast% ≥ 5 , peripheral blood (PB) blast% ≥ 1 , and cytogenetic abnormalities such as t(3;3)(q21.3; q26.2), inv(3)(q21.3; q26.2) or isolated del(5q), or the *BCR/ABL1* fusion oncogene [1, 11]. Of note, suspected cases with

$\geq 15\%$ BM RS and $\geq 1\%$ PB or $\geq 5\%$ BM blasts are classified as MDS/MPN-unclassifiable (MDS/MPN-U), while cases with leukocytosis [white blood cell (WBC) count of $\geq 13 \times 10^9/L$] might be included in the category of MDS/MPN-RS-T, even in the absence of thrombocytosis.

We have previously reported data from a large cohort of patients ($n = 135$) with MDS/MPN-U and found that patients with BM RS $\geq 15\%$ ($n = 13$) had better outcomes than those with BM RS $< 15\%$ ($n = 103$), but similar outcomes when compared to patients with MDS/MPN-RS-T patients ($n = 72$) [12]. The analysis was however limited by small sample size and differential follow-up between the two groups. Nonetheless, these data call into question the necessity of a strict MDS/MPN-RS-T definition based on the aforementioned criteria and highlight its limitations. The objectives of the current study were to (i) define the natural history of MDS/MPN-RS-T, including determination of long-term survival and prognostic factors, and (ii) formally compare clinical and prognostic features between a larger cohort of patients with MDS/MPN-RS-T ($n = 158$) and MDS/MPN-U with $\geq 15\%$ BM RS (MDS/MPN-U-RS), but not meeting criteria for MDS/MPN-RS-T

¹Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, MN, USA. ²Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA. ³Department of Malignant Hematology, H. Lee Moffitt Cancer Center, Tampa, FL, USA. ⁴These authors contributed equally: Abhishek A. Mangaonkar, Ayalew Tefferi, Rami Komrokji. ✉email: mangaonkar.abhishek@mayo.edu; Tefferi.Ayalew@mayo.edu; Rami.Komrokji@moffitt.org

Received: 17 October 2021 Revised: 16 January 2022 Accepted: 20 January 2022

Published online: 01 February 2022

Table 1. Table showing phenotypic and genomic differences among patients with WHO-defined MDS/MPN-RS-T and MDS/MPN-U patients with BM RS% \geq 15 (MDS/MPN-U-RS).

Variable; Median value (range or %)	MDS/MPN-RS-T (n = 158)	MDS/MPN-U-RS (n = 25)	P-value
Age (years)	71 (38–94)	71 (37–86)	0.9
Age \geq 70 (years)	96 (61)	13 (52)	0.4
Males (%)	82 (52)	9 (36)	0.1
Clinical parameters	<i>Evaluable = 78</i>	<i>Evaluable = 25</i>	
Hb; g/dL	9.5 (6.6–14.5)	9 (5.6–12.7)	0.2
Hb \leq 10 g/dL	51 (65)	18 (72)	0.5
WBC count $\times 10^3$ per μ L	7.6 (1.9–25.8)	6.9 (1.7–48.9)	0.5
Platelet count $\times 10^3$ per μ L	585 (454–1741)	559 (14–1798)	0.7
PB blast%	–	0 (0–9)	<0.0001 ^a
PB blasts \geq 1%	–	9	<0.0001 ^a
BM blast%	1 (0–4)	3 (0–8)	0.001 ^a
BM blast \geq 5%	–	8	<0.0001 ^a
BM RS%	47.5 (15–90)	35 (15–80)	0.2
Thrombosis %	14 (18)	2 (8)	0.3
Arterial	6 (43)	1 (50)	
Venous	6 (43)	1 (50)	
Cytogenetics	<i>Evaluable = 72</i>	<i>Evaluable = 24</i>	
Abnormal karyotype (except-Y)	11 (15)	4 (17)	0.9
Monosomal karyotype	2 (3)	2 (8)	0.3
Complex karyotype	2 (3)	2 (8)	0.3
IPSS cytogenetics			
Good	63 (88)	20 (83)	0.7
Intermediate	4 (6)	1 (4)	
Poor	5 (7)	3 (13)	
IPSS-R cytogenetics			
Very good	5 (7)	–	0.4
Good	59 (81)	20 (83)	
Intermediate	4 (5)	1 (4)	
Poor	3 (4)	1 (4)	
Very poor	2 (3)	2 (8)	
Pathogenic variants			
ASXL1	Evaluable = 49; 10 (20)	Evaluable = 17; 4 (24)	0.9
DNMT3A	Evaluable = 43; 6 (14)	Evaluable = 15; 2 (13)	0.9
TET2	Evaluable = 43; 3 (7)	Evaluable = 15; 2 (13)	0.5
SF3B1	Evaluable = 111; 103 (93)	Evaluable = 17; 10 (59)	0.0005 ^a
SRSF2	Evaluable = 43; 1 (2)	Evaluable = 15; 2 (13)	0.1
ZRSR2	Evaluable = 43; 1 (2)	Evaluable = 15; 0 (0)	0.4
U2AF1	Evaluable = 43; 1 (2)	Evaluable = 15; 2 (13)	0.1
JAK2 V617F	Evaluable = 43; 13 (30)	Evaluable = 15; 2 (13)	0.2
CALR	Evaluable = 43; 2 (5)	Evaluable = 15; 0 (0)	0.3

Table 1. continued

Variable; Median value (range or %)	MDS/MPN-RS-T (n = 158)	MDS/MPN-U-RS (n = 25)	P-value
SETBP1	Evaluable = 40; 4 (10)	Evaluable = 15; 2 (13)	0.7
TP53	Evaluable = 39; 1 (2)	Evaluable = 15; 0 (0)	0.4
Outcomes (evaluable = 183)			
Median follow-up (months)	62 (45–80)	53 (18–123)	0.9
Leukemic transformation (%)	6 (4)	–	0.0003 ^a
LFS (95% CI) years	Median not reached	Median not reached	0.4
OS (95% CI) years	6 (5–9)	7.3 (1.8–11.4)	0.3

MDS/MPN-RS-T myelodysplastic/myeloproliferative neoplasms with RS and thrombocytosis, MDS/MPN-U myelodysplastic/myeloproliferative neoplasms, unclassifiable, Hb hemoglobin, BM bone marrow, RS ring sideroblast, IPSS International Prognostic Scoring System, IPSS-R Revised International Prognostic Scoring System, LFS acute myeloid leukemia-free survival, OS overall survival.

^aDenotes statistical significance ($P < 0.05$).

($n = 25$), so as to inform future revisions of the WHO classification of myeloid malignancies.

METHODS

Clinical and pathologic data from consecutive adult patients with WHO-defined MDS/MPN-RS-T ($n = 158$) and MDS/MPN-U-RS ($n = 25$) were collected from two major institutions, Mayo Clinic (Rochester, Minnesota) and H. Lee Moffitt Cancer Center (Tampa, Florida) after institutional review board (IRB) approval at each institution. Diagnostic BM biopsy reports were carefully reviewed to ensure compliance with the latest WHO criteria. The MDS/MPN-U-RS patients did not meet MDS/MPN-RS-T criteria due to PB blast% > 1 ($n = 9$), BM blast% > 5 ($n = 8$), and the rest due to absence of thrombocytosis. There were 3 MDS/MPN-U-RS patients who did not have thrombocytosis or leukocytosis but were classified as such since they did not meet diagnostic requirements of any other MDS/MPN category. Among these three patients, two had predominance of MPN features on bone marrow assessment (atypical megakaryocytes, and/or mild reticulin fibrosis) and one had BM blast% > 5 . Next generation sequencing (NGS) was done at diagnosis or first referral using institutional or commercially available myeloid malignancy-specific gene panels (details in Supplementary Table 1). Distribution of continuous variables was statistically compared using nonparametric (Mann–Whitney or Kruskal–Wallis) tests, while nominal variables were compared using the Chi-Square test. Time to event analyses used the method of Kaplan–Meier for univariate comparisons. Significant ($P < 0.05$) continuous variables were converted into categorical variables after derivation of cut-off points through a receiver operating curve (ROC) analysis and were chosen for multivariate analysis performed through the Cox proportional hazard regression model. Overall survival (OS) was computed from the date of diagnosis to date of death or last follow-up. Leukemia-free survival (LFS) was calculated from date of diagnosis to date of acute myeloid leukemia (AML) transformation or last follow-up; in other words, AML transformation replaced death as the uncensored variable in calculating LFS. Patients who underwent allogeneic hematopoietic stem cell transplantation were censored at the time of transplantation.

RESULTS

Overall, 183 patients were included in the study: 158 MDS/MPN-RS-T and 25 MDS/MPN-U-RS. The median age of the MDS/MPN-RS-T cohort was 71 (range: 38–94) years; 83 (52%) males. At last median follow-up of 62 [95% confidence interval (CI) 45–80]

Table 2. Univariate and multivariate analysis of clinical and genomic characteristics among patients with MDS/MPN-RS-T.

Variable	Univariate analysis P-value (HR, 95% CI)	Multivariate analysis P-value (HR, 95% CI)
Age (years)	<0.0001 (1.1, 1–1.1)	–
Age ≥70 (years)	0.006 (2, 1.2–3.7) ^a	0.8 (1.1, 0.4–3)
Male gender	0.2 (1.4, 0.9–2.3)	–
Hemoglobin (g/dL)	0.004 (1.4, 0.5–1) ^a	–
Hemoglobin ≤10 (g/dL)	0.03 (2.4, 1.1–5.3) ^a	0.03 (3.12, 1.1–8.5) ^a
WBC count (x10 ³ /μL)	0.5 (1, 0.9–1)	–
Platelet count (x10 ³ /μL)	0.2 (1, 0.99–1)	–
BM blast%	0.6 (1.1, 0.7–1.7)	–
BM RS%	0.6 (1, 0.97–1.01)	–
Bone marrow fibrosis (any grade)	0.1 (2.4, 0.8–7.2)	–
Abnormal karyotype (excluding -Y)	0.008 (3.7, 1.4–9.5) ^a	0.001 (7.3, 2.2–23.8) ^a
IPSS cytogenetic categories		
Good	Reference	–
Intermediate	0.04 (3.7, 1.1–12.6) ^a	–
Poor	0.1 (3.5, 0.8–15.8)	–
IPSS-R cytogenetic categories		
Very good	Reference	–
Good	0.07 (0.4, 0.1–1.1)	–
Intermediate	0.9 (0.9, 0.2–5)	–
Poor	0.1 (4.2, 0.7–24.6)	–
Very poor	0.6 (1.9, 0.2–18.6)	–
Molecular abnormalities (only included if n ≥ 3)		
ASXL1	0.7 (1.2, 0.5–2.9)	–
ASXL1 (only frameshift and nonsense)	0.02 (3.3, 1.2–9) ^a	0.1 (2.9, 0.8–10.1)
TET2	0.1 (1.8, 0-NR)	–
DNMT3A	0.3 (0.3, 0.04–2.3)	–
SF3B1	0.4 (0.6, 0.2–1.7)	–
JAK2	0.7 (0.9, 0.4–2.01)	–
SETBP1	0.75 (1.2, 0.4–3.7)	–

Significant variables (continuous variables were converted into categorical variables after derivation of cut-off points through a ROC analysis) in a univariate analysis were chosen for multivariate analysis, which was performed through Cox proportional hazard model.

MDS/MPN-U myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis, ROC receiver operating characteristic, HR hazard ratio, WBC white blood cell, BM bone marrow, RS ring sideroblast; IPSS International Prognostic Scoring System, IPSS-R Revised International Prognostic Scoring System, NR not reached.

^aDenotes statistical significance, $P < 0.05$ in predicting overall survival.

months, there were 66 (42%) deaths and 6 (4%) AML transformations. The Kaplan–Meier estimates of median OS and LFS were 6 (95% CI 5–9) and 3 (95% CI 2–4) years, respectively. Cytogenetic abnormalities (excluding -Y) were present in 11 (15%) patients with the most frequent ones being +8 ($n = 4$, 36%), 20q- ($n = 2$, 18%), and 7q- ($n = 2$, 18%), complex ($n = 2$, 18%) and monosomal karyotype ($n = 2$, 18%, Table 1). International Prognostic Scoring System (IPSS) cytogenetic stratification included 63 (88%) good, 4 (6%) intermediate and 5 (7%) poor risk categories, while the revised IPSS (IPSS-R) cytogenetic stratification included 5 (7%) very good, 59 (81%) good, 4 (5%) intermediate, 3 (4%) poor and 2 (3%) very poor risk categories, respectively. Frequent molecular

abnormalities included *SF3B1* [$n = 103$, 93%, most commonly K700E 52%, H662Q 12%, and K666R 7%], *JAK2 V617F* ($n = 13$, 30%), *ASXL1* ($n = 11$, 22%), *DNMT3A* ($n = 6$, 14%), *SETBP1* ($n = 4$, 10%), and *TET2* ($n = 3$, 7%) among others (Table 1). Information on therapy was available for MDS/MPN-RS-T patients in the Mayo cohort ($n = 78$); 44 (56%) were treated with erythropoietin stimulating agents, 16 (21%) lenalidomide, 4 (5%) investigational agents, while 1 each was treated with danazol, hydroxurea, and splenectomy, respectively.

In univariate analysis, age ≥70 years (HR 2, 95% CI 1.2–3.7, $P = 0.005$), hemoglobin ≤10 g/dL (HR 2.4, 95% CI 1.1–5.3, $P = 0.03$), and abnormal karyotype (HR 3.7, 95% CI 1.4–9.5, $P = 0.008$) independently predicted shorter survival. In multivariate analysis, hemoglobin ≤10 g/dL (HR 3.12, 95% CI 1.1–8.5, $P = 0.03$) and abnormal karyotype (HR 7.3, 95% CI 1.1–8.5, $P = 0.001$) retained prognostic significance (Table 2). Importantly, none of the molecular abnormalities (Fig. 1), including *ASXL1* ($P = 0.7$, Fig. 1A), *SF3B1* ($P = 0.4$, Fig. 1B) or *JAK2 V617F* ($P = 0.7$, Fig. 1C), platelet count ($P = 0.2$) or BM blast% ($P = 0.6$) predicted survival. *SF3B1* VAF information was available in only 43 patients, and was also not prognostically relevant ($P = 0.3$). However, when only frameshift and nonsense *ASXL1* mutations were considered, they were able to predict an adverse OS ($P = 0.02$) in a univariate analysis, but not in a multivariate model ($P = 0.1$). The prognostic irrelevance of molecular abnormalities such as *ASXL1* ($P = 0.9$), *SF3B1* ($P = 0.4$), or *JAK2 V617F* ($P = 0.8$) persisted even in MDS/MPN-RS-T patients with a normal karyotype ($n = 61$). An operational survival model using hemoglobin ≤10 g/dL (1 point) and abnormal karyotype (1 point) delineated patients into low [0 points, median OS 10.5 years, 95% CI (3–11.3)], intermediate [1 point, median OS 4.8 years, 95% CI (3.4–6.3)] and high-risk (2 points, median OS 1.4 years, 95% CI (0.5–not reached)] survival categories (Fig. 2). Among the high-risk patients ($n = 8$), three carried chromosome 7 abnormalities (1 with monosomy 7), two had a complex monosomal karyotype and 1 patient each had *ASXL1* and *TP53* mutations at diagnosis, respectively.

Comparison of the 158 patients with MDS/MPN-RS-T and the 25 patients with MDS/MPN-U-RS revealed a higher frequency of *SF3B1* mutations (92% versus 40%, $P = 0.003$, Fig. 3A) and AML transformation rate (4% versus 0%, $P = 0.0003$) in MDS/MPN-RS-T (Table 1). Overall (median, 6 versus 7.3 years, $P = 0.3$, Fig. 3B) and leukemia-free (median not reached in either groups, $P = 0.4$) survival between the two groups was similar. Frequency of thrombosis (overall $n = 14$, 7-arterial, 7-venous, 11-before diagnosis, 3-after diagnosis) was also similar in the two groups (18% versus 8%, $P = 0.3$, Table 1). Combined analysis of both groups did not identify platelet count $<450 \times 10^9/L$ (HR 1.1, 95% CI 0.3–4.7, $P = 0.9$), BM blast% ≥5 (HR 1.2 95% CI 0.3–4.96, $P = 0.8$) or PB blast% ≥1 (HR 2.4, 95% CI 0.94–6.2, $P = 0.07$) to be prognostically relevant for OS (could not assess for LFS due to limited events). Similar to MDS/MPN-RS-T, age ≥70 years (HR 2.04, 95% CI 1.3–3.3, $P = 0.004$), Hb ≤10 g/dL (HR 2.2, 95% CI 1.14–4.1, $P = 0.02$), and abnormal cytogenetics [except -Y, HR 2.4, 95% CI 1.12–5.4, $P = 0.02$] significantly predicted inferior OS. Additionally, in the MDS/MPN-U-RS group ($n = 25$), platelet count ($P = 0.9$), BM blast% ($P = 0.8$) or PB blast% ($P = 0.2$) remained prognostically irrelevant for OS prediction.

DISCUSSION

MDS/MPN-RS-T patients, previously classified under the provisional WHO category of RARS-T, have been reported to have a median OS around 6 years, and leukemic transformation rate of ~2% [13–15]. Previously, hemoglobin <10 gm/dL, abnormal karyotype, *ASXL1*, and *SETBP1* mutations have been found to significantly predict adverse OS [13]; however, these data were based on RARS-T patients, which were not subject to MDS/MPN-RS-T exclusionary criteria such as PB blast% ≥1, BM blast% ≥5 or

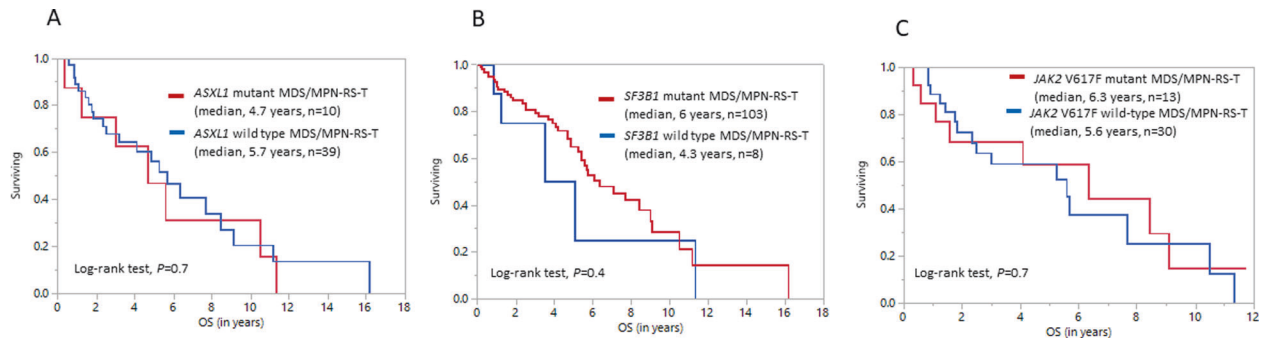


Fig. 1 Figure showing overall survival (OS) differences between *ASXL1*, *SF3B1* and *JAK2 V617F* mutated and wild-type MDS/MPN-RS-T patients. **A** shows that there is no significant Kaplan–Meier estimate of OS difference between *ASXL1* mutated and wild-type MDS/MPN-RS-T patients [median OS, 4.7 (95% CI 0.3–10.5) versus 5.7 (95% CI 2.5–8.4) years, $P = 0.7$], **B** shows that there is no significant Kaplan–Meier estimate of OS difference between *SF3B1* mutated and wild-type MDS/MPN-RS-T patients [median OS, 6.3 (95% CI 5.4–9) versus 4.3 (95% CI 0.8–11.3) years, $P = 0.4$], **C** shows that there is no significant Kaplan–Meier estimate of OS difference between *JAK2 V617F* mutated and wild-type MDS/MPN-RS-T patients [median OS, 6.3 (95% CI 1.1–9.1) versus 5.6 (95% CI 2.3–10.5) years, $P = 0.7$].

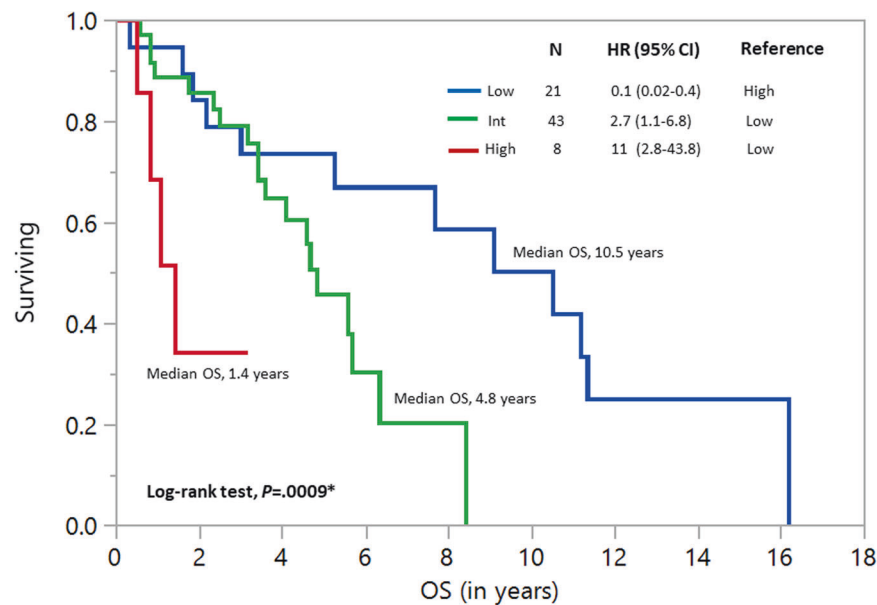


Fig. 2 Figure showing operational survival model using hemoglobin ≤ 10 gm/dL and abnormal karyotype (excluding -Y) identified as independent significant variables using multivariate analysis. Patients were diving into three survival categories; low [median OS 10.5 years 95% CI (3–11.3)], intermediate [median OS 4.8 years 95% CI (3.4–6.3)] and high-risk [median OS 1.4 years, 95% CI (0.5–not reached), $P = 0.0009$] categories. Statistical significance ($P < 0.05$) is denoted by *, calculated through the log-rank test.

cytogenetic abnormalities such as t(3;3)(q21.2;q26.2), inv(3)(q21.23q26.2) or isolated del(5q). Further, *ASXL1* and *SETBP1* mutations were not statistically significant in a multivariate model [13]. When we reclassified our patients as per the contemporary WHO definition of MDS/MPN-RS-T, only Hb ≤ 10 gm/dL and abnormal karyotype (without -Y) retained independent prognostic significance. Although the presence of any *ASXL1* mutation was unable to predict an adverse OS in a univariate analysis; frameshift and nonsense *ASXL1* mutations were able to do so, similar to previously published studies [13, 16]. Another study identified *SF3B1* and *JAK2V617F* as independent predictors of favorable prognosis, however these could not be validated in our cohort [17]. These data highlight that the contemporary WHO-defined MDS/MPN-RS-T category is clinically and molecularly less heterogeneous than RARS-T, and yet this classification has key limitations. An operational survival model relying on hemoglobin ≤ 10 g/dL (1 point) and abnormal karyotype (1 point) was able to risk stratify MDS/MPN-RS-T patients into low (0 points), intermediate (1 point), and high-risk categories (2 points), respectively. High-risk MDS/MPN-RS-T patients have an inferior median OS (1.4 years)

and can be considered for aggressive therapeutic strategies such as an allogeneic hematopoietic stem cell transplantation. However, such a risk-adapted management approach would need prospective validation.

The contemporary MDS/MPN-RS-T definition excludes patients with MDS/MPN-U with BM RS $\geq 15\%$ if the platelet count is less than $450 \times 10^9/L$, PB blast $\geq 1\%$ or BM blast% ≥ 5 . In our study, when we combined MDS/MPN-RS-T patients with MDS/MPN-U-RS, the platelet count, PB blast% or BM blast% did not predict for OS or LFS. Relevant clinical parameters such as frequency of thrombosis also did not significantly differ between the two groups. The prognostic irrelevance of platelet count, PB blast% or BM blast% remained true when MDS/MPN-U-RS cohort was separately analyzed. Application of these parameters as exclusion criteria for MDS/MPN-RS-T is therefore too restrictive and leaves out certain patients with MDS/MPN-U-RS, who have identical outcomes to MDS/MPN-RS-T patients as per the current definition. Limitations of the study include retrospective nature, heterogeneous clinical and genomic information in the two institutional cohorts, and limited sample size.

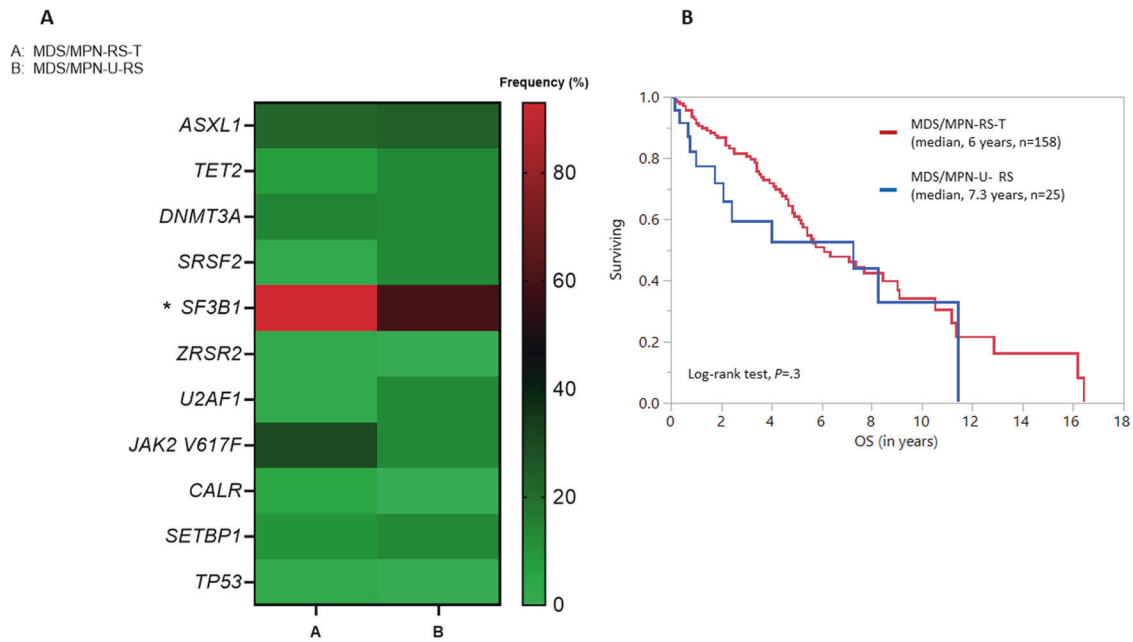


Fig. 3 Figure showing molecular landscape, OS and LFS differences between WHO-defined MDS/MPN-RS-T and MDS/MPN-U patients with BM RS \geq 15% (MDS/MPN-U-RS). **A** shows a heatmap displaying differences in mutational frequencies between MDS/MPN-RS-T and MDS/MPN-U-RS. *SF3B1* is the only gene mutated at a significantly (*) higher frequency in the MDS/MPN-RS-T group. **B** shows that the Kaplan–Meier estimate of median OS (95% CI) did not differ significantly between the two groups [6 (5–9) versus 7.3 (1.8–11.4) years, $P = 0.3$]. Log-rank test was used to calculate the P -value.

In conclusion, the findings from the current study did not identify molecular abnormalities as predictors of survival in MDS/MPN-RS-T, and also argue against the use of currently applied exclusionary criteria in defining MDS/MPN-RS-T, separate from MDS/MPN-U-RS. In other words, our observations support unification of MDS/MPN-U-RS and MDS/MPN-RS-T under a new category of “MDS/MPN-RS”, pending independent external validation. This will allow uniform inclusion of MDS/MPN patients with RS in future clinical trials with novel drugs focused on reversing erythroid arrest such as TGF β modulators, splicing inhibitors among others [18–20].

REFERENCES

- Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127:2391–405.
- Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. (Eds) WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: International Agency for Research on Cancer, 2017. p. 82–86.
- Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood*. 2009;114:937–51.
- Patnaik MM, Tefferi A. Refractory anemia with ring sideroblasts (RARS) and RARS with thrombocytosis (RARS-T): 2017 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2017;92:297–310.
- Patnaik MM, Tefferi A. Myelodysplastic syndromes with ring sideroblasts (MDS-RS) and MDS/myeloproliferative neoplasm with RS and thrombocytosis (MDS/MPN-RS-T) - “2021 update on diagnosis, risk-stratification, and management”. *Am J Hematol*. 2021;96:379–94.
- Patnaik MM, Tefferi A. Refractory anemia with ring sideroblasts (RARS) and RARS with thrombocytosis: “2019 Update on Diagnosis, Risk-stratification, and Management”. *Am J Hematol*. 2019;94:475–88.
- Patnaik MM, Tefferi A. Refractory anemia with ring sideroblasts and RARS with thrombocytosis. *Am J Hematol*. 2015;90:549–59.
- Montalban-Bravo G, Kanagal-Shamanna R, Darbanian F, Siddiqui MT, Sasaki K, Wei Y, et al. Clinical, genomic, and transcriptomic differences between myelodysplastic syndrome/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) and myelodysplastic syndrome with ring sideroblasts (MDS-RS). *Am J Hematol*. 2021;96:E246–e249.
- Patnaik MM, Lasho TL. Genomics of myelodysplastic syndrome/myeloproliferative neoplasm overlap syndromes. *Hematol Am Soc Hematol Educ Program*. 2020;2020:450–9.
- Patnaik MM, Lasho T. Myelodysplastic syndrome/myeloproliferative neoplasm overlap syndromes: a focused review. *Hematol Am Soc Hematol Educ Program*. 2020;2020:460–4.
- Talati C, Padron E. An Exercise in Extrapolation: Clinical Management of Atypical CML, MDS/MPN-Unclassifiable, and MDS/MPN-RS-T. *Curr Hematol Malig Rep*. 2016;11:425–33.
- Manganonkar AA, Swoboda DM, Coltro G, Lasho TL, Novotny PJ, Pophali P, et al. Clinicopathologic characteristics, prognostication and treatment outcomes for myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN-U): Mayo Clinic-Moffitt Cancer Center study of 135 consecutive patients. *Leukemia*. 2020;34:656–61.
- Patnaik MM, Lasho TL, Finke CM, Hanson CA, King RL, Ketterling RP, et al. Predictors of survival in refractory anemia with ring sideroblasts and thrombocytosis (RARS-T) and the role of next-generation sequencing. *Am J Hematol*. 2016;91:492–8.
- Broseus J, Florensa L, Zipperer E, Schnitger S, Malcovati L, Richebourg S, et al. Clinical features and course of refractory anemia with ring sideroblasts associated with marked thrombocytosis. *Haematologica*. 2012;97:1036–41.
- Wang SA, Hasserjian RP, Loew JM, Sechman EV, Jones D, Hao S, et al. Refractory anemia with ringed sideroblasts associated with marked thrombocytosis harbors JAK2 mutation and shows overlapping myeloproliferative and myelodysplastic features. *Leukemia*. 2006;20:1641–4.
- Palomo L, Meggendorfer M, Hutter S, Twardziok S, Ademà V, Fuhrmann I, et al. Molecular landscape and clonal architecture of adult myelodysplastic/myeloproliferative neoplasms. *Blood*. 2020;136:1851–62.
- Broséus J, Alpermann T, Wulfert M, Florensa Brichs L, Jeromin S, Lippert E, et al. Age, JAK2(V617F) and SF3B1 mutations are the main predicting factors for survival in refractory anaemia with ring sideroblasts and marked thrombocytosis. *Leukemia*. 2013;27:1826–31.
- Manganonkar AA, Patnaik MM. Treatment of acquired sideroblastic anemias. *Hematol Oncol Clin North Am*. 2020;34:401–20.
- Steenma DP, Wermke M, Klimek VM, Greenberg PL, Font P, Komrokji RS, et al. Phase I First-in-Human Dose Escalation Study of the oral SF3B1 modulator H3B-8800 in myeloid neoplasms. *Leukemia*. 2021; <https://doi.org/10.1038/s41375-021-01328-9>.
- Fenaux P, Platzbecker U, Mufti GJ, Garcia-Manero G, Buckstein R, Santini V, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Engl J Med*. 2020;382:140–51.

ACKNOWLEDGEMENTS

This publication was supported by Grant#UL1 TR002377 from the National Center for Advancing Translational Sciences (NCATS), however findings do not necessarily represent official views of NIH.

AUTHOR CONTRIBUTIONS

AM compiled the clinical and genetic data, performed data analysis, and wrote the manuscript. TL performed NGS studies on some patients. RPK and KKR reviewed the pathology information. NG, AA, KHB, AP, NHA, CT, DS, EP, RK, AT, and MP contributed patients and edited all drafts of the manuscript. AM, AT, and MP conceptualized the study and edited all manuscript drafts. All authors contributed in the writing of the manuscript.

COMPETING INTERESTS

EP has received honoraria and/or serves on advisory boards of BluePrint, CTI, Stemline Therapeutics, Taiho, and BMS; and has received research funding from Kura, Incyte, and BMS. MP is on the advisory board of Stemline Therapeutics. All other authors declare no relevant conflicts of interest in relation to the manuscript.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41408-022-00622-8>.

Correspondence and requests for materials should be addressed to Abhishek A. Mangaonkar, Ayalew Tefferi or Rami Komrokji.

Reprints and permission information is available at <http://www.nature.com/reprints>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2022