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The Effect of Serum Lactate Dehydrogenase (LDH) Level on the Response to Erythropoiesis Stimulating Agents in Patients with Low and Intermediate Risk Myelodysplastic Syndrome

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Abstract

Objective: To evaluate the effect of increased serum lactate dehydrogenase (LDH) level, known as a poor prognostic factor, on the response to erythropoiesis-stimulating agent (ESA) treatment in patients with low and intermediate-1 risk MDS –considered to be a group with good prognosis.

Methodology: We retrospectively identified 47 patients who were treated with ESA (epoetin-α or darbepoetin-α) due to low or intermediate risk MDS according to international prognostic scoring system (IPSS) the patients were evaluated from three different medical centers between 2006 and 2018. Patients' demographic, clinical and laboratory characteristics (including erythropoietin and LDH levels) were recorded and analyzed with respect to IPSS risk groups and the presence/absence of response to ESA.

Results: The low-risk group consisted of 32 patients, and the intermediate-1 group consisted of 15 patients. Thirty-three patients responded to ESA, while 14 did not. Survival analyses demonstrated that patients with low or normal LDH at baseline had longer survival than those with high LDH, and risk of death was increased by 8.868-fold in patients with high LDH. There was no relationship between LDH level and response to ESA therapy, but female gender increased the likelihood of ESA response by 9.19-fold.

Conclusion: Our findings show that LDH level is one of the predictable factor of survival among patients with MDS; however, it appears that baseline LDH is not associated with ESA response. Besides baseline erythropoietin levels were lower among ESA responders, logistic regression revealed that the only parameter associated with positive response to ESA was female gender.

Keywords: Lactate dehydrogenase, Myelodysplastic syndrome, Erythropoietin, Darbepoetin, Erythropoiesis-stimulating agent.

Introduction

Myelodysplastic Syndrome (MDS) is an acquired clonal disease in which myeloid cell maturation is impaired. Its primary feature may be considered the risk of leukemic transformation, while peripheral cytopenia may also occur due to ineffective hematopoiesis.[1,2] The clinical presentation is heterogeneous, with various types and combinations of cytopenia observed in patients, including anemia, which is present in around two-thirds of patients.[2] Treatment aims to reduce symptoms, prevent disease progression and death risk, and increase the quality of life. The decision on treatment modality is made according to the risk groups.[3]

The International Prognostic Scoring System (IPSS) is still widely used in the risk classification of patients with MDS based on three factors, the percentage of myeloblasts in the bone marrow, cytogenetic features, and the number of cytopenia types identified in peripheral blood.[4-6] According to the IPSS, MDS is divided into four prognostic categories according to risk: low, intermediate-1, intermediate-2, and high risk.[5] A revised form of the IPSS which has advanced classification does exist (IPSS-R)[7], but as mentioned before, the IPSS continues to be utilized in practice. Other prognostic factors have also been defined so far, including a high serum lactate dehydrogenase (LDH) level, which is now well accepted as a critical poor

Authorship Contribution: [1-2]Conceived and planned the idea of the study, [3,4,5]Drafting the work or revising it critically for important intellectual content final approval of the version to be published, Collecting the data, [6-10]Active Participation in active methodology.

Funding Source: none
Conflict of Interest: none
Received: Oct 29, 2021
Accepted: Jan 5, 2021

prognostic factor.[1] Additionally, the intermediate-1 risk group could be variable, and it has been shown that these patients demonstrate worse prognosis in the presence of elevated LDH. [8]

Erythropoiesis-stimulating agents (ESA), epoetin-α and darbepoetin-α, are frequently used to treat symptomatic anemia in patients with low and intermediate-1 risk, particularly in those without 5q deletion and patients who has low erythropoietin level (<500 IU/L).[9] Both of these agents are reported to have similar efficacy, but the relationship between response to ESA and LDH level is still unknown yet.

In this study, we aimed to evaluate whether increased serum LDH level, known as a poor prognostic factor, had any influence on the response to ESA treatment in patients with low and intermediate-1 risk MDS, who represent a group that is generally considered to have a good prognosis.

Methodology

We identified 47 patients who had been treated with ESA therapy from 2006 to 2018 in three tertiary referral hospitals in Turkey; Okmeydanı Training and Research Hospital, Ege University Faculty of Medicine Hospital, and İstanbul Kartal Prof. Dr. Lütfi Kırdar Training and Research Hospital. All subjects were retrospectively included through the evaluation of patient databases.

Diagnosis and evaluations: The MDS diagnosis of each patient was reevaluated and confirmed with respect to the MDS diagnostic criteria revised by Valent et al. in 2017.[10] These updated criteria consist of three major and three co-criteria, which are assessed when the patient has cytopenia of erythroid, myeloid or platelet series for at least 4 months –given that all other hematologic or non-hematologic causes of cytopenia can be excluded (pre-requisite). In addition of pre requisite the presence of one major criterion is accepted to yield a diagnosis of MDS. In the event that no major criteria are met, the presence of at least two co-criteria can confirm MDS diagnosis.[10]

Major criteria: (i) presence of at least 10% dysplasia in at least one of the erythroid, myeloid or megakaryocytic series, (ii) >15% ring sideroblasts in bone marrow smear or >5% in the presence of SF3B1 mutation, (iii) myeloblast proportion of 5–19% in bone marrow smear or 2–19% in peripheral blood smear. Co-criteria: (i) histology or immunohistochemistry abnormalities in bone marrow biopsy, (ii) myeloid and/or erythroid monoclonal population presence indicating multiple MDS-related phenotypic aberration in the immunophenotypic flow cytometry analysis of bone marrow cells, (iii) identification of MDS-related mutations with molecular sequencing studies of clonal populations of myeloid cells.

Among the patients who met the diagnostic criteria, only those who were categorized as low risk or intermediate-1 risk according to the IPSS were included in the study.[6] The type of MDS was also determined and recorded according to the French-American-British (FAB) classification due to historical importance: RA (Refractory anemia), RARS (refractory anemia with ring sideroblasts), RCMD (refractory cytopenia with multilineage dysplasia), and RCMD-RS (Refractory cytopenia with multilineage dysplasia, ring sideroblasts ≥15%).[11]

Demographic and clinical characteristics, including age, gender, comorbidities (diabetes mellitus, hypertension, coronary artery disease, cerebrovascular accident, chronic obstructive pulmonary disease, kidney diseases, thyroid diseases and hematologic diseases), duration with MDS diagnosis and treatments received, and red blood cell (RBC) transfusion requirements were recorded. The laboratory characteristics of patients consisted of total blood count, beta-2 microglobulin, erythropoietin (EPO) and lactate dehydrogenase (LDH) levels. In addition to recording quantitative values for LDH, we also categorized patients according to LDH level into three groups: low, normal and high.

Administration of ESA: All individuals included in the current study had received either epoetin-α or darbepoetin-α treatment. Epoetin was administered at a weekly dose of 30.000 IU, and darbepoetin was administered at a dose of 150 µg applied once every weeks.

Assessment of treatment response: Patients' response to ESA treatment was determined via the revised 2018 criteria of the International Working Group.[12] According to their transfusion dependency, patients were divided into three categories to assess response with respect to their defined status (transfusion-independent, low transfusion-dependent and high transfusion-dependent). The definitions for each of the transfusion-dependency groups and their response to treatment were as follows:

After treatment with ESA agents, both risk groups showed significant increase in hemoglobin level (p=<0.001 for low risk group and p=0.013 for intermediate-1 risk group, data was shown in table I). The LDH level in low-risk group increased after treatment, while the intermediate-1 risk group had similar LDH levels at pre- and post-treatment.

i) Patients who did not need a transfusion during the 1–16-week observation period were considered transfusion independent, and an increase of at least 1.5 g/dl in hemoglobin during the 16-week follow-up was accepted as positive response to treatment.

ii) During the 16-week follow-up, the patients who needed a total of 3-7 units of RBC transfusion on at least two occasions were considered low transfusion-dependent patients. Among these, during the 16–24-week follow-up period, the absence of transfusion was accepted as a positive response.

iii) Patients who needed a total of 8 units or more RBC transfusion on at least two occasions during the 16-week follow-up were considered to be high transfusion-dependent. Individuals who did not require transfusion during the 16–24-week follow-up were accepted to have major response, whereas minor response was defined among patients with a 50% reduction in transfusion need.

Apart from these three groups, patients who needed 1-2 units of RBC transfusion in 16 weeks were not included in any transfusion-dependency category, and positive response was identified as a hemoglobin increase of at least 1.5 g/dl in this group of individuals.

Statistical analyses were conducted with the SPSS software (version 21.0, IBM, Armonk, NY, USA). Comparison of categorical variables was performed with Pearson Chi-square tests. The normality of distribution of continuous variables was tested with the Shapiro-Wilk test and Q-Q histograms, and comparisons were performed with the independent samples t-test or the Mann-Whitney U test, in parametric and non-parametric continuous variables, respectively. Depiction of continuous variables was performed using the median and inter-quartile range (IQR), while categorical data were depicted with count (n) and percentage (%).

Multivariable analyses were conducted by the inclusion of parameters that demonstrated significant differences in univariate analyses to determine parameters independently associated with various characteristics (such as treatment response and survival). The Log-rank method was applied in the analysis of survival. P-values of 0.05 or lower were considered to be statistically significant.

Results

The median age was 69.5 (range, 34–85) years, and 14.8% of patients were male. The characteristics of patients which depend on IPSS risk groups (low, intermediate-1) are described in Table I. The low-risk group consisted of 32 patients, and the intermediate-1 group comprised 15 patients. The median EPO level was 31.8 (4.40 – 303.5)mIU/mL in overall and it was similar in low and intermediate-1 risk groups (28.0 vs 37.8, respectively p=0.344), 17% of the patients were transfusion-independent. Comparisons based on risk groups showed that the low-risk group had a significantly higher frequency of female gender (p=0.026). These two groups were also significantly different in terms of white blood cell count (WBC) (5.88 (3.69 – 10.62) vs 3.38 (2.14 – 8.44), p=0.003) and neutrophil levels (3.79 (0.69 – 8.02) vs. 1.83 (0.97 – 4.61), p=0.015) at the time of diagnosis. All patients had low hb level (<10 g/dl) when ESA therapy was started. Gender distribution according to ESA response is shown in Figure 1.

Therapy response: Epoetin and darbepoetin were used in 38 (81%) and 9 (19%) patients, respectively. Response rates were similar in the epoetin (n = 27; 71%) and darbepoetin (n = 6; 67%) treated groups (p = 1). Overall, 33 patients showed a response to treatment, and the median response duration was 37 (IQR: 7–119) months. When treatment groups were compared, almost all characteristics were similar among the groups, the only differences was: and follow-up duration was longer in the epoetin group compared to the darbepoetin group (48 [9–158] months vs. 16 [7–62] months, p = 0.005). After treatment, patients in both the epoetin and darbepoetin groups demonstrated a statistically significant increase in hemoglobin level (p <0.001 and p = 0.021, respectively). Additionally, after treatment, the epoetin group showed a significant increase in LDH (p = 0.026), whereas the change was non-significant in the darbepoetin group (p = 0.214).

When individuals with (n = 33) and without (n = 14) response to ESA treatment were compared, we found that female frequency was higher and baseline

Table I: Summary of patient characteristics and analysis results according to IPSS groups				
	IPSS groups			
	Low (n=32)	Intermediate-1 (n=15)	Overall (n=47)	P value
Age	70 (34 – 85)	69 (52 – 81)	69.5 (34 – 85)	1.000
< 60	5 (16.13%)	3 (20.00%)	8 (17.39%)	1.000
≥ 60	26 (83.87%)	12 (80.00%)	38 (82.61%)	
Gender				
Male	2 (6.25%)	5 (33.33%)	7 (14.89%)	0.026
Female	30 (93.75%)	10 (66.67%)	40 (85.11%)	
Type of MDS				
RA	32 (100.00%)	12 (80.00%)	44 (93.62%)	0.077
RARS	0 (0.00%)	1 (6.67%)	1 (2.13%)	
RCMD	0 (0.00%)	1 (6.67%)	1 (2.13%)	
MDRS	0 (0.00%)	1 (6.67%)	1 (2.13%)	
Comorbidities	22 (70.97%)	12 (80.00%)	34 (73.91%)	0.723
Accompanying malignancy	3 (9.38%)	1 (6.67%)	4 (8.51%)	1.000
Splenomegaly	1 (3.23%)	2 (13.33%)	3 (6.52%)	0.244
Lymphadenopathy	0 (0.00%)	0 (0.00%)	0 (0.00%)	N/A
Abnormal cytogenetics	1 (3.13%)	4 (26.67%)	5 (10.64%)	0.030
Genetic mutation	3 (9.38%)	2 (14.29%)	5 (10.87%)	0.633
Erythropoietin	28.0 (4.4 – 303.5)	37.8 (5.1 – 297.0)	31.8 (4.40 – 303.5)	0.344
Hemoglobin at diagnosis	9.75 (6.10 – 11.72)	9.70 (5.60 – 11.00)	9.70 (5.60 – 11.72)	0.991
WBC at diagnosis (x1000)	5.88 (3.69 – 10.62)	3.38 (2.14 – 8.44)	5.46 (2.14 – 10.62)	0.003
Neutrophil at diagnosis (x1000)	3.79 (0.69 – 8.02)	1.83 (0.97 – 4.61)	3.52 (0.69 – 8.02)	0.015
Platelet at diagnosis (x1000)	226 (17.9 – 434)	199 (70 – 401)	208 (17.9 – 434)	0.708
Beta-2 microglobulin	365.5 (193 – 1650)	632 (171 – 3443)	426 (171 – 3443)	0.169
Anemia	31 (96.88%)	15 (100.00%)	46 (97.87%)	1.000
Leukopenia	3 (9.68%)	8 (53.33%)	11 (23.91%)	0.002
Leukocytosis	1 (3.23%)	0 (0.00%)	1 (2.17%)	1.000
Thrombocytopenia	4 (12.90%)	5 (33.33%)	9 (19.57%)	0.127
Pancytopenia at diagnosis	2 (6.25%)	2 (13.33%)	4 (8.51%)	0.583
Bicytopenia at diagnosis	5 (16.67%)	7 (46.67%)	12 (26.67%)	0.070
Transfusion dependency				
Low	1 (3.13%)	1 (6.67%)	2 (4.26%)	0.848
High	4 (12.50%)	2 (13.33%)	6 (12.77%)	
Erythropoiesis-stimulating agent				
Epoetin	25 (78.13%)	13 (86.67%)	38 (80.85%)	0.697
Darbepoetin	7 (21.88%)	2 (13.33%)	9 (19.15%)	
Response to ESA				
Absent	9 (28.13%)	5 (33.33%)	14 (29.79%)	0.742
Present	23 (71.88%)	10 (66.67%)	33 (70.21%)	
Hemoglobin				
Before treatment	9.54 (6.10 – 10.80)	9.60 (7.30 – 10.80)	9.54 (6.10 – 10.80)	0.991
After treatment	11.70 (7.79 – 14.70)	10.80 (7.80 – 12.90)	11.70 (7.79 – 14.70)	0.213
p (within variables)	<0.001	0.013	<0.001	
Change in hemoglobin	2.02 (-0.07 – 4.60)	1.40 (-2.90 – 3.80)	1.80 (-2.90 – 4.60)	0.126
LDH				
Before treatment	191 (121 – 431)	182 (119 – 305)	190 (119 – 431)	0.632
After treatment	212 (122 – 416)	174 (128 – 279)	200 (122 – 416)	0.349
p (within variables)	0.016	0.443	0.016	
LDH categories				
Before treatment				
Low	3 (9.38%)	2 (13.33%)	5 (10.64%)	0.848
Normal	23 (71.88%)	11 (73.33%)	34 (72.34%)	
High	6 (18.75%)	2 (13.33%)	8 (17.02%)	
After treatment				
Low	3 (9.38%)	0 (0.00%)	3 (6.38%)	0.074
Normal	17 (53.13%)	13 (86.67%)	30 (63.83%)	
High	12 (37.50%)	2 (13.33%)	14 (29.79%)	
p (within variables)	0.058	0.317	0.033	
Transformation to acute leukemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	N/A
Follow-up time (months)	44.5 (7 - 158)	44 (9 - 108)	44 (7 - 158)	1.000
Status				
Alive	28 (87.50%)	13 (86.67%)	41 (87.23%)	1.000
Exitus	4 (12.50%)	2 (13.33%)	6 (12.77%)	
Data are given as median (minimum-maximum) for continuous variables according to the normality of distribution and as frequency (percentage) for categorical variables				

Table II. Summary of patient characteristics and analysis results with regard to ESA response

	Response to ESA			
	Absent (n=14)	Present (n=33)	Total	**p**
Age	69.5 (34 - 80)	69.5 (44 - 85)	69.5 (34 – 85)	0.839
< 60	2 (14.29%)	6 (18.75%)	8 (17.39%)	1.000
≥ 60	12 (85.71%)	26 (81.25%)	38 (82.61%)	
Gender				
Male	5 (35.71%)	2 (6.06%)	7 (14.89%)	0.018
Female	9 (64.29%)	31 (93.94%)	40 (85.11%)	
Type of MDS				
RA	12 (85.71%)	32 (96.97%)	44 (93.62%)	0.153
RARS	1 (7.14%)	0 (0.00%)	1 (2.13%)	
RCMD	1 (7.14%)	0 (0.00%)	1 (2.13%)	
MDRS	0 (0.00%)	1 (3.03%)	1 (2.13%)	
IPSS group				
Low	9 (64.29%)	23 (69.70%)	32 (68.09%)	0.742
Intermediate-1	5 (35.71%)	10 (30.30%)	15 (31.91%)	
Abnormal cytogenetics	1 (7.14%)	4 (12.12%)	5 (10.64%)	1.000
Genetic mutation	1 (7.14%)	4 (12.50%)	5 (10.87%)	1.000
Erythropoietin	60.1 (6.1 - 297)	23 (4.4 - 303.5)	31.8 (4.40 – 303.5)	0.023
Hemoglobin at diagnosis	9.15 (5.60 - 11.10)	9.80 (6.10 - 11.72)	9.70 (5.60 – 11.72)	0.122
WBC at diagnosis (x1000)	5.37 (2.14 - 9.03)	5.46 (2.84 - 10.62)	5.46 (2.14 – 10.62)	0.346
Neutrophil at diagnosis (x1000)	2.71 (1.29 - 4.50)	3.74 (0.69 - 8.02)	3.52 (0.69 – 8.02)	0.223
Platelet at diagnosis (x1000)	196 (17.9 - 362)	216.5 (40 - 434)	208 (17.9 – 434)	0.599
Erythropoiesis-stimulating agent				
Epoetin	11 (78.57%)	27 (81.82%)	38 (80.85%)	1.000
Darbepoetin	3 (21.43%)	6 (18.18%)	9 (19.15%)	
G-CSF usage	0 (0.00%)	1 (3.03%)	1 (2.13%)	1.000
Hemoglobin				
Before treatment	9.35 (7.30 – 10.80)	9.54 (6.10 – 10.80)	9.54 (6.10 – 10.80)	0.780
After treatment	10.13 (7.80 – 12.20)	11.80 (7.79 – 14.70)	11.70 (7.79 – 14.70)	0.002
p (within variables)	0.048	<0.001	<0.001	
Change in hemoglobin	0.99 (-2.90 – 3.32)	2.20 (0.17 – 4.60)	1.80 (-2.90 – 4.60)	<0.001
LDH				
Before treatment	210 (135 – 305)	181 (119 – 431)	190 (119 – 431)	0.170
After treatment	223.5 (122 – 416)	191 (128 – 318)	200 (122 – 416)	0.340
p (within variables)	0.433	0.019	0.016	
LDH categories Before treatment				
Low	0 (0.00%)	5 (15.15%)	5 (10.64%)	0.293
Normal	11 (78.57%)	23 (69.70%)	34 (72.34%)	
High	3 (21.43%)	5 (15.15%)	8 (17.02%)	
After treatment				
Low	1 (7.14%)	2 (6.06%)	3 (6.38%)	0.986
Normal	9 (64.29%)	21 (63.64%)	30 (63.83%)	
High	4 (28.57%)	10 (30.30%)	14 (29.79%)	
p (within variables)	1.000	0.011	0.033	
Transformation to acute leukemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	N/A
Follow-up time (months)	55.5 (8 - 158)	37 (7 - 119)	44 (7 - 158)	0.205
Status				
Alive	11 (78.57%)	30 (90.91%)	41 (87.23%)	0.344
Exitus	3 (21.43%)	3 (9.09%)	6 (12.77%)	
BM blasts at diagnosis, %; median	0 (0-3)	0 (0-2)	0 (0-2)	0.190
RBC transfusion at baseline	3 (21.4%)	5 (15.2%)	8 (17%)	0.601
BM fibrosis, n (%)	7 (50.0%)	26 (78.8%)	33 (70.2%)	0.048

erythropoietin levels were lower in responders; all other characteristics were similar at baseline. After treatment, a significant increase in hemoglobin level was observed in both non-responders (p = 0.048) and responders (p <0.001). However, the amount of Hb increase was significantly greater among responders (p <0.001) and these patients also had significantly higher Hb level after treatment when compared to non-responders (p = 0.002). Pre- and post-treatment LDH levels were similar in non-responders, but a significant increase was observed in responders (p = 0.019) (Table II). Response to ESA according to risk groups and ESA agents (darbepoetin vs. epoetin) are shown in Figure 2 and Figure 3, respectively. Patients' distribution to LDH categories according to ESA response is shown in Figure 4.

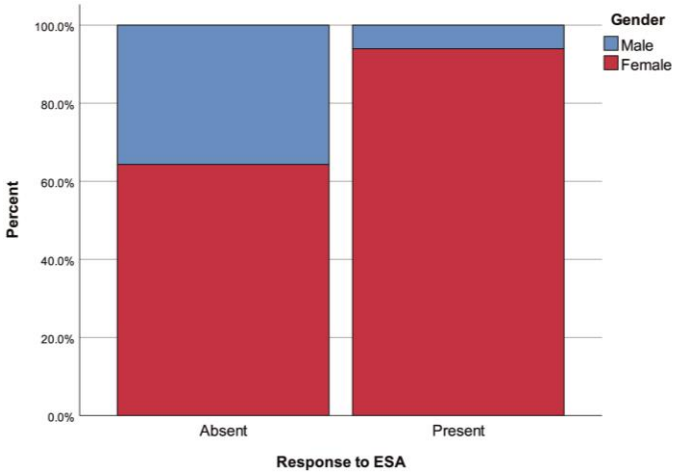

Figure 1. Gender distribution with respect to ESA response groups

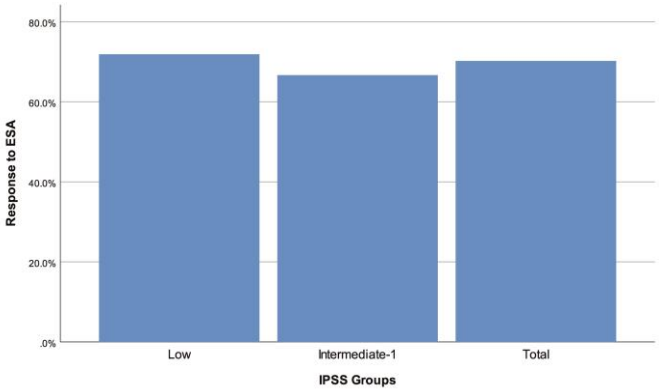

Figure 2. Response to ESA according to IPSS Groups

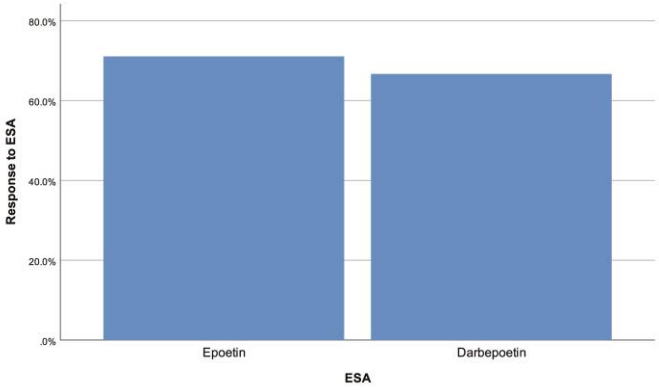

Figure 3. Response to ESA according to treatment type

Survival functions based on LDH categories (low or normal versus high) demonstrates that patients with low or normal LDH had longer survival (Figure 5). The cumulative survival analysis is shown in Figure 6. We performed Cox regression analysis to determine

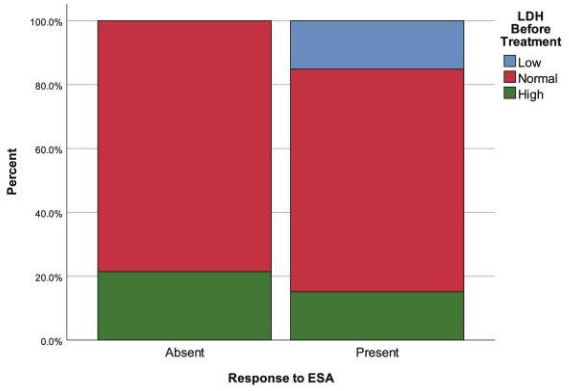

Figure 4. Comparison of patients' distribution to LDH categories with respect to ESA response

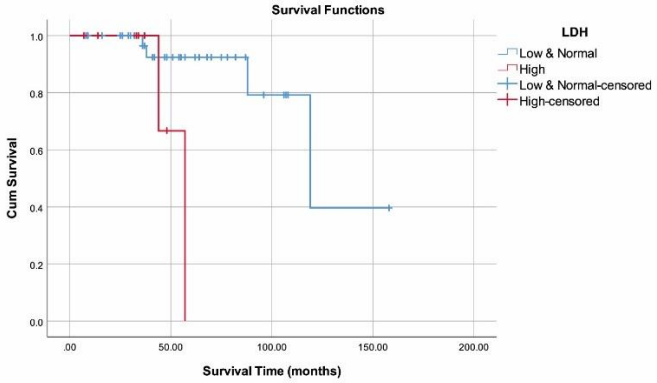

Figure 5. Survival functions with respect to LDH categorization (low or normal LDH vs. high LDH)

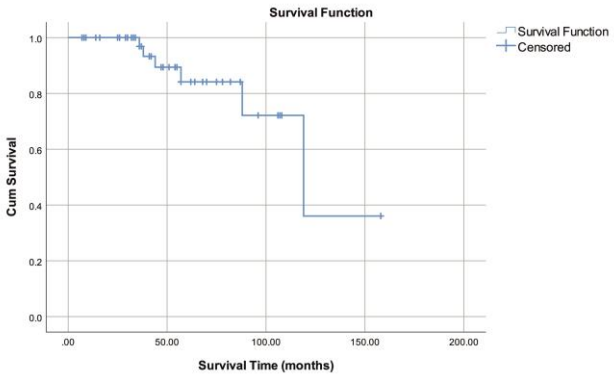

Figure 6. The Cumulative Survival Function

significant prognostic factors in MDS. Patients with high LDH values had 8.868-fold higher risk of death compared to other patients (HR: 8.868, 95% CI: 1.214–64.751, p = 0.031). Other variables included in the model, age (p = 0.066), gender (p = 0.150), IPSS group (p = 0.570), transfusion dependency (p = 0.079), ESA (p = 0.067) and response to ESA (p = 0.509) were found to be non-significant. We also performed logistic regression to determine factors that were influential on treatment

response. We included gender and baseline EPO values in the model because they were the only variables with a p-value below 0.100 in univariate analysis. Females were found to have a 9.19-fold greater likelihood of demonstrating positive response to ESA treatment (OR: 9.19, 95% CI: 1.47–57.39, p = 0.018), whereas baseline EPO levels were non-significant (p = 0.093).

Discussion

This study demonstrated that patients with low-risk and intermediate-1-risk MDS (according to IPSS) had similar characteristics at baseline, except for gender distribution and WBC and neutrophil counts. The comparison of patients classified as 'responders' or 'non-responders' (regarding ESA treatment) showed that both groups had a significant increase in Hb level after ESA administration, while the LDH increase was only significant among responders. Cox regression analysis revealed that patients with high LDH at baseline had an 8.868-fold higher risk of death compared to those with low or normal LDH. This finding is in agreement with prior studies which have shown that LDH level is a prognostic factor in MDS. We did not find any relationship between baseline LDH levels and response to ESA treatment. The only parameter that affected treatment response was gender, with females having a 9.19-fold greater likelihood of responding to ESA therapy.

The majority of patients at low or intermediate-1 risk had an erythroid response after treatment with ESA, consistent with previous studies.[13-15] Transfusion dependence and iron overload have been linked with poor survival and worse health outcome in MDS, including cardiovascular, hepatic, and endocrine dysfunctions.[16] Achieving erythroid response is critical; because it has been shown that reducing transfusion-related incidents in MDS patients can have a significant survival impact that differs by risk stratification, with median survival extending to three years in low-risk patients while it can remain as low as two months in high-risk patients.[17] Our results agreed with contemporary literature, as demonstrated by the significant increases in Hb level in patients with positive response to ESA (either epoetin or darbepoetin). Similarly, a previous meta-analysis reported that epoetin and darbepoetin yielded similar erythroid response rates in anemic MDS patients.[18]

There was no relationship between LDH level and response to ESA therapy. Although, improvement of Hh level was significantly higher among responders ($p<0.001$) Hb level was increased among both the responders and non-responders after treatment. Noteworthy, this finding is confounded by the fact that the assessment of treatment response includes threshold values for hemoglobin change (1.5 g/dl). The frequency of females was higher and baseline EPO levels were lower among responders, suggesting a relationship between ESA response and these two parameters. Logistic regression revealed that female gender was associated with positive response to ESA, while EPO levels did not influence the likelihood of ESA response.

Various other studies have also attempted to correlate clinical outcomes with LDH levels in MDS. In a study evaluating hypomethylating agent (HMA) therapy, Coston et al. found that HMA response was correlated with lower serum LDH levels.[19] In another study, Moon et al. revealed that high LDH levels were significantly associated with worse survival in patients receiving azacitidine.[20] Similarly, Park et al. also obtained a result indicating that increased levels of LDH had negative effects on patient survival in addition to age.[21] Although we also found a relationship between high LDH level and survival, our results showed a lack of relationship between ESA response and LDH level.

The current study demonstrated that patients with low or normal LDH levels had a significantly extended duration of survival. Interestingly, our patients' overall survival duration was 117.66 (92.06–143.26) months, a value that exceeds the results reported by the majority of the literature on this topic (ranging from 3.1 to 37 months).[20, 22-24] This controversial result may be associated with various factors, including patient-based and treatment-dependent differences; however, the extreme difference in survival warrants further studies in which the possible phenotypical differences can be assessed among patients with MDS. Considering the previously reported role of LDH levels in patients with MDS and the fact that we found it to be the most important factor associated with survival, we believe that future studies would benefit from prospective analyses that employ patient stratification based on not only treatment characteristics, but also other parameters, including LDH levels, race, genetic factors and related efficacy of different treatment modalities.

Recent changes in classification have resulted in the use of the 5-group IPSS-R (revised) for risk assessment in MDS, which enables a reliable categorization in terms of length of survival and risk of leukemic transformation. However, the approach to treatment does not differ with each of the 5 risk groups, and it has been noted that research is required for the elucidation of this problem. [7] The last issue that has to be noted is that there is no pharmaceutical agent licensed according to IPSS-R classification. So, when deciding to use a certain treatment, current approaches require the consideration of FAB criteria and IPSS criteria. For these reasons, we did not re-classify patients with respect to IPSS-R in this study. Newman et al. reported that growth factors such as G-CSF and EPO provided substantial advantages in treating patients with MDS, but there were concerns regarding the application of thrombopoietic growth factors in patients with MDS.[25]

Finally, one of the most notable findings of this study was the fact that both responders and non-responders had significant improvement in Hb after treatment. Even though the increase in Hb and the post-treatment comparison between groups indicate a greater change in the responder group compared to non-responders, this finding may raise questions pertaining to the definition of response to ESA treatment in patients with MDS. Previous studies have also indicated that there may be a need for new approaches to determine ESA response and have proposed different methods throughout the last twenty years.[26-29] In the face of such limitations, we suggest that future studies should assess ESA response based on more than one method or scoring system.

Conclusion

In summary, our results support current evidence that high LDH levels at baseline are associated with poor survival in low- and intermediate-1-risk patients with MDS. Although the amount of increase in Hb was superior among responders compared to non-responders and the fact that post-treatment comparisons showed higher values among responders, this is highly likely to be a direct result of the response classification utilized in this study (which includes hemoglobin increase). Additionally, contrary to our hypothesis, LDH levels were not found to be associated with the response to ESA therapy; in fact, responders had a significant increase in LDH after treatment, whereas non-responders did not demonstrate any change. Additionally, female gender appears to be associated with a greater likelihood of benefitting from ESA therapy. These conclusions require extensive studies for confirmation, especially those including patient stratification based on LDH levels, gender and other parameters that could cause variations in treatment response.

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