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ORIGINAL ARTICLE

Prognostic Impact of Transfusion Dependency in Patients with Lower-Risk Myelodysplastic Syndrome

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SUMMARY

Background: **This study retrospectively analyzed the prognostic impact of transfusion burden in patients with lower-risk myelodysplastic syndrome (LR-MDS) and the outcomes of each treatment option.**
Methods: **Data on 168 patients with LR-MDS between July 2011 and April 2020 were retrospectively reviewed. Non-transfusion dependent (NTD) was defined as no transfusion history in a period of 16 weeks, low transfusion burden (LTB) as receiving 3 - 7 red blood cell (RBC) units in a period of 16 weeks, and high transfusion burden (HTB) as receiving ≥ 8 RBC units in a period of 16 weeks.**
Results: **The treatment response was observed over 4 - 6 months after treatment. Among the 168 patients, 105 were treated with anabolic steroids (n = 65), erythroid stimulating agents (n = 12), or hypomethylating agents (n = 28). The overall response rate was 53.3% (56/105), with 53 patients showing hematologic improvement (50.5%). The clinical benefit rate was 78.1% (82/105). The 5-year overall survival (OS) rates were 75.5%, 45.8%, and 33.3% for NTD, LTB, and HTB, respectively (p = 0.001). The 5-year incidences of acute myeloid leukemia were 0%, 9.9%, and 32.5% in NTD, LTB, and HTB, respectively (p < 0.001). In the multivariate analysis, age (hazard ratio [HR] 1.04, p = 0.009), LTB (HR 3.77, p = 0.002), HTB (HR 4.59, p < 0.001), and hemoglobin response (HR 0.45, p = 0.036) were significant factors for OS.**
Conclusions: **Our findings show transfusion dependency is an adverse prognostic factor in LR-MDS. HTB presented a higher risk of leukemic transformation.**
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KEYWORDS

lower-risk MDS, transfusion dependency, transfusion burden

INTRODUCTION

Myelodysplastic syndrome (MDS) is a heterogenous group of clonal myeloid neoplasms characterized by defective bone marrow (BM) hematopoiesis with peripheral blood cytopenias and a risk of progression to acute myeloid leukemia (AML) [1]. Accurate classification of MDS and risk scoring are critical in selecting the appropriate therapy and predicting the prognosis of patients with MDS. The most commonly used prognostic scor-

ing system in MDS has been the International Prognostic Scoring System (IPSS), which has been recently revised to IPSS-R for improved prognostication [2,3]. Lower-risk (LR) patients are those in the IPSS low to intermediate-1 group, comprised of IPSS-R very low, low, or intermediate scores of up to 3.5 points [3].

The treatment goals in LR-MDS are hematologic improvement to prevent complications related with cytopenias, reduce the transfusion burden, and improve the quality of life [4,5]. However, some patients with LR-MDS show high-risk features, such as early progression to AML and shorter overall survival (OS). To improve cytopenias, anabolic steroids, erythroid stimulating agents (ESAs), and immunosuppressive therapy are primarily used [6,7]. Patients who do not respond to these therapies could be treated with hypomethylating agents (HMAs), the standard treatment option for higher risk MDS [8,9]. HMAs are also used to treat patients with LR-MDS who initially present cytopenias in more than two blood lineages [10-12].

The transfusion burden differs among patients with LR-MDS, and those receiving red blood cell (RBC) transfusions are at risk of iron overload [13]. In such cases, the binding capacity of transferrin for iron is surpassed, resulting in non-transferrin-bound iron circulating in the blood and subsequent deposition of free iron in tissues, which can cause significant organ damage and is an important cause of morbidity and mortality [13,14]. Although new agents such as luspatercept showed a notable response in transfusion-dependent patients with LR-MDS, many patients still need RBC transfusions. Therefore, determining the clinical outcomes of transfusion burden and optimizing treatment for patients with MDS with transfusion dependencies are important [15]. Recently, the MDS International Working Group (IWG) has established criteria for transfusion dependency and defined three categories: no transfusion dependency (NTD), low transfusion burden (LTB), and high transfusion burden (HTB) [16]. This study retrospectively analyzed the prognostic impact of transfusion burden in patients with LR-MDS and the outcomes of each treatment option. Furthermore, we determined whether transfusion burden manifested high-risk features of LR-MDS.

MATERIALS AND METHODS

Data collection

Data on 401 patients with MDS from Kyungpook National University Hospital between July 2011 and April 2020 were retrospectively reviewed (Figure S1). Those with LR-MDS, defined as having an IPSS-R very low to intermediate score of up to 3.5, were included in the current study [17]. Patients with uncontrolled infection and uncontrolled illnesses and those treated with investigational agents were excluded. To evaluate the clinical significance of transfusion burden, baseline characteristics and transfusion history of the patients were collected. This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Kyungpook National University Hospital (IRB No. 2022-03-002).

Treatments and supportive care

RBC transfusions were performed for symptomatic anemia or in patients with a hemoglobin level lower than 7 - 8 g/dL, and platelets were transfused for thrombocytopenic bleeding or in patients with platelet count < 2.0×10^9/L. Antibiotics and antifungal agents were used for prophylaxis in patients with recurrent infections. If the serum erythropoietin (EPO) level was lower than 500 mU/mL, ESAs, such as recombinant human EPO or long-acting darbepoetin, were considered to improve anemia. EPO was administered at a dose of 40,000 - 60,000 units subcutaneously, once to twice per week. Darbepoetin alfa was used at the dose of 150 - 300 mcg subcutaneously, per week [18,19]. HMAs were administered to symptomatic and/or growth factor-unresponsive patients. For patients treated with HMAs, azacitidine was given subcutaneously at a dose of 75 mg/m^2 per day for 7 days every 28 days. Treatment with ESA or HMA was continued until progression for the patients who showed responses within 4 - 6 months. Patients who were not considered for ESA or HMA were treated with anabolic steroids (e.g. danazol or oxymetholone).

Definition of transfusion dependency

Transfusion burden was defined according to the IWG 2018 guidelines [16]. The NTD category included patients who received no transfusion in a period of 16 weeks. LTB was defined as receiving 3 - 7 RBC units in a period of 16 weeks, in at least two transfusion episodes. High transfusion burden (HTB) was defined as receiving ≥ 8 RBC units in a period of 16 weeks, in at least two transfusion episodes.

Response evaluation

Blood counts were performed every 4 weeks, and BM examination was repeated 4 to 6 months after treatment. The treatment response was observed over 4 - 6 months after treatment. Responses were evaluated using the IWG response criteria for MDS [20]. For example, hematological improvements were defined as follows: for patients with pretreatment Hb < 11 g/dL, > 2 g/dL increase in Hb; for RBC transfusion-dependent patients, transfusion independence. Minor erythroid response (HI-E minor) was defined as follows: for patients with pretreatment Hb < 11 g/dL, a 1 - 2 g/dL increase in Hb; for RBC transfusion-dependent patients, 50% decrease in transfusion requirement. Overall response rate (ORR) included the complete response (CR), partial responses (PR), and hematologic improvements (HI), and clinical benefit rate consisted of CR, PR, HI, and stable disease.

Table 1. Patient characteristics.

Variables	n (%)
Number of patients	168
Age, median year (range)	63 (20 - 92)
Gender	
Male	94 (56.0)
Female	74 (44.0)
WHO classification	
SLD	29 (17.3)
MLD	116 (69.0)
RS-SLD	8 (4.8)
RS-MLD	6 (3.6)
EB-1	7 (4.2)
del(5q)	3 (1.8)
BM blast%, median (range)	1.1 (0.0 - 9.5)
Hb (g/dL), median (range)	8.9 (2.3 - 15.4)
ANC ($\times 10^3$/L)	1.34 (0.15 - 10.1)
Platelet ($\times 10^9$/L)	74 (4 - 604)
Cytogenetic risk by IPSS-R	
Very good	12 (7.1)
Good	145 (86.3)
Intermediate	11 (6.5)
Erythropoietin level, U/L (n = 79)	
< 200	50 (63.3)
200 - 500	11 (13.9)
> 500	18 (22.8)
Transfusion burden	
Non-transfusion dependent	113 (67.3)
Low transfusion burden	34 (20.2)
High transfusion burden	21 (12.5)
IPSS-R risk group	
Very low	26 (15.5)
Low	99 (58.9)
Intermediate	43 (25.6)
LR-PSS by MD Anderson	
Category 1	56 (33.3)
Category 2	90 (53.6)
Category 3	22 (13.1)
Treatment	
No treatment	63 (37.5)
Anabolic steroids	65 (38.7)
Erythroid stimulating agents	12 (7.1)
Hypomethylating agents	28 (16.7)

SLD - single lineage dysplasia, MLD - multi-lineage dysplasia, RS - ringed sideroblast, EB - excess of blast, BM - bone marrow, Hb - hemoglobin, ANC - absolute neutrophil counts, IPSS-R - Revised International Prognostic Scoring System, LR-PSS - lower risk prognostic scoring system.

Table 2. Treatment response.

n (%)	Overall patients (n = 105)	Anabolic steroids (n = 65)	ESA (n = 12)	HMA (n = 28)	p
Response					0.158
Complete response	1 (1.0)	0	0	1 (3.6)	
Partial response	2 (1.9)	0	0	2 (7.1)	
Hematologic improvement	53 (50.5)	31 (47.7)	5 (41.7)	17 (60.7)	
Stable disease	26 (24.8)	20 (30.8)	4 (33.3)	2 (7.1)	
Progression	5 (4.8)	3 (4.6)	1 (8.3)	1 (3.6)	
Failure	18 (17.1)	11 (16.9)	2 (16.7)	5 (17.9)	
Overall response rate	56 (53.3)	31 (47.7)	5 (41.7)	20 (71.4)	0.075
Clinical benefit rate	82 (78.1)	51 (78.5)	9 (75.0)	22 (78.6)	0.963
Hematologic improvement					
Hemoglobin	38 (36.2)	19 (29.2)	3 (25.0)	16 (57.1)	0.026
Neutrophil	20 (19.0)	13 (20.0)	1 (8.3)	6 (21.4)	0.596
Platelet	20 (19.0)	10 (15.4)	3 (25.0)	7 (25.0)	0.476

ESA - erythroid stimulating agents, HMA - hypomethylating agents.

Statistical analysis

Baseline characteristics were analyzed by descriptive methods. Categorical variables were analyzed using the chi-squared test and continuous data by ANOVA. OS was defined as the time of diagnosis until death from any cause or until lost to follow-up. The patients who received allogeneic hematopoietic cell transplantation were censored at the time of transplantation. OS values were plotted using the Kaplan–Meier method, and differences between curves were evaluated using the log-rank test. The cumulative incidence of AML was calculated using Gray's method using the "cmprsk" package, considering death without leukemic transformation as a competing event. The significances of covariates affecting OS were determined using the Cox proportional hazards model. Covariates with p-value < 0.1 in the univariate analysis were included in the multivariate model. Factors with p-value < 0.05 were considered significant. For the statistical analyses, the R statistical software 4.0.3 and SPSS software version 20 (IBM Corp., Armonk, NY, USA) were used.

RESULTS

Among 401 patients with MDS, 168 (42.0%) diagnosed with LR-MDS on the IPSS-R were included in the study. The median age was 63 years (range: 20 - 92 years) at the time of diagnosis, and 94 patients (56.0%) were male. Most patients had multilineage dysplasia (69.0%) or single lineage dysplasia (17.3%), and 7 (4.2%) were excess blast 1 on the WHO classification [21]. IPSS-R risk group classification was very low, low, and intermediate for 26 (15.5%), 99 (58.9%), and 43 patients (25.6%), respectively. One hundred and thirteen patients (67.3%) had no transfusion episodes, whereas 34 (20.2%) and 21 patients (12.5%) showed LTB and HTB, respectively. The patient characteristics are summarized in Table 1.

Out of the 168 patients with LR-MDS, 105 (62.5%) received treatments: ESA for 12 patients (7.1%), HMA for 28 (16.7%), and anabolic steroids for 65 (38.7%) (Table S1). Azacitidine and decitabine were administered in 27 patients and 1 patient, respectively. HMA was administered for a median of 5 cycles (range: 1 - 26 cycles). ORR was achieved in 56 patients (53.3%), with complete response in 1 (1.0%), partial response in 2 (1.9%), and hematologic improvement in 53 patients (50.5%). Including 26 patients with stable disease (24.8%), the clinical benefit rate was 78.1% in treated patients (Table 2). ORR according to treatment option was 47.7% in anabolic steroids (31/65), 41.7% in ESA (5/12), and 71.4% in HMA (20/28) (Table 2). The clinical benefit rate was also similar among treatments: 78.1% in anabolic steroids (51/65), 75.0% in ESA (9/12), and 78.6% in HMA (22/28) (Table 2). Nine patients (5.4%) progressed to AML, and 52 deaths (31.0%) occurred.

The median follow-up duration of treated patients was 36 months (range: 0.6 - 119 months). OS varied with transfusion burden (Figure 1A). The 5-year OS rate was 75.5 ± 5.1% in NTD, 45.8 ± 9.1% in LTB, and 33.3 ± 10.8% in HTB (p = 0.001). Progression to AML occurred in 9 patients, 3 with LTB and 6 with HTB. The 5-year cumulative incidence of AML also differed according to the transfusion burden (Figure 1B) at 0%, 9.9 ±

Table 3. Factors affecting overall survival.

	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Age, years	1.04	1.01 - 1.06	0.003	1.04	1.01 - 1.08	0.009
Gender, female vs. male	0.49	0.27 - 0.87	0.015	0.66	0.36 - 1.20	0.170
BM blast%, ≥ 5 vs. < 5	2.21	0.69 - 7.14	0.184			
Hemoglobin (g/dL)						
≥ 10	1.00			1.00		
8 to 10	1.45	0.73 - 2.88	0.288	1.19	0.58 - 2.44	0.643
< 8	1.85	0.95 - 3.62	0.072	1.22	0.59 - 2.51	0.587
ANC (x 10^3/L)						
≥ 0.8	1.00					
< 0.8	1.28	0.67 - 2.44	0.454			
Platelet (x 10^9/L)						
> 100	1.00					
50 - 100	0.96	0.51 - 1.81	0.906			
< 50	0.93	0.48 - 1.82	0.829			
Cytogenetic risk group						
Very good	1.00			1.00		
Good	0.35	0.16 - 0.74	0.006	0.79	0.34 - 1.86	0.587
Intermediate	0.47	0.15 - 1.45	0.189	1.06	0.30 - 3.70	0.929
EPO level (U/L)						
< 200	1.00					
200 - 500	0.95	0.27 - 3.31	0.934			
> 500	0.80	0.26 - 2.43	0.694			
Transfusion burden						
NTD	1.00			1.00		
LTB	2.42	1.29 - 4.56	0.006	3.77	1.65 - 8.61	0.002
HTB	2.81	1.43 - 5.52	0.003	4.59	2.01 – 10.5	< 0.001
IPSS-R risk group						
Very low	1.00					
Low	1.51	0.63 - 3.63	0.355			
Intermediate	1.88	0.74 - 4.82	0.186			
LR-PSS						
Category 1	1.00					
Category 2	1.39	0.73 - 2.65	0.311			
Category 3	1.55	0.62 - 3.88	0.351			
Hematologic improvement						
Hemoglobin response	0.50	0.24 - 1.03	0.060	0.45	0.22 - 0.95	0.036
Neutrophil response	0.94	0.41 - 2.14	0.884			
Platelet response	0.62	0.24 - 1.59	0.321			

SLD - single lineage dysplasia, MLD - multi-lineage dysplasia, RS - ringed sideroblast, EB - excess of blast, BM - bone marrow, Hb - hemoglobin, ANC - absolute neutrophil counts, NTD - no transfusion dependency, LTB - low transfusion burden, HTB - high transfusion burden, IPSS-R - Revised International Prognostic Scoring System, LR-PSS - lower risk prognostic scoring system, Hb - haemoglobin, ANC - absolute neutrophil counts.

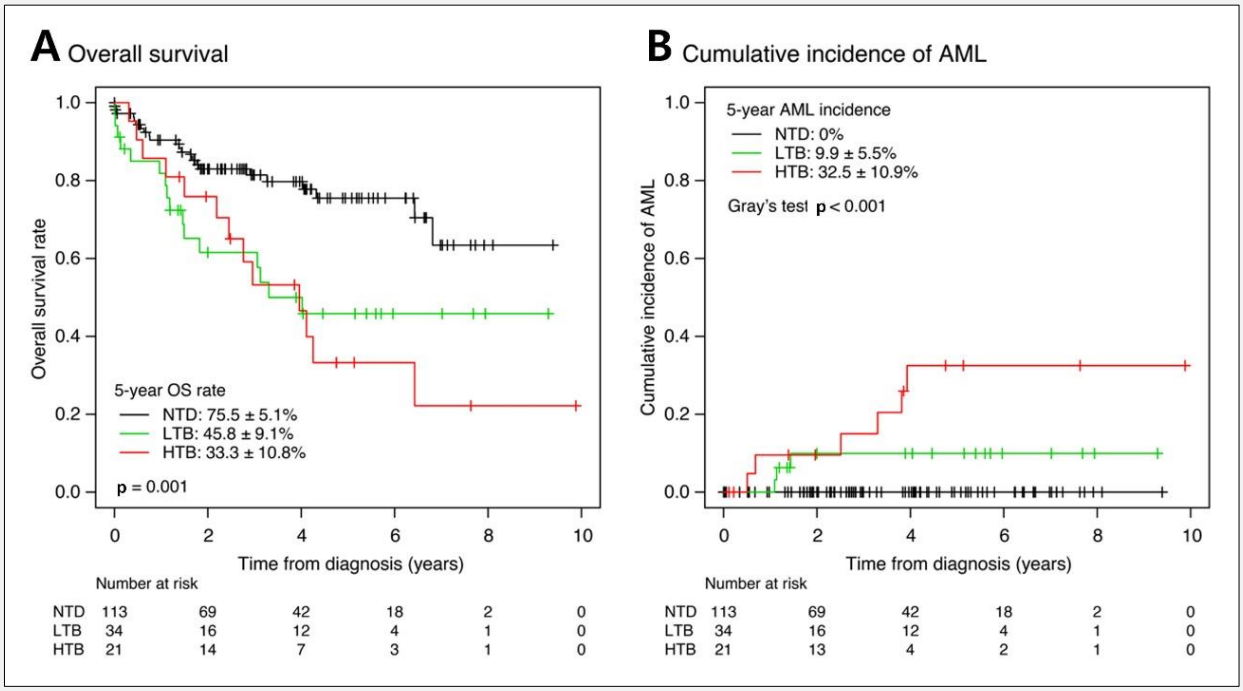

Figure 1. Survival outcomes according to the transfusion dependency.

NTD – Non-transfusion dependent, LTB - low transfusion burden, HTB - high transfusion burden, AML - acute myeloid leukemia.

5.5%, and 32.5 ± 10.9% for NTD, LTB, and HTB, respectively ($p < 0.001$).

The treatment options did not affect OS rate; the 5-year OS rate was 71.9 ± 6.7% in the no treatment group, 55.2 ± 7.7% with anabolic steroids, 82.5 ± 12.6% with ESA, and 51.3 ± 11.1% with HMA ($p = 0.413$) (Figure S2). However, the patients with treatment response showed improved OS (Figure 2), especially hemoglobin responders, with a 5-year OS rate of 67.0 ± 8.8% for hemoglobin responders and 52.0 ± 7.4% for hemoglobin non-responders (Figure 2B). Neutrophil and platelet responses were not significantly related to OS (Figure 2C and 2D).

In the univariate analyses, age (HR [hazard ratio] 1.04, $p = 0.003$), sex (female vs. male; HR 0.49, $p = 0.015$), hemoglobin (< 8 vs. ≥ 10; HR 1.85, $p = 0.072$), good risk cytogenetics (HR 0.35, $p = 0.006$), transfusion burden, and hemoglobin response (HR 0.50, $p = 0.060$) were significant factors and were thus included in the multivariate analysis (Table 3). In the multivariate analysis, age (HR 1.04, 95% confidence interval [CI] 1.02 - 1.08, $p = 0.009$), LTB (HR 3.77, 95% CI 1.65 – 8.61, $p = 0.002$), HTB (HR 4.59, 95% CI 2.01 – 10.5, $p < 0.001$), and hemoglobin response (HR 0.45, 95% CI 0.22 - 0.95, $p = 0.036$) were significant factors for OS (Table 3).

DISCUSSION

This study retrospectively analyzed the prognostic impact of transfusion burden in patients with LR-MDS. Our findings showed that transfusion burden was an adverse prognostic factor for patients with LR-MDS, with a high transfusion burden presenting an increased risk of leukemic transformation. The treatment options did not affect the treatment response and survival outcomes, but a survival benefit was observed for responders to anemia.

In the current study, patients with RBC transfusion dependency showed a poorer OS rate compared with patients with NTD. The severity of anemia in patients may be a risk factor for early mortality. In a retrospective analysis of 840 patients with MDS, the degree of anemia was a significant predictor of cardiovascular death ($p < 0.001$), independent of transfusion status and IPSS risk [22]. In patients with NTD with LR MDS and del(5q), the 5-year OS rates were 65.4% for patients with Hb levels < 10 g/dL vs. 81.6% for patients with Hb levels ≥ 10.5 g/dL [23]. However, an increased risk was also apparent for moderately transfused patients; therefore, direct toxicity from transfusions, such as toxic iron radicals, even at a relatively low iron load, may adversely impact survival [13,14]. Recent treatment op-

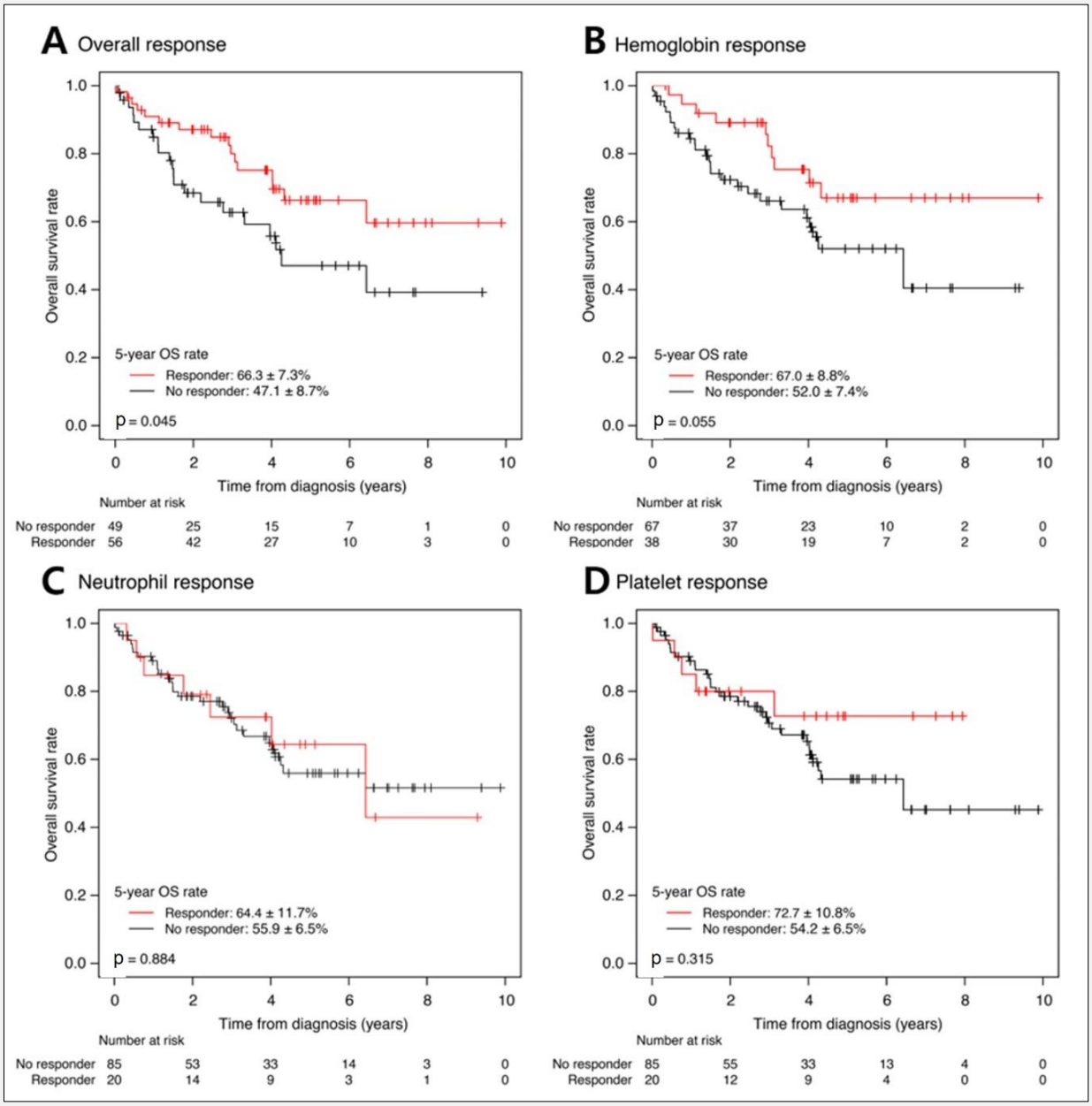

Figure 2. Overall survival according to response.

tions for anemia have shortcomings. The use of ESAs is dependent on serum EPO level, and not all patients have a durable response to ESAs [23,24]. With new agents that became recently available for patients with transfusion-dependent MDS, such as luspatercept, optimizing treatment and defining valuable groups for transfusion-dependent MDS is crucial in managing LR-MDS [15,24].

Some of the patients with LR-MDS show high-risk features, such as leukemic transformation. Identifying the patients who would progress or not is important because those patients should be treated differently. The results of our study imply that HTB could be a surrogate marker for increased risk of leukemic transformation. Louise et al. reported that progression-free survival (PFS) in patients with LR-MDS treated with RBC transfusions was usually reduced, but whether transfusion dose density is an independent prognostic factor is unclear. The overall PFS of the three groups of patients, stratified according to the dose density at the third visit, differed

significantly [25]. The HRs for patients in the low- and high-density groups were 1.85 (95% CI: 1.24 - 2.76) and 3.79 (95% CI: 2.65 - 5.42) relative to the non-transfused group, respectively. In the current study, the patients with HTB received more HMAs (66.7%, 14/21) than LTB (11.8%, 4/34) or NTD (8.8%, 10/113) (Table S2). The patients treated with HMA had multiple and severe cytopenias or adverse disease status. Nevertheless, HMA treatment produced ORR and hematologic improvements. Our study suggests that HMA is effective for symptomatic patients with LR-MDS. However, the long-term survival outcomes need to be elucidated to ensure accurate treatment with HMA. Baseline genetic profiling may be useful to find candidates for HMA among patients with LR-MDS [12].

Regarding the therapeutic options for patients with LR-MDS, recent guidelines suggest stratifying patients into several groups with regards to clinically significant cytopenia [17]. Our study showed that the treatment options did not affect the response rates and survival outcomes. However, survival benefit was observed for responders to anemia (Figures 2 and S1). The goals of LR-MDS treatment include improving cytopenia and quality of life. ESA and growth factors are recommended as initial therapy for patients with LR-MDS with symptomatic or transfusion-dependent anemia [26]. The high-risk of leukemic transformation in patients with HTB and an inferior OS rate in hemoglobin non-responders were not supported by clinical parameters. In previous studies, transfusion burden was related to a significantly higher risk of progression to AML. AML progression at 2 years was reported in 16.3% of transfusion-dependent (TD) patients compared with 6.6% of transfusion-independent (TI) patients, which increased to 17.9% and 11.4% at 5 years in TD and TI patients, respectively [27,28]. Therefore, patients with LR-MDS who have HTB could be regarded as a higher risk group, and allo-HCT may be considered for transplant-eligible patients. However, the optimal timing of allo-HCT for patients with LR-MDS with HTB, as well as other high-risk features, should be elucidated in the following studies [29,30].

Although the present data identified RBC transfusion dependency as a prognostic factor in LR-MDS, the study has some limitations. First, the sample size was too small to make meaningful comparisons between AML progression groups. Second, only a small number of patients were treated with ESA. Third, the current study was a retrospective evaluation, and recent genetic information was not evaluated.

CONCLUSION

Our findings showed that transfusion dependency was an adverse prognostic factor for patients with LR-MDS. Specifically, HTB indicated a higher risk of leukemic transformation, which suggests that transfusion burden is a high-risk feature in LR-MDS.

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Declaration of Interest:
The authors have no conflicts of interest to declare.

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