VoxSanguinis
The International Journal of Transfusion Medicine
ISBT International Society of Blood Transfusion
Vox Sanguinis (2021) **116**, 581–590

ORIGINAL PAPER

DOI: 10.1111/vox.13034

Costs associated with transfusion therapy in patients with myelodysplastic syndromes in Sweden: a nationwide retrospective cohort study

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Vox Sanguinis

Received: 1 September 2020, revised 24 October 2020, accepted 2 November 2020, published online 18 November 2020

Abstract

Background and objectives Blood transfusion is a cornerstone therapy for many patients with myelodysplastic syndromes (MDS), but ranges from few to no transfusions to intensive transfusion therapy. To date, no large studies have described transfusion use or costs for patients with MDS, accounting for the range of disease severity.

Materials and methods A nationwide cohort study was conducted with all patients diagnosed with MDS in Sweden between 2008 and 2017, based on the Swedish MDS register and the Swedish part of the Scandinavian Donations and Transfusions Database 3 (SCANDAT3-S). Patients were followed from diagnosis until death, emigration, allogeneic hematopoietic stem cell transplantation or end of follow-up. Average cumulative transfusion count and costs over time were calculated, stratified by the revised international prognostic scoring system (IPSS-R) and age at diagnosis. Costs calculations used data on incident transfusions and laboratory testing and were divided into: direct material costs, direct labour costs and laboratory costs.

Results In total, 2311 patients were included in the cohort. In the first four years after diagnosis, patients in the very low IPSS-R category received on average 25 red cell (95% confidence interval, 20–32) and 4 (3–7) platelet transfusions. Conversely, patients in the very high-risk category received on average 171 (135–200) red cell and 66 (51–78) platelet transfusions. Correspondingly, transfusion costs ranged from $8805 ($6482–$11 625) to $80 106 ($61 460–$95 792).

Conclusion Transfusion count and costs for patients with MDS increased markedly with IPSS-R risk category, but were similar across age groups. Transfusion costs were considerable for the highest IPSS-R risk categories.

Key words: myelodysplastic syndromes, blood transfusion, transfusion costs.

Background

Myelodysplastic syndromes (MDS) are a heterogeneous group of chronic haematological disorders with highly variable clinical presentation [1,2]. Indolent cases of MDS typically present with mild anaemia, often not requiring treatment at all, whilst fulminant cases present with pancytopenia that require intensive transfusion therapy and are associated with high mortality [3]. Using the revised international prognostic scoring system (IPSS-R), patients with MDS can be divided into categories with vastly different prognosis, requiring different therapeutic modalities [4].

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Whilst many patients with MDS respond favourably to erythrocyte stimulating agents, for example erythropoietin analogs, as well as to hypomethylating agents, or to the thalidomide analog lenalidomide, regular blood transfusion remains a cornerstone of therapy [5].

We have previously reported that, on average, blood product costs alone for patients with MDS can exceed 20,000 USD in the first two years after diagnosis [6]. However, prior data did not allow the stratification of patients into different prognostic categories, did not take patient mortality into consideration, and cost estimates only included blood product costs. As patients with MDS span from requiring little to no transfusion therapy to intensive transfusion therapy over multiple years, more detailed characterization of transfusion patterns and costs is needed for transfusion planning, as well as health economic analyses of treatment alternatives.

Therefore, we used nationwide registers in Sweden to investigate patterns of transfusion use in MDS patients, stratified by the revised international prognostic scoring system, IPSS-R. Furthermore, using incident data on transfusions and laboratory results, we produced comprehensive estimates of transfusion costs, including costs of blood products, disposables, laboratory testing and labour costs.

Methods and materials

Setting, data sources and record linkages

All patients diagnosed with MDS in Sweden were identified through the Swedish MDS register, a nationwide quality-of-care register, which also included details on date of diagnosis, and disease characteristics, and the IPSS-R score [7]. Data linkages to other registers and databases were conducted using national registration numbers (NRNs) [8]. Data on all administered blood transfusions were ascertained from Swedish part of the recently updated Scandinavian Donations and Transfusions (SCANDAT3-S) database [9]. The SCANDAT3-S database included the date and type of all transfusions as well as results from blood typing, antibody screening and antibody identification panels for all patients in the MDS cohort. Dates for hospital stays were extracted from the National Patient Register, to differentiate between inpatient and outpatient transfusions, and admissions for allogeneic hematopoietic stem cell transplantations were identified using procedure codes (DR041, DR042, DR044, DR045, DR046 and DR047). Vital status and any dates of emigration and death were determined through linkages to national population registers.

Study design

Analyses were restricted to patients diagnosed with MDS between 2008 and 2017. We excluded patients without a known IPSS-R category, as well as patients who were not recorded to be living in Sweden at the time of their diagnosis. Patients were followed from the date of their MDS diagnosis until death, emigration or end of follow-up (December 31, 2017), whichever occurred first. Follow-up was also terminated upon being admitted to hospital for hematopoietic stem cell transplantation, using date of admission as the date of transplantation.

Calculation of costs

Transfusion costs were divided into three groups: direct material costs for blood products and disposables, direct labour costs and additional transfusion-related laboratory costs.

Direct material costs were calculated using data on incident transfusions based on the type of blood product. Cost for intravenous infusion sets was added for each day of transfusion, as they are typically reused for multiple transfusions for the same patient in the same day. Costs for both blood products and disposables were determined from publicly available regional price lists from Stockholm, Sweden (Appendix 1).

Direct labour costs were calculated based on a previously published approach, which was modified to allow differential costs for inpatient and outpatient transfusions [10]. Labour costs were calculated as the product of the median hourly cost to employ a registered nurse, based on publicly available data from the Stockholm Regional Council in Sweden, and the approximate time taken to administer the transfusion. Based on previously published data and supplemental interviews with head nurses in haematological inpatient and outpatient clinics at a major hospital in Stockholm, Sweden, four different administration times were estimated depending on whether it was the first transfusion on a given day or the second, or later unit, and whether they were administered in an inpatient or outpatient setting. Due to variation and uncertainty in administration time, a lower and upper range was established for each of the four administration scenarios. For details, see Appendix 2.

Additional transfusion-related laboratory costs were calculated based on incident data on laboratory tests, including blood typing and antibody screening (Appendix 3). Positive antibody screening incurred a one-time cost for an antibody identification panel, and cross-matching costs for subsequent red cell transfusions. Costs were determined from public price lists. Currency

conversion from SEK to USD was done using mid-2018 conversion rate of 8·998 SEK to 1 USD.

Statistical analysis

For both transfusions and transfusion costs, the number of persons in the study was calculated per day, to account for the high mortality of the MDS population. Patients who emigrated, underwent hematopoietic stem cell transplantation or died were excluded at the end of the day. The daily mean number of transfusions was calculated as the number of transfusions in each day divided by the number of people alive at the beginning of the day; these were accrued to form the expected cumulative number of transfusions. The expected cumulative transfusion cost was calculated in a similar fashion. Both the cumulative number of transfusions and the ensuing cumulative cost were calculated per day since diagnosis, stratified by IPSS-R category and age at diagnosis (<65 years, 65–80 years, >80 years). Costs were also calculated separately for only red cell transfusions.

For all analyses, 95% confidence intervals were calculated using bootstrapping, with 10,000 runs. The presented confidence intervals for transfusion costs were modified in such a way that the lower range for nurse administration times was used for the lower bound of the confidence interval and the upper range for nurse administration times for the upper bound of the confidence interval. The figures are censored when there were less than 10 persons in study.

The proportion of transfusions conducted inpatient, including confidence intervals, was calculated using logistic regression, with time since diagnosis modelled as a restricted cubic spline (with knots at 0, 3, 7, 180, 360, 720, 1460 days).

All data processing and statistical analyses were performed using SAS Statistical Analysis Software, version 9.4 (Cary, NC, USA). The creation of the SCANDAT3-S database and the conduct of this study was approved by the regional ethics committee in Stockholm, Sweden and the Swedish Ethics Review Authority (ref. nr. 2018/167-31, 2019-02636).

Results

We identified a total of 2858 patients with a diagnosis of MDS between 2008 and 2017 from the Swedish MDS register. After excluding patients who had an unknown date of diagnosis (N = 1), no recorded IPSS-R score (N = 449), a diagnosis date after date of death (N = 1), a prior allogenic hematopoietic stem cell transplantation (HSCT) (N = 3), or who were not recorded to be living in Sweden at the time of their diagnosis (N = 93), a total of 2311 patients remained for analysis.

Baseline characteristics of the study cohort, stratified by IPSS-R score, are presented in Table 1. There were 423 (18·3%), 741 (32·1%), 463 (20·0%), 364 (15·8%) and 320 (13·8%) patients in the very low, low, intermediate, high and very high prognostic categories, respectively. The proportion of females ranged from 34·8% in the very low-risk group to 46·3% in the very high-risk group, and the mean age from 74·4 years (standard deviation [SD], 9·5) in patients with low risk, to 71·0 years (SD, 12·8) in patients with very high risk. The median length of follow-up was progressively shorter with higher IPSS-R score, ranging from 2·4 years (interquartile range [IQR], 1·2–4·5) in patients with very low-risk disease, to 0·5 years (IQR, 0·3–1·0) in patients with very high-risk disease.

The average cumulative number of transfusions stratified by IPSS-R at diagnosis is presented in Table 2. Further stratification by age at diagnosis, is presented in Figure 1. Frequency of red cell and platelet transfusions increased with higher IPSS-R category, whereas plasma transfusions were rare in all IPSS-R categories. Amongst patients in the very low category, those >80 years at diagnosis received more red cell transfusions but fewer platelet transfusions compared to those <65 years, on average. Interestingly, the number of transfusions was otherwise similar between age groups within the same IPSS-R prognosis category. In the first 4 years after diagnosis, patients in the very low-risk category overall received 25 red cell (95% confidence interval [CI], 20–32), and 4 platelet transfusions (95% CI, 3–7), whereas patients younger than 65 years at diagnosis received on average 16 red cell (95% CI, 9–25) and 9 platelet (95% CI, 3–16) transfusions. Conversely, patients in the very high-risk category had on average 171 red cell (95% CI, 135–200) and 66 platelet transfusions (95% CI, 51–78) 4 years after their diagnosis. More than half of patients younger than 65 years of age in the intermediate, high and very high categories underwent HSCT (53%, 53% and 52%, respectively), and very few remained in the study after 2 years since diagnosis (22, 5 and 2 patients, respectively). Amongst patients older than 80 years at diagnosis in the high and very high-risk categories, few remained alive after two years after diagnosis; however, none underwent HSCT.

The average cumulative cost of transfusions stratified by IPSS-R category is presented in Table 3 and further stratified by age group at diagnosis in Figure 2. Trends in transfusion costs are congruent with transfusion trends and increased with increasingly severe IPSS-R category at diagnosis. Across all age groups, transfusion costs were highest on average for the very high-risk category,

Table 1 Baseline characteristics of study population

	IPSS-R Risk score				
	Very low risk	Low risk	Intermediate risk	High risk	Very high risk
No. subjects (% of total)	423 (18·3)	741 (32·1)	463 (20·0)	364 (15·8)	320 (13·8)
Females, N (%)	147 (34·8)	310 (41·8)	179 (38·7)	149 (40·9)	148 (46·3)
Age at diagnosis, N (%)					
<65 years	63 (14·9)	116 (15·7)	93 (20·1)	92 (25·3)	81 (25·3)
65–79 years	232 (54·8)	398 (53·7)	267 (57·7)	188 (51·6)	165 (51·6)
≥80 years	128 (30·3)	227 (30·6)	103 (22·2)	84 (23·1)	74 (23·1)
Mean, years (SD)	74·2 (9·5)	74·4 (9·5)	71·9 (10·6)	70·3 (12·9)	71·0 (12·8)
Length of follow-up, N (%)					
<1 year	169 (40·0)	346 (46·7)	319 (68·9)	321 (88·2)	297 (92·8)
1–4 years	164 (38·8)	274 (37·0)	120 (25·9)	39 (10·7)	21 (6·6)
≥5 years	90 (21·3)	121 (16·3)	24 (5·2)	4 (1·1)	2 (0·6)
Median, years (IQR)	2·4 (1·2–4·5)	2·1 (1·1–3·8)	1·2 (0·4–1·4)	0·8 (0·4–1·4)	0·5 (0·3–1·0)
Hematopoietic transplant during follow-up, N (%)	11 (2·6)	41 (5·5)	69 (14·9)	62 (17·0)	53 (16·6)

Table 2 Cumulative average number of transfusions over time, stratified by IPSS-R category at diagnosis.

	Duration of follow-up				
IPSS-R score	**90 days**	**1 year**	**2 years**	**3 years**	**4 years**
Average no. of red cell transfusions (95% confidence limit)					
Very low	1 (1–1)	4 (3–5)	10 (8–13)	17 (14–21)	25 (20–32)
Low	3 (2–3)	11 (10–13)	26 (23–29)	41 (36–45)	56 (50–63)
Intermediate	4 (4–5)	20 (18–22)	39 (35–45)	61 (54–70)	85 (73–99)
High	9 (9–11)	35 (32–39)	72 (65–81)	102 (90–117)	136 (111–165)
Very high	13 (12–14)	44 (40–50)	82 (74–93)	135 (119–153)	171 (135–200)
Average no. of platelet transfusions (95% confidence limit)					
Very low	0 (0–0)	1 (0–1)	2 (1–3)	3 (2–5)	4 (3–7)
Low	0 (0–1)	2 (1–2)	4 (3–5)	7 (5–10)	10 (7–14)
Intermediate	1 (1–2)	6 (5–7)	12 (10–16)	17 (14–22)	22 (17–28)
High	3 (2–4)	12 (10–15)	24 (20–30)	34 (26–44)	45 (31–63)
Very high	5 (5–6)	20 (17–24)	34 (28–41)	62 (49–77)	66 (51–78)
Average no. of plasma transfusions (95% confidence limit)					
Very low	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–1)
Low	0 (0–0)	0 (0–0)	0 (0–1)	1 (0–2)	1 (0–2)
Intermediate	0 (0–0)	0 (0–1)	1 (0–1)	1 (1–1)	1 (1–2)
High	1 (0–1)	1 (1–2)	1 (1–2)	2 (1–3)	2 (1–4)
Very high	0 (0–0)	0 (0–1)	0 (0–1)	1 (0–1)	1 (0–1)

amounting to $80 106 (95% CI, $61 460–95 792), and lowest in the very low-risk category, amounting to $8805 (95% CI, $6482–11 625) after four years. Costs for red cell transfusion support only is presented in Appendix 4.

The proportion of transfusions given in an inpatient setting is shown in Figure 3. Trends were similar for all IPSS-R groups, with a higher proportion of transfusions given inpatient during the first months after diagnosis that stabilized to around 30% after about half a year.

Discussion

In this nationwide cohort study of transfusion patterns and costs for patients with HSCT-naïve MDS, average

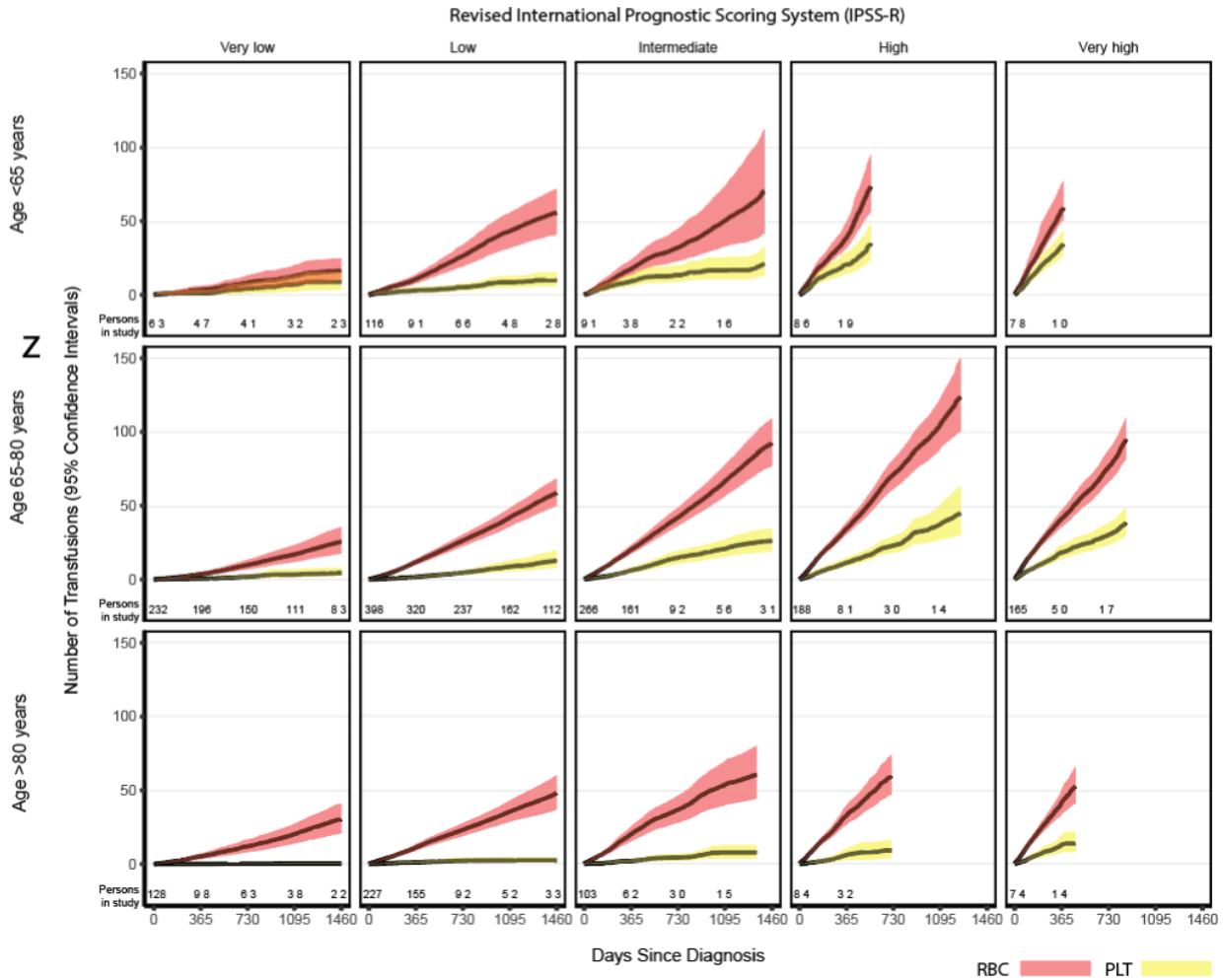

Figure 1 Cumulative mean number of RBC and PLT transfusions over time, stratified by IPSS-R and age at diagnosis. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 3 Total costs of transfusion therapy during follow-up, stratified by IPSS-R category at diagnosis

	Duration of follow-up				
	90 days	**1 year**	**2 years**	**3 years**	**4 years**
IPSS-R score	Average total cost in USD* (95% confidence limit)				
Very low	337 (186–538)	1335 (947–1810)	3600 (2567–4798)	6191 (4451–8201)	8805 (6482–11 625)
Low	864 (671–1088)	3941 (3231–4728)	8937 (7402–10 632)	14 631 (11 882–17 764)	20 184 (16 127–25 098)
Intermediate	1894 (1481–2368)	8341 (6863–9997)	17 072 (13 888–20 631)	25 457 (20 562–30 888)	34 068 (27 334–41 877)
High	4074 (3320–4941)	15 850 (13 252–18 720)	31 964 (26 371–38 486)	45 629 (36 925–56 061)	60 514 (44 936–80 410)
Very high	6121 (5226–7094)	22 560 (18 929–26 616)	39 862 (33 155–47 863)	69 034 (55 711–84 334)	80 106 (61 460–95 792)

*Using mid-2018 SEK to USD exchange rate of 8·9984.

costs for transfusions in the first 4 years after diagnosis were found to be as high as $80 106 for patients in the very high IPSS-R prognostic category and as low as $8805 for patients in the very low prognostic category.

As far as we know, this is the largest and most detailed study of transfusion costs in this patient group. Our method for calculating costs expands on previously reported methods, by differentiating between inpatient

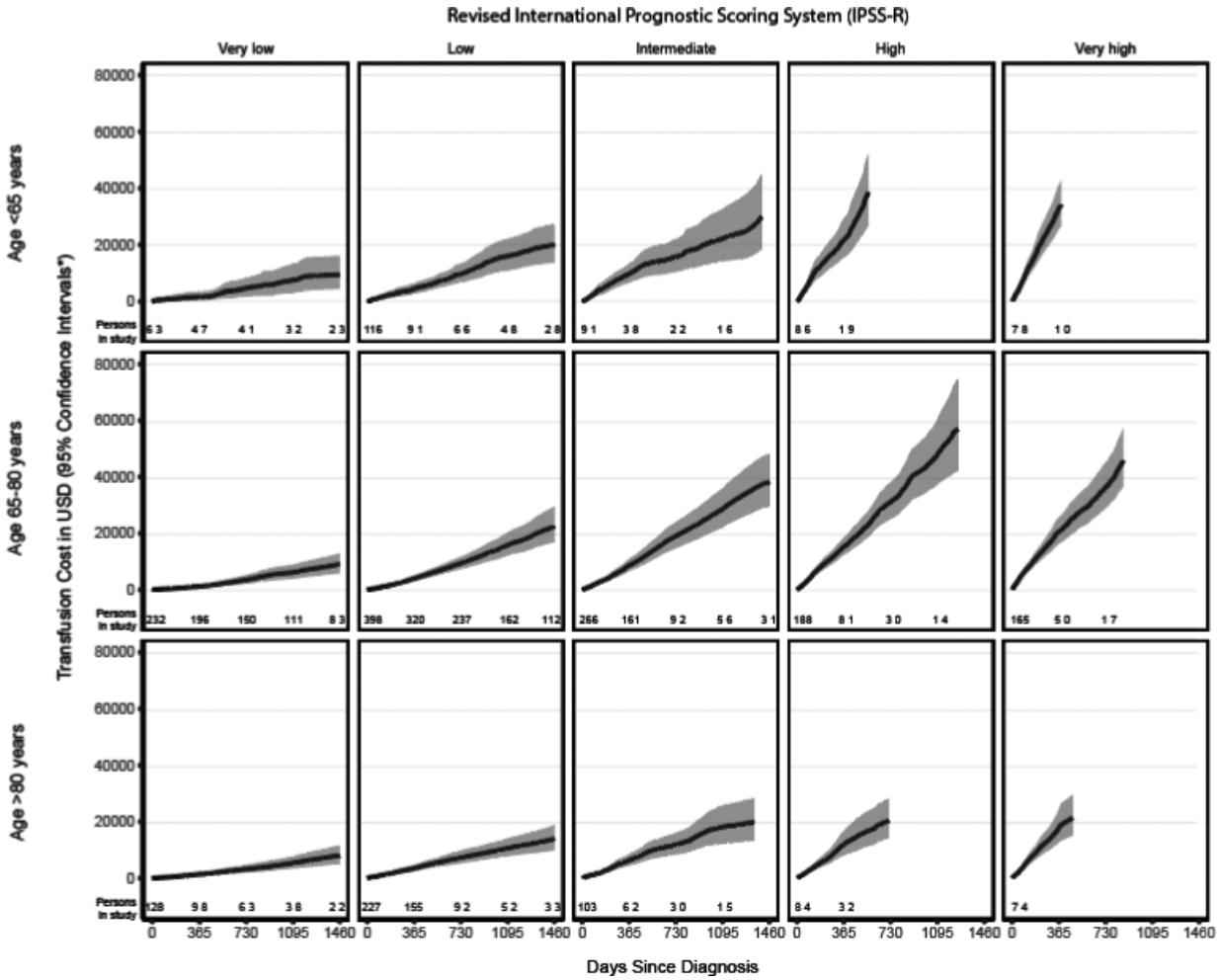

Figure 2 Cumulative mean cost of transfusions in USD over time, stratified by IPSS-R and age at diagnosis. *Upper and lower confidence interval uses the upper and lower bound of nurse administration time, respectively.

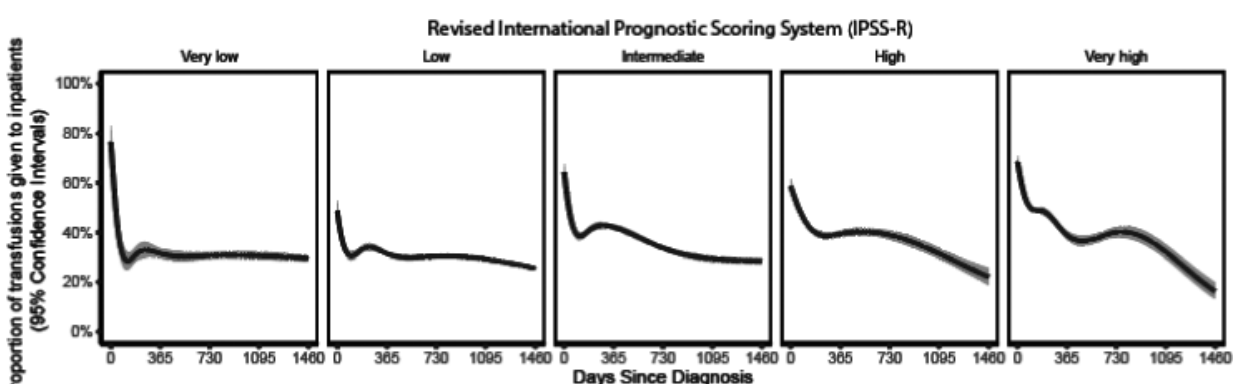

Figure 3 Proportion of transfusions in an inpatient setting, stratified by IPSS-R.

and outpatient transfusions, as well as incorporating results from antibody screening to include costs for cross-matching and antibody panels. Furthermore, we incorporate the high mortality of the MDS patients by calculating transfusion counts and costs daily. Interestingly, transfusion incidence and cost were mainly driven

by IPSS-R risk category, whereas it was generally similar across age groups within the same IPSS-R category.

In a previous study, blood product costs for MDS patients were calculated to exceed 20 000 USD in the first 2 years after diagnosis [6]. However, there are several differences that lead to differential results in this study. Firstly, the previous study included only blood product costs and did not include costs for laboratory testing, labour or materials. Secondly, the previous study did not stratify on disease severity and was an average across different age groups. Thirdly, the previous study calculated average costs based on the number of patients at baseline which may lead to a downward bias in costs, particularly if mortality is high. In this study, we compensated for mortality by using the number of patients at risk of transfusions, updated daily, as the denominator. Finally, the previous study used data from 2000 to 2010, whereas this study uses more contemporary data from 2008 to 2017. As such, the figures are not directly comparable, and this study offers a more accurate characterization of transfusion incidence and costs for patients with MDS. Furthermore, whilst we have earlier reported that transfusion costs were markedly higher in older patients above 65 years at diagnosis, we show here that this is no longer the case after incorporating patient mortality and disease severity [6].

The major strengths include the use of incident transfusions, as well as transfusion laboratory tests and results from a nationwide transfusion database, together with data on IPSS-R prognosis categories from nationwide quality registers, to calculate transfusion costs. Furthermore, using national health and population registers, we were able to identify the date for migration, HSCT and death. This allowed us to use the average transfusion count and cost on a daily basis, as weekly or monthly time-periods would likely underestimate the results due to the high mortality.

There are several limitations to the study. Firstly, costs are limited to blood product costs, direct labour costs and additional transfusion-related laboratory costs. We did not incorporate societal costs in a wider sense (e.g. costs for donor transportation and absence from work), or costs for possible transfusion complications. Costs for relevant medications, such as erythropoietin analogs and iron chelation, which may affect or be necessitated by long-term transfusions therapy, are also not included. Following Nordic MDS group guidelines, iron chelation is typically indicated if ferritin levels are above 1500 μg/L, or after approximately 25 red cell transfusions [11]. More indirect costs such as cost of hospital facilities or equipment were not included as they are largely determined by local circumstance, such as cost of rent, resource utilization rates, and alternative costs for resources and assets. Secondly, the cost algorithms assume that all first-time positive antibody screens lead to one antibody panel and cross-matching for subsequent units, disregarding more complex scenarios with positive direct antiglobulin tests, or need for additional antibody panels or blood group genotyping. Thirdly, we do not account for the need of phenotype-matched blood products, which are typically at least twice as expensive. Our projected costs therefore likely underestimate true costs, but the extent of the underestimation is difficult to assess without more detailed clinical data and may vary according to local circumstances.

At the same time, we were not able to differentiate transfusions necessitated by the disease *per se* from transfusions driven by other indications such as high-dose chemotherapy. Whilst we did censor follow-up upon undergoing transplantation, the available data do not reliably capture other instances of chemotherapy and therefore does not allow the same strategy to remove transfusions due to cytopenia following chemotherapy, including patients that may have transformed to acute myeloid leukaemia. We speculate that transfusions given for such indications would predominantly be seen in the higher risk categories and that interpretation of blood use and costs in these groups must consider such effects, whilst likely having less impact on lower risk categories. In conclusion, in this nationwide study on costs associated with blood transfusions in patients with MDS, higher risk IPSS-R prognosis category at diagnosis was associated with significant costs. On average in the first 4 years, transfusion costs ranged from $8805 to $80 106.

Acknowledgements

We are greatly indebted to all the blood banks in Sweden for both collecting and contributing data to this study. Furthermore, we would like to thank Roland Fiskesund MD PhD (Region Stockholm) for information on costs associated with transfusions. JZ and GE performed the data collection. JZ, TD, and GE designed the study, performed the analyses, and wrote the manuscript.

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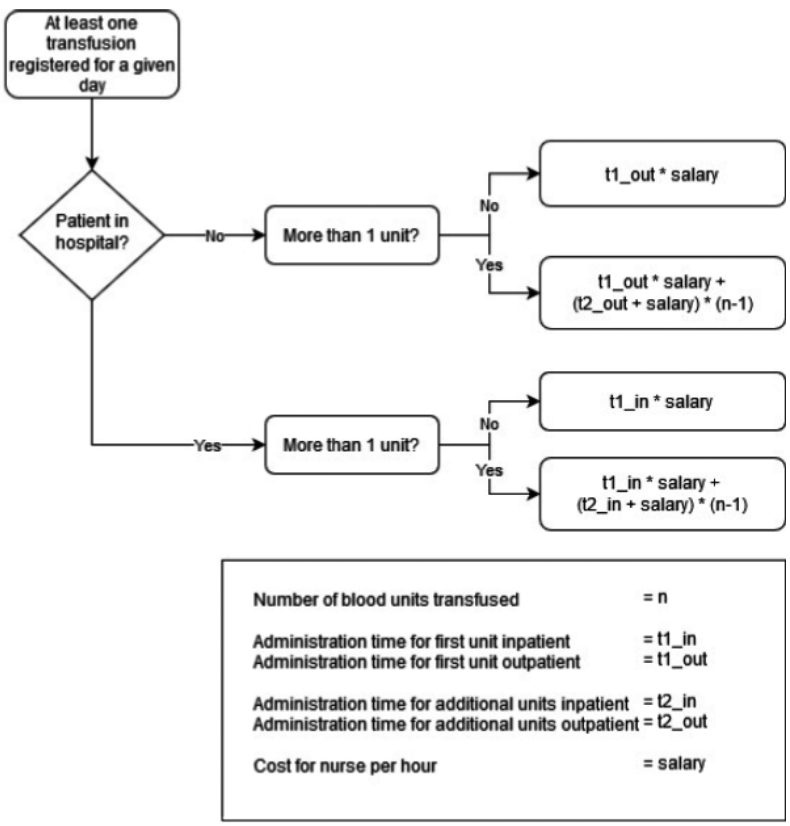
Appendix 1 Cost modelling inputs

Item	Costs (SEK/USD)*
Blood products and disposables	
Red cells	1523 SEK/$169
Platelets	4751 SEK/$528
Plasma	846 SEK/$94
IV administration sets	100 SEK/$11
Labour	
Nurse median cost per hour**	254 SEK/$28
Laboratory	
Blood typing and antibody screening	390 SEK/$43
Antibody identification panel	803 SEK/$89
Cross test per unit	282 SEK/$31
Activity	Time (lower-upper limits)
Inpatient setting	
First administered unit	60 min (30–90 min)
Additional units	24 min (18–30 min)
Outpatient setting	
First administered unit	90 min (60–120 min)
Additional units	60 min (30–90 min)

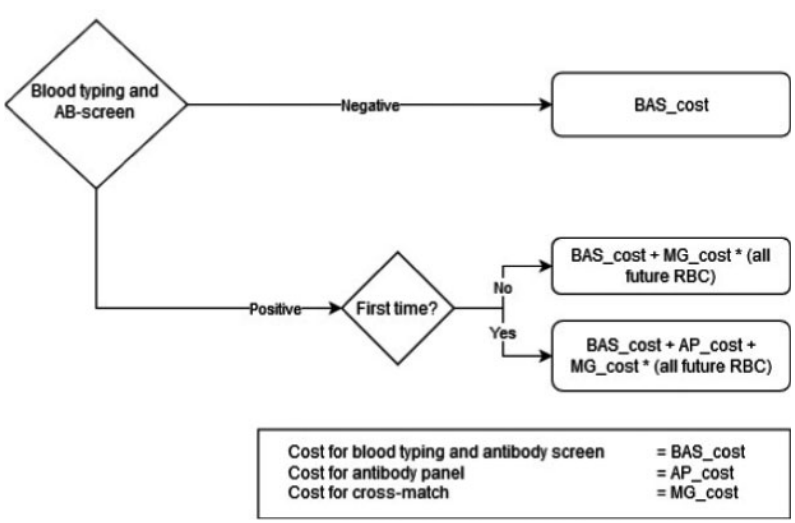
NOTES

*Using mid-2018 SEK to USD exchange rate of 8·9984.
**Sum of salary employer and employers' social security contribution.

Appendix 2 Algorithm for direct labour costs



Appendix 3 Algorithm for transfusion laboratory costs.



Appendix 4 Total costs of red cell transfusion therapy during follow-up, stratified by IPSS-R category at diagnosis.

	Duration of follow-up				
	90 days	**1 year**	**2 years**	**3 years**	**4 years**
IPSS-R score	*Average total cost in USD* (95% confidence limit)*				
Very low	200 (186–215)	1020 (944–1096)	2597 (2402–2792)	4376 (4049–4704)	6413 (5934–6891)
Low	652 (604–700)	2924 (2708–3141)	6584 (6095–7074)	10 455 (9676–11 233)	14 401 (13 328–15 474)
Intermediate	1126 (1045–1207)	4980 (4615–5345)	9948 (9211–10 685)	15 508 (14 352–16 663)	21 515 (19 903–23 128)
High	2340 (2170–2511)	8884 (8235–9533)	18 351 (17 004–19 698)	26 055 (24 131–27 980)	34 570 (32 013–37 127)
Very high	3116 (2892–3340)	11 010 (10 212–11 808)	20 683 (19 172–22 194)	33 909 (31 423–36 395)	42 958 (39 794–46 122)

NOTES

*Using mid-2018 SEK to USD exchange rate of 8·9984.