Red blood cell transfusion dependence is associated with greater healthcare resource utilization, higher medical cost, and poorer prognosis in patients with lower-risk myelodysplastic syndromes: a 28-Year retrospective observation study result

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Introduction

- Myelodysplastic syndromes (MDS) are a group of clonal hematopoietic neoplasms that cause cytopenia and morphologic dysplasia in bone marrow (BM), leading to a higher risk of acute myeloid leukemia (AML) or early mortality.[1]
- MDS patients frequently develop refractory anemia with red blood cell transfusion dependence (RBC TD), which may increase the risk of leukemic progression, cardiac complications, and subsequent early mortality. These risks are more prominent in patients with lower-risk MDS (LR-MDS) than in those with higher-risk MDS (HR-MDS).[2-7]
- Erythropoiesis-stimulating agents (ESAs) have been used to treat anemia in MDS patients, but they may only be effective for those with endogenous EPO levels <200U/L.[8-9] The median response duration is limited, with reported ranging from 6 to 18 months.[10-13].
- There are few reports on the economic burden of RBC TD and its impact on healthcare resource use (HCRU) in patients with LR-MDS.
- We conducted a 28-year retrospective observational study to determine the burden of RBC TD in terms of HCRU use, medical cost, and clinical outcomes among Korean patients with LR-MDS.

Objectives

- Primary Objective: To compare RBC transfusion burden in terms of HCRU and medical cost between TD and non-TD (NTD) LR-MDS patients in South Korea.
- Secondary objective: To evaluate clinical outcomes of LR-MDS in terms of treatment pattern, ESA response, overall survival (OS), and AML-free survival (AFS) in South Korea.

Methods

Study design

- Retrospective observational study using the electronic medical record (EMR) and expense database of Samsung Medical Center (SMC) between Sep 1, 1994 and Sep 30, 2022 (observation period) **(Figure 1a).**
- Index date was defined as the date of the first documented diagnosis of MDS in the EMR database of SMC between Sep 1, 1994 and Apr 1, 2022 (baseline period) **(Figure 1a).**
- After the index date, the earliest laboratory result before initiating treatment was defined as the baseline laboratory value.

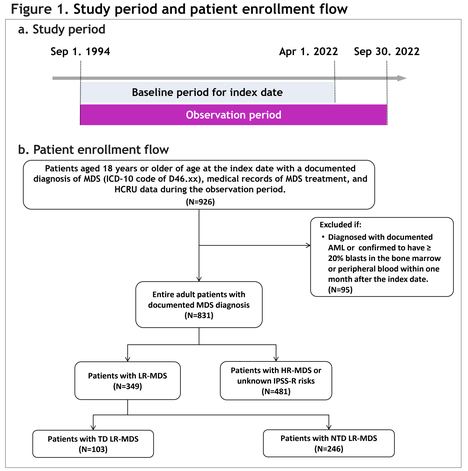
Population

- Adult patients who were newly diagnosed with and initiated treatment for MDS at SMC during index period.

Inclusion and exclusion criteria

- Patients were included in the study if both following criteria were met **(Figure 1b)**.
  - Patients who were at least 18 years old and had a documented diagnosis of MDS (ICD-10 code of D46.X) during the baseline period at SMC.
  - Patients who had medical records of MDS treatment and HCRU data during the observation period at SMC.
- Patients were excluded from the study if the patient was diagnosed with documented AML or confirmed to have ≥ 20% blasts in the bone marrow or peripheral blood within a month after the index date **(Figure 1b).**

Figure 1. Study period and patient enrollment flow



Outcomes of interest

- **Primary endpoints**
  - HCRU indices per 1,000 person-years
    - No. of outpatient visits, emergency room visits, and hospitalizations
    - Days of hospital stay
    - Required units of RBC transfusion
  - Medical costs in USD per 1,000 person-years (accessible from 2001)
    - Total cost, outpatient cost, emergency room cost and hospitalization cost
    - All cost data were adjusted to the 2022 value according to the South Korean consumer price index (CPI) and converted to US dollars (USD) using the 2022 currency exchange rate as 1USD=1,205.25 Korean Won (KRW).
- **Secondary endpoints**
  - ESA treatment response including no initial response, permanent discontinuation, and ≥8-week or ≥16-week RBC transfusion independence (TI) achievement during consecutive ESA treatment.
    - Since ESA treatment is recommended for only patients with EPO levels ≤ 500 U/L by Korean national health insurance (NHI) reimbursement criteria, patients with baseline EPO levels ≤500 U/L were selected to estimate the response to subsequent ESA treatment.
  - OS and AFS
    - OS was estimated from the index date of MDS diagnosis to the date of documented death.
    - AFS was estimated from the index date of MDS diagnosis to the date of documented death or the diagnosis of AML progression. AML progression was defined as the documented AML diagnosis or BM blasts ≥20%, whichever comes first.
    - OS and AFS from the first TD event were also estimated in TD LR-MDS patients to approximate the impact of TD on prognosis.

Definitions

- **Baseline risk categorization**
  - Using the revised international prognostic scoring system (IPSS-R), patients were scored and categorized into LR- and HR-MDS as follows **(Fig 1b)**.
    - LR-MDS: very low, low or intermediate risks
    - HR-MDS: high or very high risks
- **RBC TD**
  - The occurrence of any 16-week period with RBC transfusion of ≥2 units per 8 weeks, without a consecutive 56-day period without transfusion.
  - Patients who experienced an RBC TD event at least once was categorized to TD group while the others were to NTD group
- **No initial response to ESA is defined as one of the following criteria.**
  - Lack of 1.5g/dL or greater increase in Hb levels in the absence of RBC transfusion after the initial 8 weeks (±7 days, 49 to 63 days) of ESA treatment, when compared to the most recent ESA-naïve Hb levels prior to commencing ESA administration.
  - Lack of a reduction in RBC transfusion during the initial 8 weeks of ESA treatment, in comparison to the 8 weeks preceding the initiation of ESA administration.
- **Permanent discontinuation of ESA treatment**
  - A cessation of ESA use longer than 120 days without any subsequent re-initiation of ESA treatment during the entire observation period.

Statistical analysis

- Baseline characteristics, treatment pattern, and clinical outcomes are reported with observed rates with 95% confidence intervals (95% CIs).
- In LR-MDS patients, TD and NTD patients were compared to evaluate baseline characteristics, HCRU, medical cost, and clinical outcomes.
- HCRU and medical cost data were analyzed per 1,000 person-years.
- As appropriate, Wilcoxon's rank sum test was used for continuous variables, and Chi-square or Fisher's exact test for categorical variables.
- OS and AFS were analyzed using Kaplan-Meier methods and log-rank test between TD and non-TD LR-MDS patients from the index day of MDS diagnosis.
- Statistical significance was assessed using a two-sided *P*-value <0.05.

Results

Baseline characteristics

- Out of 831 MDS patients, 543 had baseline IPSS-R scores calculated, and 349 were classified as LR-MDS at baseline; among them, 29.5% (103/349) experienced TD **(Table 1).**
- No significant differences in median age or gender was observed between TD and NTD LR-MDS patients **(Table 1).**
- TD patients had lower baseline hemoglobin levels (8.7g/dL vs 9.4g/dL, *P*=0.0003) and a higher proportion of patients with baseline EPO levels >200U/L (67.1% vs. 37.6%, *P*<0.0001) compared to NTD patients **(Table 1).**
- Median baseline EPO level was also significantly higher in TD patients than in NTD patients (290.5U/L vs 112U/L, *P*<0.001) **(Table 1).**

Median duration of follow-up

- Median durations of follow-up were 116.5 months for TD LR-MDS and 61.1 for NTD LR-MDS patients (*P* <0.0001) **(Table 1).**

Table 1. Baseline Characteristics and median duration of follow-up

	LR-MDS patients		P-value[a]
	TD (N=103)	NTD (N=246)	
Median age, years (95% CI)	61 (57-64)	63 (62-65)	0.161
Male sex, no. (%)	74 (71.8%)	150 (61.0%)	0.053
IPSS-R score group, no. (%)			
Very-Low	6 (5.8%)	36 (14.6%)	
Low	42 (40.8%)	123 (50.0%)	0.003
Intermediate	55 (53.4%)	87 (35.4%)	
Median BM blasts, % (95%CI)	1.5 (1. 0-2.3)	1.2 (1.0-1.5)	0.121
Median hemoglobin level, g/dL (95% CI)	8.7 (8.2-9.1)	9.4 (8.9-9.9)	0.004
Median platelet count, X10³/μL (95% CI)	103 (84-138)	100 (89-114)	0.534
Median ANC, X10³/μL (95% CI)	1.46 (1.23-1.69)	1.56 (1.22-1.80)	0.800
Patients with baseline EPO level data, no.	*76*	*178*	
Median EPO level, U/L (95% CI)	290.5 (255.7-450.0)	112 (88.8-164.0)	0.002
EPO Level category, no. (%)			
0-200U/L	25 (32.9%)	111 (62.4%)	<0.0001
>200U/L	51 (67.1%)	67 (37.6%)	
>200-500U/L	26 (34.2%)	26 (14.6%)	
>500U/L	25 (32.9%)	41 (23.0%)	
Median duration of follow-up, months (95% CI)	116.5 (103.5-129.1)	61.1 (56.6-69.6)	<0.0001

ANC: absolute neutrophil count, BM: bone marrow, CI: confidence interval, EPO: erythropoietin, IPSS-R: revised international prognostic scoring system, LR-MDS: lower-risk myelodysplastic syndrome, NTD: non-transfusion dependent, TD: transfusion-dependent,
[a]Wilcoxon's rank sum test for continuous values and Chi-square test for categorical values

HCRU and medical costs by RBC transfusion burden

- TD patients had higher transfusion burden in terms of HCRU and medical costs compared to non-TD patients across all sub-criteria; notably, the negative impact of RBC TD on HCRU and medical costs was more prominent in lower-risk MDS (LR-MDS) patients compared to what was observed in the all MDS patients **(Table 2)**.

Table 2. HCRU and medical costs by RBC transfusion group

	LR-MDS patients (N=349)		All MDS patients (N=831)	
	TD (N=103)	NTD (N=246)	TD (N=194)	NTD (N=637)
HCRU per 1,000 person-years[a]				
No. of outpatient visits	15,676	8,303	14,671	9,879
No. of hospitalizations	709	456	896	700
No. of emergency room visits	587	328	716	500
Days of hospital stay	13,343	8,272	18,089	12,127
Required units of packed RBC	31,107	7,073	28,191	11,657
Medical cost per 1,000 person-years[a, b]				
Total medical cost, USD	13,501,635	6,086,585	16,673,597	8,461,821
Outpatient cost, USD	6,304,150	2,658,964	6,411,754	3,525,449
Hospitalization cost, USD	10,194,199	8,261,935	13,356,746	11,486,250
Emergency room cost, USD	335,715	228,910	446,963	300,810

HCRU: healthcare resource use, RBC: red blood cell, LR: lower-risk, MDS: myelodysplastic syndrome, NTD: non-transfusion dependent, TD: transfusion dependent, USD: US Dollar
[a]HCRU data were accessible from 1994 while were cost data from 2001.
[b]1 USD = 1,205.25 Korean Won (KRW)

Impact of RBC TD on HCRU and medical costs in TD LR-MDS patients

- In TD LR-MDS patients, HCRU and medical costs increased after an RBC TD event occurred (Table 3).

Table 3. Impact of RBC TD on HCRU and medical costs in TD LR-MDS patients

	TD LR-MDS patients (N=101)	
	Pre-TD	Post-TD
HCRU per 1,000 person-years[a]		
No. of outpatient visits	15,780	24,645
No. of hospitalizations	484	1,318
No. of emergency room visits	672	1,152
Days of hospital stay	4,354	26,495
Required units of packed RBC	10,920	45,390
Medical cost per 1,000 person-years[a, b]		
Total medical cost, USD	6,094,896	9,696,803
Outpatient cost, USD	4,427,825	7,427,134
Hospitalization cost, USD	7,694,993	18,842,667
Emergency room cost, USD	329,244	573,497

HCRU: healthcare resource use, RBC: red blood cell, LR: lower-risk, MDS: myelodysplastic syndrome, TD: transfusion dependent, USD: US dollar
[a]HCRU data were accessible from 1994 while were cost data from 2001.
[b]1 USD = 1,205.25 Korean won (KRW); all cost data were adjusted to 2022 value.

ESA treatment pattern and outcomes in TD LR-MDS patients

- Among 76 TD LR-MDS patients with baseline EPO levels, 51 (67.1%) had EPO levels ≤500U/L **(Table 1).**
- Darbepoetin-α was the only ESA used for MDS patients.
- Only 20 patients with baseline EPO levels ≤500 U/L received ESA treatment after the first TD event and their median baseline EPO level was 283.0U/L **(Table 4).**
- Although 85% of them (17/20) failed to achieve the initial response at 8 weeks of ESA use, median accumulative time of ESA prescription was 29.5 weeks **(Table 4).**
- 95% (19/20) discontinued ESA treatment without subsequent re-initiation. Median time from the first ESA administration to the permanent discontinuation was about 2 years **(Table 4).**
- 40% (8/20) and 15% (3/20) achieved ≥8-week and ≥16-week RBC TI respectively, during 24 weeks of ESA treatment. After week-24 of ESA treatment, only half of ≥8-week TI responders (4/8) maintained the response, and there were no additional achievement of ≥8-week RBC TI between week-25 and 48 **(Table 4).**

Table 4. ESA[a] treatment pattern and outcomes in TD LR-MDS patients

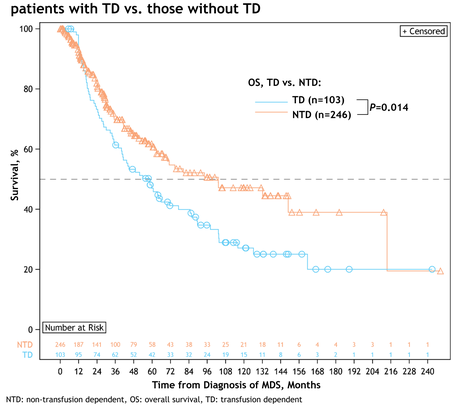
LR-MDS patients with baseline EPO levels ≤500U/L who received ESA[a] treatment after the first TD event	N=20
Median baseline EPO level, U/L (95% CI)	283.0 (146.0-300.0)
Median weekly dose, μg (95% CI)	185.0 (151.1-238.6)
Median accumulative time of ESA[a] prescription, weeks (95% CI)	29.5 (14.0-48.0)
No initial response to ESA[a] treatment, no. (%)	17 (85.0%)
Permanent discontinuation of ESA[a] treatment, no. (%)	19 (95.0%)
Median time from the first administration to permanent discontinuation, months (95% CI)	23.5 (9.8-42.5)
RBC TI achievement[b]	
Attainment of ≥8-week RBC TI during 24 weeks of ESA[a] treatment, no. (%)	8 (40.0%)
Attainment of ≥16-week RBC TI during 24 weeks of ESA[a] treatment, no. (%)	3 (15.0%)
Attainment of ≥8-week RBC TI between week 25 and 48 of ESA[a] treatment, no. (%)	4 (20.0%)
Attainment of ≥16-week RBC TI between week 25 and 48 of ESA[a] treatment, no. (%)	3 (15.0%)

CI: confidence interval, EPO: erythropoietin, ESA: erythropoiesis stimulatind agent, LR-MDS: lower-risk myelodysplastic syndrome, RBC: red blood cell, TD: transfusion-dependent, TI: transfusion-independence
[a]Darbepoetin-α was the only ESA prescribed for MDS patients.
[b]After week 24 of darbepoetin-α treatment, no additional patients achieved ≥8-week RBC TI.

OS and AFS in LR-MDS patients with RBC TD vs. those without TD

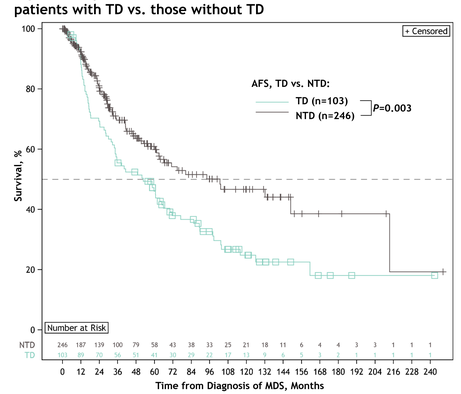
- TD LR-MDS patients exhibited significantly shorter median OS (58.4 vs. 103.1 months, *P*=0.014) and AFS (52.7 vs. 102.7 months, *P*=0.003) than NTD LR-MDS patients **(Figure 2, Figure 3 and Table 5).**
- The differences in OS and AFS between TD and NTD patients were not significant in the all MDS patients **(Table 5).**
- In TD LR-MDS patients, median OS and AFS from the first RBC TD were 33.8 (95% CI: 24.7-52.9) and 33.6 months (95% CI: 20.4-51.7), respectively.

Figure 2. Kaplan-Meier estimated overall survival of LR-MDS patients with TD vs. those without TD



NTD: non-transfusion dependent, OS: overall survival, TD: transfusion dependent

Figure 3. Kaplan-Meier estimated AML-free survival of LR-MDS patients with TD vs. those without TD



AFS: AML-free survival, NTD: non-transfusion dependent, TD: transfusion dependent

Table 5. Overall survival and AML-free survival in MDS patients with TD vs. those without TD[a]

	LR-MDS patients (N=349)			All MDS patients (N=831)		
	TD (N=103)	NTD (N=246)	*P*-value[b]	TD (N=194)	NTD (N=637)	*P*-value[b]
Median OS, months (95% CI)	58.4 (40.0-77.2)	103.1 (67.6-213.4)	0.014	39.2 (31.5-51.1)	41.5 (33.6-60.4)	0.357
Median AFS, months (95% CI)	52.7 (34.3-70.0)	102.7 (62.9-213.4)	0.003	33.8 (25.3-42.5)	40.9 (32.9-55.7)	0.143

AFS: AML-free survival, CI: confidence interval MDS: myelodysplastic syndrome, LR: lower-risk, NTD: non-transfusion dependent, OS: overall survival, TD: transfusion dependent
[a]OS and AFS were estimated from the index date of MDS diagnosis
[b]Log-rank test

Conclusions

- In this 28-year retrospective study of patients with MDS, RBC TD was associated with increased HCRU and medical costs, as well as higher risks of AML progression and premature death for over 20 years after MDS diagnosis
- The negative impact of RBC TD was more prominent in patients with LR-MDS than in the all MDS cohort.
- We observed the real-world effectiveness of ESA treatment for TD patients with LR-MDS to be limited, but without an alternative treatment option, patients received ESAs for up to approximately 2 years and the majority discontinued, suggesting ESAs may only be a temporary option to manage TD anemia.
- These results highlight the need for alternative treatment options to reduce RBC transfusion burden in LR-MDS.

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