


# Patterns of transfusion burden in an unselected population of patients with myelodysplastic syndromes: A population-based study

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## Abstract

**Background:** Ineffective hematopoiesis in patients with myelodysplastic syndromes (MDS) often results in transfusion dependence. The burden of frequent transfusions in the real-world MDS population is largely unknown.

**Study design and methods:** An observational, retrospective, population-based study, using the HemoBase registry, was performed including all patients diagnosed with MDS between 2005 and 2017 in Friesland, a province in the Netherlands with approximately 650,000 inhabitants. Detailed clinical information was collected from the electronic health records. Transfusion burden was classified according to the International Working Group 2018 criteria: not transfusion dependent, low (LTB), or high transfusion burden (HTB). Univariate and multivariable regression analyses were performed.

**Results:** Of 292 patients, 136 (46.6%) had a HTB of  $\geq 8$  units/16 weeks and 17 (5.8%) had a LTB of 3–7 units/16 weeks. This was present in all types of MDS patients, but patients aged 75–84 years (odds ratio [OR] 4.02, 95% confidence interval [CI]: 1.84–8.82), high-risk MDS patients (OR 2.88, 95% CI: 1.08–7.68) and MDS-EB-2 patients (OR 7.07, 95% CI: 2.17–22.90) were particularly at risk for a HTB.

**Discussion:** This study provides a reliable estimate of the transfusion burden in real-world MDS patients, with almost half of the patients having a HTB. A HTB was observed in all MDS subtypes and both low- and high-risk MDS. Therefore, we conclude that the entire MDS population might benefit from

**Abbreviations:** BSC, best supportive care; DMT, disease modifying treatment; EB, excess blasts; ESA, erythropoiesis stimulating agents; HMA, hypomethylating agents; HTB, high transfusion burden; IPSS, International Prognostic Scoring System; IPSS-R, Revised International Prognostic Scoring System; LTB, low transfusion burden; MDS, myelodysplastic syndromes; MLD, multi lineage dysplasia; NTD, not transfusion dependent; OS, overall survival; RBC, red blood cell; RCT, randomized controlled trials; RS, ring sideroblasts; SLD, single lineage dysplasia.

A list of the HemoBase Population Registry Consortium appears in the Appendix.

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novel agents that reduce the transfusion need and that might have beneficial effects on patient outcomes and healthcare utilization outcomes.

#### KEYWORDS

blood transfusion, myelodysplastic syndromes, population-based, transfusion dependence

## 1 | INTRODUCTION

Due to ineffective hematopoiesis, patients suffering from myelodysplastic syndromes (MDS) often receive blood transfusions and become transfusion dependent during the course of their disease.<sup>1, 2</sup> The median age at diagnosis of MDS is 74–79 years and the majority of MDS patients have comorbidities.<sup>2–5</sup> Randomized controlled trials (RCTs) have shed some light on the burden of frequent blood transfusions in MDS patients, but this often only applies to a selection of the MDS population, such as low-risk MDS patients with International Prognostic Scoring System (IPSS) <1.5 or patients without comorbidities.<sup>6–8</sup> Given the heterogenic population of MDS patients, there is a relative knowledge-to-care gap on the transfusion burden in patients suffering from MDS in daily clinical practice.<sup>2, 9–12</sup>

Population-based studies focusing on transfusions in MDS patients can complement the data of RCTs, but only few have been performed, each providing merely an overview of the transfusion burden according to ICD codes.<sup>2, 13</sup> To the best of our knowledge, population-based studies in MDS patients with data on the distribution of blood transfusion units are not available. The transfusion burden in general and the difference in transfusion burden in both low-risk and high-risk MDS patients (according to the [Revised] International Prognostic Scoring System [IPSS-R]) and patients with different MDS subtypes in the real-world population are therefore largely unknown.

With several new pharmaceutical agents for transfusion-dependent MDS patients that became available recently or that are in the late stages of development, it is pivotal to early identify patient groups that could benefit from these new agents and to recognize patients that remain in need of new therapies.<sup>14</sup> For example, luspatercept, an erythropoiesis maturing agent, was recently approved by the Food and Drug administration and the European Medicines Agency for treatment of MDS patients with ring sideroblasts (MDS-RS) who require  $\geq 2$  red blood cell (RBC) units over 8 weeks and who are refractory to or ineligible for erythropoietin-based therapy.<sup>10, 11, 15–17</sup> Knowing the treatment and transfusion needs of the MDS population could aid in defining the place of new agents.

Optimizing treatment and defining valuable and rational care for (regularly) transfused MDS patients can only be

accomplished when the transfusion burden of MDS patients is known. In most national guidelines, indication for transfusion is dependent on a hemoglobin level of 5.5–6.0 mmol/L (8.9–9.7 g/dl) and age, but concurrent cardiovascular comorbidities or other patient-specific characteristics can influence the decision to transfuse.<sup>18</sup> The transfusion burden can be based on the amount of transfusions a patient receives in a certain time period; a cutoff value of  $\geq 2$  RBC units over 8 weeks is generally defined as transfusion dependence.<sup>9, 19–21</sup> Recently, the MDS International Working Group (IWG) 2018 has established the criteria for transfusion dependence and defines three categories: not transfusion dependent (NTD), low transfusion burden (LTB) or high transfusion burden (HTB).<sup>9</sup> In former studies, different definitions for transfusion burden have been used, making cross-study comparison problematic.<sup>19, 22–24</sup> The purpose of this population-based study was to give a reliable estimate of the transfusion burden in an unselected population of MDS patients. Furthermore, we aimed to study the potential heterogeneity in transfusion burden in a real-world cohort of patients. For this, a real-world cohort of low- and high-risk MDS patients was evaluated, using the IWG 2018 criteria for transfusion burden.

## 2 | MATERIALS AND METHODS

An observational, population-based study, using the HemoBase registry, was performed (previously described).<sup>8, 25</sup> HemoBase includes all patients diagnosed with a hemato-oncologic disease since 2005 in Friesland, a Dutch province with 650,000 inhabitants. All MDS patients diagnosed between January 1, 2005 and December 31, 2017 were selected and their diagnosis was blindly confirmed by an expert panel according to the World Health Organization 2016 classification.<sup>4, 25</sup> Formal exclusion criteria were not applicable. Information about diagnosis, treatment, and all distributed transfusions of RBC and platelets since diagnosis, was collected from the electronic health records and laboratory systems. Patients were retrospectively followed from date of diagnosis through March 2019 or death, whichever occurred first. The study was in accordance with the Helsinki declaration (revision 2013). The Medical Ethics Committee in Leeuwarden confirmed the conduct of this retrospective study without the need for

ethical review, and the institutional boards approved the execution of the study without the need for consent in accordance with Dutch regulations.

RBC units were administered to patients according to and following national guidelines.<sup>18</sup> Transfusion burden was defined according to the IWG 2018 guidelines: NTD, LTB, or HTB.<sup>9</sup> The NTD category included patients that received no transfusion in a period of 16 weeks. Patients who received 1–2 RBC units in a period of 16 weeks without any regularity were also considered NTD. LTB was defined as 3–7 RBC units in a period of 16 weeks. HTB was defined as  $\geq 8$  RBC units in a period of 16 weeks. Each patient was assessed individually. In case a patient had multiple periods of regular transfusions, the period with the highest transfusion burden was used for the determination of the transfusion burden. Patients who received RBC transfusions and platelet transfusions were also considered dependent for platelet transfusions when  $\geq 3$  units were given in a period of 16 weeks. Patients who only received transfusions before MDS diagnosis were categorized as NTD, as only transfusions since date of diagnosis were taken into consideration. Low-risk MDS was defined as IPSS-R (very) low and intermediate, and high-risk MDS as IPSS-R (very) high.<sup>26, 27</sup> Due to missing cytogenetic data or unsuccessful bone marrow biopsies the IPSS-R could not be determined for all MDS patients; as missing data are not at random, these patients were not discarded but analyzed as a separate category. Disease modifying treatment (DMT) was defined as hypomethylating agents, lenalidomide, and chemotherapy. Treatment with erythropoiesis stimulating agents (ESA) was defined as any ESA, including combinations with granulocyte colony stimulating factors. Best supportive care (BSC) was defined as all supportive measures for alleviating symptoms, not focused on cure or prevention of disease progression (e.g. antibiotics, [anti]coagulants). Patients were treated according to (inter)national treatment guidelines for MDS.<sup>3, 28</sup> Pearson chi-square and Kruskal-Wallis tests were performed to study differences between HTB patients and LTB or NTD patients. Logistic regression analyses were performed to investigate potential prognostic factors for HTB. Variables with  $p < .15$  in univariate analysis were included in the multivariable analysis to determine potential prognostic factors for HTB. The significance level for prognostic factors in multivariable analysis was kept at  $p < .05$ . Only baseline parameters were included in the multivariable analysis; the number of transfusions, (change in) treatment, or transplants were therefore not included, but presented to provide context. Kaplan–Meier survival analyses were performed to provide additional information about the study population regarding differences in overall survival (OS). Median follow-up was estimated

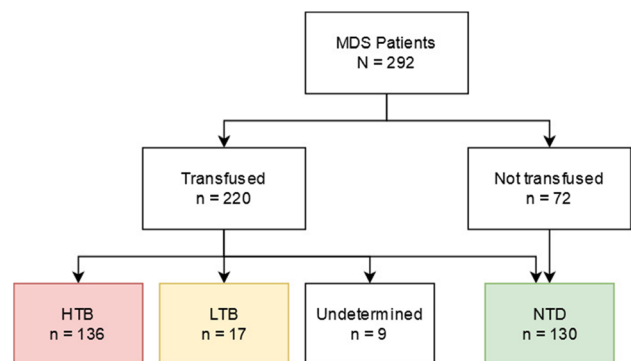
using a reverse Kaplan–Meier analysis.<sup>29</sup> Patient numbers can differ between analyses due to missing data. Statistical analyses were performed using IBM SPSS v.24.

## 2.1 | Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## 3 | RESULTS

A total of 292 MDS patients were identified, 283 of which were included in the study. Nine patients were omitted from further analyses because their observation period was insufficient ( $< 56$  days) for determination of the transfusion burden. The median age of the study population was 75 years and median time of follow-up was 76.8 months (95% confidence interval [CI]: 63.0–90.5). More than half of the study population ( $n = 153$ , 52.4%) received regular transfusions and were considered LTB ( $n = 17$ , 5.8%) or HTB ( $n = 136$ , 46.6%) (Figure 1, Table 1). Of the HTB patients, 115 patients were HTB as soon as they became transfusion dependent and 21 patients progressed from LTB to HTB. All MDS subtypes were represented in the group of transfused patients (Table 1). The proportion of patients  $< 65$  years and 65–74 years was higher in patients with NTD compared to patients with LTB or HTB ( $p = .049$ ). LTB patients received a median of 12 RBC units (range: 2–37) and HTB patients received a median of 36 RBC units (range: 7–322). Twenty-four patients (10.9%) of the HTB population were also dependent on platelet units. Of



**FIGURE 1** Flow chart of transfusion burden in Frisian MDS patients. HTB, High transfusion burden; LTB, Low transfusion burden; NTD, Not transfusion dependent; MDS, Myelodysplastic syndromes; undetermined, Patients whose observation period was insufficient ( $< 56$  days) to examine the transfusion burden

TABLE 1 Characteristics of the NTD, LTB, and HTB patients

	Total n (%)	NTD n (%)	LTB n (%)	HTB n (%)	p-value
Total	283 (100)	130 (100)	17 (100)	136 (100)	-
Median follow-up (months [95% CI])	76.8 (63.0–90.5)	53.2 (35.4–71.0)	64.5 (44.9–84.1)	85.9 (71.4–100.4)	-
Male gender	199 (70.3)	89 (68.5)	11 (64.7)	99 (72.8)	.65
Age					.049
< 65	55 (19.4)	31 (23.8)	5 (29.4)	19 (14.0)	
65–74	85 (30.0)	43 (33.1)	3 (17.6)	39 (28.7)	
75–84	116 (41.0)	47 (36.2)	5 (29.4)	64 (47.1)	
≥ 85	27 (9.5)	9 (6.9)	4 (23.5)	14 (10.3)	
Median age (year [range]) at diagnosis	75.2 (18.2–92.0)	73.0 (18.2–92.0)	75.1 (43.7–87.0)	76.1 (27.5–91.7)	.046
MDS subtype					<.01
SLD	42 (14.8)	25 (19.2)	3 (17.6)	14 (10.3)	
MLD	41 (14.5)	17 (13.1)	3 (17.6)	21 (15.4)	
RS-SLD	45 (15.9)	29 (22.3)	4 (23.5)	12 (8.8)	
RS-MLD	30 (10.6)	17 (13.1)	1 (5.9)	12 (8.8)	
Del (5q)	6 (2.1)	2 (1.5)	0 (0)	4 (2.9)	
EB-1	49 (17.3)	19 (14.6)	2 (11.8)	28 (20.6)	
EB-2	35 (12.4)	6 (4.6)	1 (5.9)	28 (20.6)	
U	6 (2.1)	3 (2.3)	1 (5.9)	2 (1.5)	
Not specified	29 (10.2)	12 (9.2)	2 (11.8)	15 (11.0)	
IPSS-R score					.01
Low-risk	150 (53.0)	80 (61.5)	10 (58.8)	60 (44.1)	
Very Low	19 (6.7)	13 (10.0)	0 (0)	6 (4.4)	
Low	88 (31.1)	47 (36.2)	6 (35.3)	35 (25.7)	
Intermediate	43 (15.2)	20 (15.4)	4 (23.5)	19 (14.0)	
High-risk	37 (13.1)	7 (5.4)	1 (5.9)	29 (21.3)	
High	22 (7.8)	5 (3.8)	1 (5.9)	16 (11.8)	
Very High	15 (5.3)	2 (1.5)	0 (0)	13 (9.6)	
Unknown	96 (33.9)	43 (33.1)	6 (35.3)	47 (34.6)	
RBCs					-
Median no. of units (range)		0 (0–27)	12 (2–37)	36 (7–322)	
> 40 units		0 (0)	0 (0)	58 (42.6)	
PLTs					-
Median no. of units (range)		0 (0–15)	0 (0–1)	1 (0–45)	
Transfusion dependent (PLT)		0 (0)	0 (0)	24 (17.6)	
Treatment					<.01
BSC only	123 (43.5)	74 (56.9)	4 (23.5)	45 (33.1)	
ESA	81 (28.6)	30 (23.1)	11 (64.7)	40 (29.4)	
DMT	92 (32.5)	26 (20.0)	5 (29.4)	61 (44.9)	
Unknown	3 (1.1)	2 (1.5)	1 (5.9)	0 (0)	
Transplantation	24 (8.5)	12 (9.2)	3 (17.6)	9 (6.6)	.07

Note: Values are reported as number (%) of patients, unless stated otherwise. Note that patients whose transfusion burden could not be determined ( $n = 9$ ) are not presented in this Table.

Abbreviations: BSC, best supportive care; CI, confidence interval; DMT, disease modifying treatment; EB, excess blasts; ESA, erythropoiesis stimulating agents; HTB, high transfusion burden; IPSS-R: revised international prognostic scoring system; LTB, low transfusion burden; MLD, multi lineage dysplasia; NTD, not transfusion dependent; PLTs, platelets; RBCs, red blood cells; RS, ring sideroblasts; SLD, single lineage dysplasia; U, unclassified.

TABLE 2 Differences between patients with a HTB compared to patients with NTD/LTB

	HTB n (%)	NTD/LTB n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Total	136 (100)	147 (100)	-	-
IPSS-R risk group			<b>p &lt; .01</b>	<i>p</i> = .09
LR-MDS	60 (44.1)	90 (61.2)	Ref.	Ref.
HR-MDS	29 (21.3)	8 (5.4)	5.44 (2.33–12.70)	2.88 (1.08–7.68)
Unknown	47 (34.6)	49 (33.3)	1.44 (0.86–2.41)	1.03 (0.56–1.89)
MDS subtype			<b>p &lt; .01</b>	<i>p</i> < .01
SLD	14 (10.3)	28 (19.0)	Ref.	Ref.
MLD	21 (15.4)	20 (13.6)	2.10 (0.87–5.10)	2.51 (1.00–6.29)
RS-SLD	12 (8.8)	33 (22.4)	0.73 (0.29–1.83)	0.63 (0.25–1.63)
RS-MLD	12 (8.8)	18 (12.2)	1.33 (0.50–3.53)	1.19 (0.43–3.25)
Del5q	4 (2.9)	2 (1.4)	4.00 (0.65–24.55)	2.97 (0.46–19.09)
EB-1	28 (20.6)	21 (14.3)	2.67 (1.13–6.27)	2.36 (0.95–5.91)
EB-2	28 (20.6)	7 (4.8)	8.00 (2.81–22.81)	7.05 (2.17–22.90)
MDS-U	2 (1.5)	4 (2.7)	1.00 (0.16–6.14)	1.37 (0.20–9.40)
Not specified	15 (11.0)	14 (9.5)	2.14 (0.81–5.66)	2.34 (0.83–6.65)
Gender			<i>p</i> = .38	-
Female	37 (27.2)	47 (32.0)	Ref.	
Male	99 (72.8)	100 (68.0)	1.26 (0.75–2.10)	
Age (years)			<b>p = .09</b>	<i>p</i> < .01
<65	19 (14.0)	36 (24.5)	Ref.	Ref.
65–74	39 (28.7)	46 (31.3)	1.61 (0.80–3.24)	2.43 (1.09–5.40)
75–84	64 (47.1)	52 (35.4)	2.33 (1.20–4.54)	4.02 (1.84–8.82)
≥85	14 (10.3)	13 (8.8)	2.04 (0.80–5.21)	3.08 (1.04–9.16)
Treatment <sup>ab</sup>				
ESA			<i>p</i> = .86	-
No	96 (70.6)	103 (70.1)	Ref.	
Yes	40 (29.4)	41 (27.9)	1.05 (0.62–1.76)	
DMT			<b>p &lt; .01</b>	-
No	75 (55.1)	113 (76.9)	Ref.	
Yes	61 (44.9)	31 (21.1)	2.97 (1.76–5.00)	

Note: Patients whose transfusion burden could not be determined were omitted from this analysis. Patient numbers can differ between analyses due to missing data.

Abbreviations: CI, confidence interval; DMT, disease modifying treatment; EB, excess blasts; ESA, erythropoiesis stimulating agents; HTB, high transfusion burden; IPSS-R, revised international prognostic scoring system; LTB, low transfusion burden; MLD, multilineage dysplasia; NTD, not transfusion dependent; OR, odds ratio; RS, ring sideroblasts; SLD, single lineage dysplasia; U, unclassified.

<sup>a</sup>Treatment was not included in multivariable analysis, but was only presented to provide information about patient numbers in the NTD/LTB and HTB categories.

<sup>b</sup>Information on treatment was missing for 3 patients, hence the totals of patients with ESA and DMT therefore do not add up to 147.

The *p*-values are stated in the table. IPSS-R risk group: *p* < 0.01 (*p* = 0.000429); MDS subtype: *p* < 0.01 (*p* = 0.000657); Age: *p* = 0.09 (*p* = 0.0870); DMT: *p* < 0.01 (*p* = 0.000044).

these patients, 17 (70.8%) were diagnosed with MDS-EB. An ESA was given to 28% and DMT was given to 32% of all MDS patients (Table 1). For further analyses, LTB patients were combined with NTD patients due to the low number of LTB patients.

High-risk MDS patients had a higher transfusion burden compared to low-risk MDS patients (crude OR: 5.44, 95% CI: 2.33–12.70, *p* < .01, Table 2). MDS-EB-1 and EB-2 were associated with a higher transfusion burden than other MDS subtypes (crude OR: 2.67 [95% CI:

1.13–6.27] and 8.00 [95% CI: 2.80–22.81], respectively) (Table 2). Multivariable logistic regression analysis showed a significant association for several patient groups: older patients (>65 years), patients with high-risk MDS, and patients with MDS-EB-2 or MDS-MLD had a higher risk for HTB (Table 2).

We performed a Kaplan–Meier survival analysis to study the differences in OS in our population (Figure S1). Patients in the HTB category had a significantly shorter median OS compared to LTB or NTD patients (20.9 [95% CI: 15.2–26.5], 40.2 [95% CI: 16.6–63.9] and 47.5 [95% CI: 32.1–63.0] months, respectively).

## 4 | DISCUSSION

In our study, we found that 136 (46.6%) and 17 (5.8%) of the MDS patients had HTB and LTB, respectively, during the course of their disease. This study identified patients >65 years old, high-risk MDS patients, and patients with MDS-MLD or MDS-EB to be at increased risk for developing HTB, but HTB was a clinical condition observed in all MDS subtypes, and in both low-risk and high-risk MDS.

The number of transfusion-dependent MDS patients is in accordance with previous findings.<sup>1, 2, 23</sup> However, it is difficult to compare our results with previous studies, as definitions for transfusion burden differ, as well as the MDS population under study. Still, our results, based on a population-based cohort, are in line with previous research where patients with MDS-EB and MDS-MLD were at risk for HTB. These studies also show that HTB was not exclusively observed in a single MDS subtype, and that both low- and high-risk patients were at risk for HTB.<sup>1, 2, 23</sup> Considering the pathology of MDS, this is a logical outcome, as anemia is not limited to a single MDS subtype.<sup>4</sup>

The median OS of HTB patients was almost half of the median OS of LTB or NTD patients and was significantly compromised. HTB was associated with inferior outcomes in MDS, but our data could not demonstrate a causal relationship. HTB is likely a proxy for the severity of the disease.<sup>2, 10, 23, 30</sup> This theory is supported by our data that showed that aggressive disease, reflected by high IPSS-R score and need for treatment such as DMT, was associated with a higher transfusion burden in univariate analysis. In addition, looking at the outcomes of the multivariable analysis that identified age, IPSS-R, and MDS subtype as prognostic factors for HTB, our results underscore the need for better treatment options with the capacity to delay disease progression and thus reduce transfusion burden. Multiple novel agents are currently in phase II and III trials, mostly for low-risk-MDS.<sup>14</sup>

Luspatercept, for example, has recently become available for prescription and led to 38% of the patients becoming transfusion independent for  $\geq 8$  weeks.<sup>10, 11, 14, 16, 30</sup> Imetelstat, currently under investigation in a phase III trial, induced transfusion independence for  $\geq 8$  weeks in 37% of low-risk MDS patients with HTB and showed potential disease-modifying effects.<sup>14, 31</sup> Newer therapies that focus on pathogenetic pathways associated with transfusion burden could improve the transfusion burden and may subsequently improve OS. In addition to impaired survival, regular transfusions are accompanied by risks for transfusion-related adverse events; they put pressure on the blood banks and donor population, are associated with financial concerns, and require regular hospital visits for patients.<sup>1, 2, 9, 32</sup> Newer therapies for patients with LTB and HTB might therefore have beneficial effects on patient outcomes and healthcare utilization outcomes.

Our study population is unique in several aspects. It is, to our knowledge, the first population-based study comprising all types of patients with MDS, both low-risk and high-risk, with long-term results and using the IWG 2018 criteria for transfusion burden. It is this population that deals with the actual burden and complications of frequent transfusions. This study provides a reliable estimate of the transfusion burden in MDS patients and the results could be of interest for evaluation of new therapeutic agents for transfusion-dependent MDS patients. We encourage the use of the IWG 2018 criteria for transfusion burden to promote the opportunities for data comparison. Secondly, detailed patient and transfusion data were available. The laboratory information systems contained extensive information about all transfused blood products and their distribution and patients had a median follow-up of over 6 years.

This study also had certain limitations. Firstly, we were unable to distinguish between MDS-related transfusions and transfusions that were given for other causes, such as surgery or trauma. This was not expected to influence the outcomes of the study considerably because the IWG 2018 criteria require the assessment of transfusion burden on at least two different points in time to classify a patient as LTB or HTB. Patients predominantly had more than two points in time during their follow-up and a median of 12 RBC units (LTB patients) to 36 RBC units (HTB patients). Any transfusions that were given for surgery or trauma will therefore most likely not change the overall assessment. Secondly, the primary outcome (transfusion burden) was scored as worst possible outcome: the period with the highest transfusion burden was used for the determination of the transfusion burden. However, patients had a minimum follow-up of approximately 1.5 years and follow-up of LTB and HTB patients

was comparable. We therefore felt that patients had sufficient time to develop HTB. Thirdly, logistic regression analysis focused on HTB patients, due to the low numbers of LTB patients. These low numbers are an interesting outcome by itself, given the new IWG 2018 definition distinctly separates LTB patients from HTB patients. The Kaplan–Meier plot showed no significant difference between NTD and LTB patients, whereas HTB patients behaved clearly different. Patients with HTB are the main group that requires medical attention, partly because of the mortality. Therefore, it would be important to early identify this patient group. Another limitation is that this study was not designed to analyze treatment response on transfusion burden (i.e. treatment failure or a synergistic effect between transfusions and treatment, resulting in a [relatively] lower transfusion burden), because these data were incomplete and treatment response analysis based on retrospective data was not feasible. Because of lacking response data, observed changes cannot be attributed to the use of HMA or other therapies with certainty, as they might also be due to other (unstudied) factors. Furthermore, the IPSS-R score could not always be determined. This is a known hurdle in population-based studies with an unselected patient cohort, as the clinician's choice is paramount and in daily practice additional cytogenetic analyses are not always performed when the results would not affect the treatment choice.<sup>33</sup> Missing data occurred throughout the entire follow-up and was not limited to earlier years. Nevertheless, this study showed that the majority of MDS patients needed regular blood transfusions while receiving treatment and it provides valuable information about transfusion burden in all MDS patients in a population-based setting.

In summary, this study showed that in a real-life population of MDS patients, almost half of the MDS patients had a transfusion burden of  $\geq 8$  RBC units in 16 weeks. This study identified patients  $>65$  years old, high-risk MDS patients, and patients with MDS-MLD or MDS-EB to be at increased risk for developing HTB, but HTB was observed in all MDS subtypes and both low-risk MDS and high-risk MDS patients, demonstrating that the entire MDS population might benefit from novel agents that reduce the need for transfusions. We encourage the development of new therapies that could benefit the entire MDS population.


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## CONFLICT OF INTEREST

JR has disclosed financial support by Celgene for attendance of MDS Foundation meeting in 2019. All other authors have disclosed no conflicts of interest.

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## REFERENCES

- Balducci L. Transfusion independence in patients with myelodysplastic syndromes: impact on outcomes and quality of life. *Cancer*. 2006;106:2087–94.
- McQuilten ZK, Polizzotto MN, Wood EM, Sundararajan V. Myelodysplastic syndrome incidence, transfusion dependence, health care use, and complications: an Australian population-based study 1998 to 2008. *Transfusion*. 2013;53:1714–21.
- Dinmohamed AG, Visser O, van Norden Y, Huijgens PC, Sonneveld P, van de Loosdrecht AA, et al. Trends in incidence, initial treatment and survival of myelodysplastic syndromes: a population-based study of 5144 patients diagnosed in The Netherlands from 2001 to 2010. *Eur J Cancer*. 2014;50:1004–12.
- 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.
- Steensma DP. Myelodysplastic syndromes current treatment algorithm 2018. *Blood Cancer J*. 2018;8:1–7.
- Zeidan AM, Stahl M, Sekeres MA, Steensma DP, Komrokji RS, Gore SD. A call for action: increasing enrollment of untreated patients with higher-risk myelodysplastic syndromes in first-line clinical trials. *Cancer*. 2017;123:3662–72.
- Angelucci E, Li J, Greenberg P, Wu D, Hou M, Montano Figueroa EH, et al. Iron chelation in transfusion-dependent patients with low- to intermediate-1-risk myelodysplastic syndromes: a randomized trial. *Ann Intern Med*. 2020;172:513–22.
- Kibbelaar RE, Oortgiesen BE, van der Wal-Oost AM, Boslooper K, Coebergh JW, Veeger NJGM, et al. Bridging the gap between the randomised clinical trial world and the real world by combination of population-based registry and electronic health record data: a case study in haemato-oncology. *Eur J Cancer*. 2017;86:178–85.
- Platzbecker U, Fenaux P, Ades L, Giagounidis A, Santini V, van de Loosdrecht AA, et al. Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. *Blood*. 2019;133:1020–30.
- Platzbecker U, Germing U, Gotze KS, Kiewe P, Mayer K, Chromik J, et al. Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study. *Lancet Oncol*. 2017;18:1338–47.
- 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.
- Braga Lemos M, Rodrigues SR, Schroeder T, Kulasekararaj AG, Matos JE, Tang D. Association between red blood cell transfusion dependence and burden in patients with myelodysplastic syndromes: a systematic literature review and meta-analysis. *Eur J Haematol*. 2021;14:3–23.

13. Zeidan AM, Zhu W, Stahl M, Wang R, Huntington SF, Giri S, et al. RBC transfusion independence among lower risk MDS patients receiving hypomethylating agents: a population-level analysis. *Leuk Lymphoma*. 2019;7:1–7.
14. Bewersdorf JP, Zeidan AM. Evolving therapies for lower-risk myelodysplastic syndromes. *Ann Hematol*. 2020;99:677–92.
15. Novel drug approvals for 2019 [homepage on the Internet]. 2020. Available from: <https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biologic-al-products/novel-drug-approvals-2019>.
16. Fenaux P, Kiladjian JJ, Platzbecker U. Luspatercept for the treatment of anemia in myelodysplastic syndromes and primary myelofibrosis. *Blood*. 2019;133:790–4.
17. Reblozyl—european medicines agency [homepage on the Internet]. 2020 Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/reblozyl>.
18. de Vries R, Haas F. Working group for revision of the Dutch blood transfusion guideline 2011. English translation of the dutch blood transfusion guideline 2011. *Clin Chem*. 2012;58:1266–7.
19. Gale RP, Barosi G, Barbui T, Cervantes F, Dohner K, Dupriez B, et al. What are RBC-transfusion-dependence and -independence? *Leuk Res*. 2011;35:8–11.
20. Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the international working group (IWG) response criteria in myelodysplasia. *Blood*. 2006;108:419–25.
21. Savona MR, Malcovati L, Komrokji R, Tiu RV, Mughal TI, Orazi A, et al. An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults. *Blood*. 2015;125:1857–65.
22. Malcovati L, Germing U, Kuendgen A, Della Porta MG, Pascutto C, Invernizzi R, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. *J Clin Oncol*. 2007;25:3503–10.
23. Malcovati L, Porta MG, Pascutto C, Invernizzi R, Boni M, Travaglino E, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. *J Clin Oncol*. 2005;23:7594–603.
24. Wood EM, McQuilten ZK. Outpatient transfusions for myelodysplastic syndromes. *Hematology Am Soc Hematol Educ Program*. 2020;1:167–74.
25. Rozema J, Slim CL, Veeger NJGM, Kibbelaar RE, de Wit H, van Roon EN, et al. A clinical effect of disease-modifying treatment on alloimmunisation in transfused patients with myelodysplastic syndromes: data from a population-based study. *Blood Transfus*. 2020;16.
26. Stauder R, Yu G, Koinig KA, Bagguley T, Fenaux P, Symeonidis A, et al. Health-related quality of life in lower-risk MDS patients compared with age- and sex-matched reference populations: a European Leukemia Net study. *Leukemia*. 2018;32:1380–92.
27. Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012;120:2454–65.
28. van de Loosdrecht AA, Huls G, Wijermans P, Löwenberg B, Jongen-Lavrencic M, De Witte T, et al. Het myelodysplastisch syndroom: richtlijnen voor therapie 2013. *Ned Tijdschr Hematol*. 2013;10:43.
29. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials*. 1996;17:343–6.
30. Komrokji RS. Luspatercept in myelodysplastic syndromes: who and when? *Hematol Oncol Clin North Am*. 2020;34:393–400.
31. Steensma DP, Fenaux P, Van Eygen K, Raza A, Santini V, Germing U, et al. Imetelstat achieves meaningful and durable transfusion independence in high transfusion-burden patients with lower-risk myelodysplastic syndromes in a phase II study. *J Clin Oncol*. 2020;27:JCO2001895.
32. Zhao J, Dahlén T, Edgren G. Costs associated with transfusion therapy in patients with myelodysplastic syndromes in Sweden: a nationwide retrospective cohort study. *Vox Sang*. 2020;116:581–90.
33. Moreno Berggren D, Folkvaljon Y, Engvall M, Sundberg J, Lambe M, Antunovic P, et al. Prognostic scoring systems for myelodysplastic syndromes (MDS) in a population-based setting: a report from the Swedish MDS register. *Br J Haematol*. 2018;181:614–27.

## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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## APPENDIX A.: HemoBase Population Registry Consortium

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