ORIGINAL RESEARCH

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Ferritin: Is it a Predictor of Prognosis in Myelodysplastic Syndrome?

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ABSTRACT Objective: Although transfusion load is considered to be the main cause of iron overload (IO) in myelodysplastic syndrome (MDS), patients without transfusion history may also present with IO at diagnosis. This retrospective study was assessed to investigate the potential role of baseline ferritin in MDS prognosis. **Material and Methods:** A total of 87 patients [median age: 62(21-83); male/female: 53/34] were included in this study. **Results:** Serum ferritin levels, which were positively correlated with International Prognostic Scoring System (IPSS), World Health Organization Prognostic Scoring System (WPSS), C reactive protein (CRP) and lactate dehydrogenase (LDH) levels, were relatively higher in patients with excess marrow blasts (≥5%) at diagnosis. Serum CRP, reticulocyte percentage, LDH and alanine transaminase levels were higher as well as IPSS and WPSS, while hemoglobin and platelet count were lower in the high-ferritin group. Percentage of marrow blasts at diagnosis, IPSS and WPSS had significant prognostic impact on overall survival. Although ferritin levels were associated with certain prognostic markers, an independent impact of ferritin on prognosis or survival was not demonstrated. **Conclusion:** The prognostic role of ferritin should be confirmed in larger prospective studies in order to include this feasible candidate in standard prognostic scoring systems in MDS.

Keywords: Ferritins; myelodysplastic syndromes; ıron overload; prognosis; oxidative stress

Myelodysplastic syndromes (MDS) are clonal hematopoietic stem cell disorders characterized by cytopenias and ineffective hematopoiesis with a variable risk of progression to acute myeloid leukemia (AML). Approximately 80% of the patients present with anemia at diagnosis and become transfusion dependent subsequently. Although transfusion load is considered to be the main cause of iron overload (IO) in MDS, patients without transfusion history may also present with IO at diagnosis, which may be attributed to ineffective erythropoiesis.[1-10] As iron is not used in hemoglobin (Hb) synthesis, it accumulates in non-erythroid cells and non-hematopoietic tissues as well as hematopoietic stem cells. As ferritin is the major iron-binding protein in non-erythroid cells, higher serum ferritin levels due to ineffective erythropoiesis and increased iron absorbtion are generally observed in transfusion independent MDS patients.[8]

Ferritin expression is modulated by a variety of factors in association with oxidative stress. Recent discovery of a new ferritin molecule, which is known as mitochondrial ferritin (MtF), highlights the relationship between

iron, oxidative damage and free radicals. Mitochondria is involved in iron trafficking as well as cellular activities including respiration, production of reactive oxygen species (ROS) and regulation of apoptosis. Hence, MtF may be a potential regulator of iron homeostasis which protects mitochondria from iron-induced damage.[11] Excess intracellular iron may increase the production of ROS including superoxide and hydroxyl radicals, which are indicated to directly induce lipid peroxidation, oxidative deoxyribonucleic acid (DNA) damage, gene mutations and DNA double strand breaks.[8]

Several studies have underlined the relationship between ferritin levels and MDS course. Although an impact of baseline ferritin levels on prognosis and survival was reported, probably due to the heterogenous and complex biology of the disease, an accurate association has not been demonstrated yet.[4,6,8,12,13] This retrospective study was assessed to investigate the potential role of ferritin in MDS prognosis.

MATERIAL AND METHODS

A total of 87 patients [median age: 62(21-83); male/female: 53/34] who were diagnosed as MDS or chronic myelomonocytic leukemia (CMML) between 1998 and 2015 at Gazi University Hospital were included in this retrospective study. Risk stratification was based on International Prognostic Scoring System (IPSS) and World Health Organization (WHO) Prognostic Scoring System (WPSS).[14] Baseline iron parameters, including serum iron, total iron binding capacity, transferrin saturation and ferritin levels were measured at diagnosis. The impact of iron parameters, particularly ferritin, on prognosis and survival was evaluated. Patient characteristics are summarized in (Table 1).

STATISTICAL ANALYSIS

Continuous variables in two groups were compared by Mann–Whitney U test and categorical variables with Chi–squared test. Spearman test was used for correlation analysis. Kaplan Meier method was performed for survival analysis and Cox regression models for univariate/multivariate models. A threshold value of p<0,05 was considered as statistically significant. The calculations were made with SPSS 15.0 and 22.0 (SPSS Inc, Chicago, Illinois).

The study was approved by the Ethical Committee of Gazi Medical School.

RESULTS

Serum ferritin levels at diagnosis were positively correlated with IPSS (p=0.018; r=0.290), WPSS (p=0.004; r=0.346), C reactive protein (CRP) (p=0.029, r=0.421) and lactate dehydrogenase (LDH) levels (p=0.015, r=0.295). Serum ferritin levels were relatively higher in patients with excess marrow blasts (≥5%) at diagnosis, when compared to patients with <5% blasts [340(35-1405) ng/mL vs 110.5(7-5411) ng/mL; p=0.056].

The study cohort was divided into 'high' and 'low' ferritin groups based on a threshold value which was defined as 500 ng/mL. Serum CRP [26.5(2.34-138) g/L vs 4.2(1.84-96) g/L; p=0.029], reticulocyte percentage [2.96(0.15-10)% vs 1.71(0.58-6.4)%; p=0.009], LDH [339(113-1034) U/L vs 199(192-3530) U/L; p=0.023] and ALT levels [23(10-84) U/L vs 16(3-48) U/L; p=0.01] were higher, while Hb [8.67(4.6-12.8) g/dL vs 10.8(4.9-15.8) g/dL; p=0.001] and platelet count [39000(12000-263000)/μL vs 91000(3000-602000)/μL; p=0.013] were found to be lower in the high-ferritin group. Furthermore, IPSS [0.5(0-3) vs 0.5(0-2); p=0.012] and WPSS [1(1-6) vs 1(0-4); p=0.004] were higher in the high-ferritin group. When 1000 ng/mL is considered as a threshold value for ferritin, serum CRP [66(2.9-138) g/L vs 7.8(1.84-96) g/L; p=0.029], LDH [383(181-644) U/L vs 212(92-3530) U/L; p=0.007] and absolute reticulocyte count [113.8(73-295) vs 60.2(5.3-168; p=0.01] were found to be higher in patients with a ferritin level greater than 1000 ng/ml.

In univariate analysis, percentage of marrow blasts at diagnosis (p=0.025), IPSS (p=0.058) and WPSS (p=0.024) were indicated to have significant prognostic impact on overall survival (OS), with a relatively sustained impact of WPSS on multivariate analysis (p=0.054).

TABLE 1: Patient characteristics.

Age [Median (range)] (years)	62 (21-83)
Gender (Male/Female)	53 / 34
Diagnosis	
Myelodyplastic Syndrome Classification (World Health Organization 2008) (n=79) [n(%)]	39 (49.4)
Refractory cytopenia with unilineage dysplasia (RCUD)	2 (2.5)
Refractory anemia with ringed sideroblasts (RARS)	13 (16.4)
Refractory cytopenia with multilineage dysplasia (RCMD)	12 (15.2)
Refractory anemia with excess blasts I (RAEB-I)	12 (15.2)
Refractory anemia with excess blasts II (RAEB-II)	1 (1.3)
5q syndrome	
Chronic Myelomonocytic Leukemia (n=8)	
Fluorescence in situ Hybridization at Diagnosis (n=46) [n(%)]	
Normal	41(89.1)
17p deletion	1 (2.2)
5q deletion	3 (6.5)
7q deletion	1 (2.2)
Conventional Cytogenetics at Diagnosis (n=53) [n(%)]	
Normal	31 (58.5)
Hypodiploidy	12 (22.6)
Polydiploidy	1 (1.9)
Monosomy 7	1 (1.9)
Trisomy 8	2 (3.8)
20q deletion	1 (1.9)
Clonal deletion of Y chromosome	2 (3.8)
Complex karyotype	3 (5.6)
International Prognostic Scoring System (IPSS) (n=76) [n(%)]	
Low	27 (35.5)
Intermediate-I	38 (50)
Intermediate-II	9 (11.9)
High	2 (2.6)
World Health Organization Prognostic Scoring System (WPSS) (n=76) [n(%)]	
Very low	18 (23.7)
Low	31 (40.8)
Intermediate	10 (13.1)
High	14 (18.4)
Very high	3 (4)
Bone Marrow Cellularity at Diagnosis (n=80) [n(%)]	
Hypocellular	5 (6.25)
Normocellular	24 (30)
Hypercellular	51 (63.75)
Bone Marrow Fibrosis at Diagnosis (n=80) [n(%)]	
No fibrosis	29 (36.25)
Grade 1	29 (36.25)
Grade 2	18 (22.5)
Grade 3	4 (5)
Transferrin saturation (%) [Median (range)]	28 (4-144)
Ferritin (ng/ml) [Median (range)]	230 (7-5411)
C reactive protein (g/L) [Median (range)]	8.25 (1.84-138)
Lactate dehydrogenase (U/L) [Median (range)]	219 (92-3530)

At a median follow-up of 763(9-5589) days, a total of 42 patients (48.3%) required medical treatment. 5-azacytidine (5-AZA) was used in 15 patients (17.2%). Immunosuppressive agents, systemic chemotherapy, immunomodulatory drugs (thalidomide, lenalidomide) and allogeneic HSCT were alternative treatment options. A total of 19 patients (21.8%) underwent allogeneic HSCT. Survival probability was 51% in the whole cohort (Figure 1). Overall survival was similar between high and low-ferritin groups, based on 500 ng/mL and 1000 ng/mL as certain cut-off levels (Figure 2, 3). A total of 25 patients (28.7%) died during follow-up. Cause of mortality was disease related in 19 patients (76%), transplant related in 4 (16%) and other causes in 2 patients (8%).

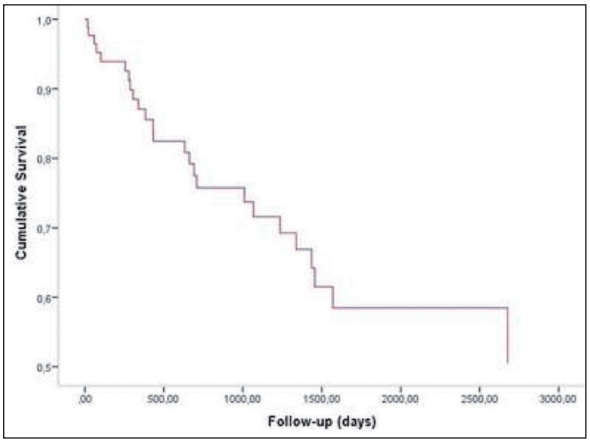

FIGURE 1: Survival probability for the study cohort.

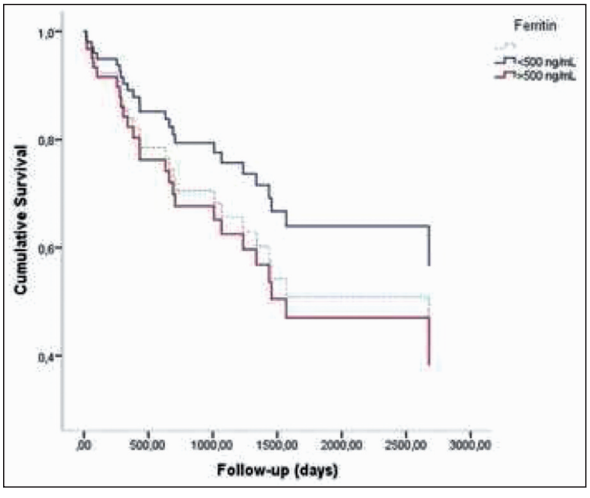

FIGURE 2: Survival probability based on ferritin levels (<500 ng/mL vs >500 ng/mL).

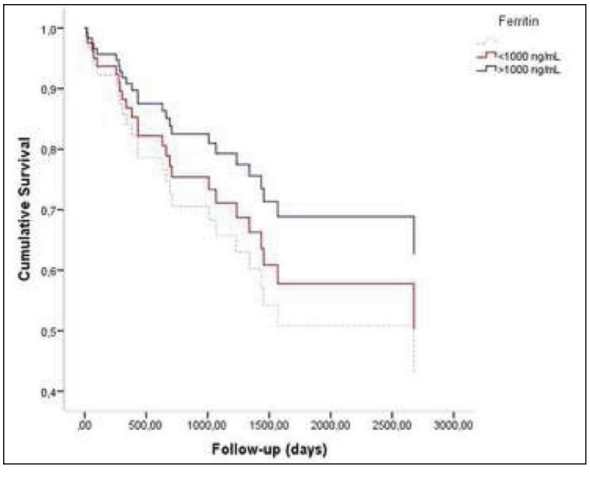

FIGURE 3: Survival probability based on ferritin levels (<1000 ng/mL vs >1000 ng/mL).

DISCUSSION

In this retrospective study, serum ferritin levels, which were positively correlated with IPSS, WPSS, CRP and LDH, were relatively higher in patients with excess marrow blasts (≥5%) at diagnosis. Serum CRP, reticulocyte percentage, LDH and ALT levels as well as IPSS and WPSS were higher, while Hb and platelet count were found to be lower in the high-ferritin group. In univariate analysis, percentage of marrow blasts at diagnosis, IPSS and WPSS were indicated to have significant prognostic impact on OS, with a persistent impact of WPSS on multivariate analysis. Overall survival was not different between high and low-ferritin groups. Although serum ferritin levels were found to be associated with certain prognostic markers, an independent impact of ferritin on prognosis or survival was not demonstrated.

Several studies have investigated the potential relationship between MDS prognosis and serum ferritin levels whether due to IO secondary to transfusion support or ineffective erythropoiesis at the time of diagnosis. No standard cutoff value was defined for ferritin. The Düsseldorf MDS registry recorded baseline serum ferritin levels of 650 MDS patients which were around 1000 ng/mL in 5% of the patients.[15,16] Elevated serum ferritin levels at diagnosis may be related to increased intestinal iron absorbtion caused by low hepcidin concentrations

and ineffective erythropoiesis. High serum ferritin levels may reflect the severity of anemia and degree of ineffective erythropoiesis due to bone marrow failure, as well as inflammation, infection and leukemia cell mass. Furthermore, as iron accumulates in early erythroid precursors in the form of MtF, oxidative stress and apoptosis may also be triggered in MDS patients.[13,15] Li et al found that serum ferritin level ≥500 μg/l at diagnosis was a strong independent predictor of survival. In this study, baseline serum ferritin level was found to be inversely correlated with Hb level.[13] Similarly, Park et al reported that higher ferritin levels were associated with anemia and high MCV in concordance with our results. Thus, ineffective erythropoiesis may be an explanation for increased serum ferritin at diagnosis.[12]

Garcia-Manero et al investigated potential prognostic markers in 856 patients with lower risk MDS. Low platelet count, anemia, older age, higher percentage of marrow blasts and poor risk cytogenetics were found to be associated with worse survival on multivariate analysis. Serum ferritin level >1000 ng/ml was shown to be an adverse prognostic predictor in a subgroup of 95 patients.[4] Messa et al reported serum ferritin ≥800 μg/l was significantly correlated with poorer survival.[17] Sperr et al. developed a prognostic scoring system for MDS in 400 patients. Age, IPSS, ferritin and comorbidities were found to be independent predictive variables for survival. The threshold value for ferritin was considered as 900 ng/mL in this study.[18] In another study by Sotirova et al, patients with ferritin <500 μg/L were shown to have better OS.[19]

Kikuchi et al found that serum ferritin levels of higher risk MDS patients were significantly higher than lower risk patients. Interestingly, ferritin levels of MDS patients with chromosomal abnormality were significantly higher than patients with normal karyotype. Furthermore, elevated ferritin at diagnosis was significantly associated with future development of transfusion dependency, probably due to the severity of anemia and ineffective erythropoiesis.[8] Malcovati et al showed that transfusion dependent patients had a significantly shorter survival than patients who did not require transfusions in a cohort of 467 MDS patients.[20] Secondary IO significantly affects the survival of transfusion dependent patients.[2,10,15,20,21]

In contrast with these results, the prognostic impact of ferritin could not be validated in several studies. Chee et al retrospectively investigated the impact of ferritin on OS in 126 patients with refractory anemia with ringed sideroblasts (RARS). There was no correlation between survival and serum ferritin level either at diagnosis or follow-up. There was no difference in survival when patients were stratified based on a threshold of 1000 ng/ml for ferritin.[22] In a study of 176 MDS patients, IPSS was found to be the only independent prognostic variable, whereas ferritin levels failed to show a significant impact on survival.[6] In a study by Park et al increased baseline serum ferritin level (>300 ng/ml) was correlated with male gender, anemia and diagnosis of RARS, without an impact on survival or progression to leukemia.[12]

Various components of iron metabolism, particularly hepcidin and ROS, have been investigated in MDS patients. Although prolonged transfusion appears to be the main contributor, many patients develop IO at an early stage of the disease prior to transfusion. Altered production of hepcidin, the key hormone in the regulation of iron homeostasis, may play a role in this course.[1,2,9,10,23] Gonçalves et al. investigated the role of oxidative stress and mitochondrial dysfunction in the biology of MDS. They showed that marrow cells from MDS patients had increased peroxide levels and decreased glutathione (GSH) content, when compared to normal subjects. Transfusion dependency was negatively correlated with GSH content, while intracellular peroxide levels were positively correlated with ferritin. Furthermore, patients with high ROS or low GSH levels had lower OS. Based on this relationship between serum ferritin and ROS levels in MDS patients, IO may be attributed to increased apoptosis and ineffective hematopoiesis.[3]

In another study from Japan, a positive correlation was indicated between ROS and serum ferritin levels.[24] The relationship between IO and oxidative stress was also demonstrated in HSCT re-

cipients. A significant impact of non transferrin bound iron (NTBI) on survival was shown, particularly in auto-transplanted patients.[25] Cortelezzi et al. evaluated NTBI levels and lipid peroxidation in 33 transfusion independent MDS patients. Non transferrin bound iron levels were found to be significantly higher in lower risk MDS patients. Bone marrow progenitor cells with high NTBI levels showed a higher degree of apoptosis. Non transferrin bound iron is associated with the degree of ineffective erythropoiesis and apoptosis in MDS bone marrow precursors.[26]

Prognostic impact of ferritin was also investigated in transplant patients. Iron overload was initially identified as an adverse prognostic factor in patients undergoing allogeneic HSCT for thalassemia. Excess iron may serve as a free radical catalyst promoting tissue damage and end organ toxicity. Non-transferrin bound iron has a particular role in this course, as it may provoke oxidative cellular damage and tissue toxicity, resulting in post-transplant complications.[7] In a previous retrospective study, we investigated the role of ferritin on transplant outcome. Elevated ferritin levels were significantly associated with toxic and infectious complications including mucositis, fungal infections, pneumonia, and sinusoidal obstruction syndrome in the early post-HSCT setting. A significant effect of pre-HSCT ferritin concentration on OS and transplant-related mortality (TRM) was observed.[27] In a retrospective study by Lim et al, the impact of pre-HSCT ferritin on transplant outcome was evaluated in 99 MDS patients receiving reduced intensity conditioning HSCT. Elevated serum ferritin and pre-HSCT >5% marrow blasts were independent predictors of an inferior OS.[7] Tachibana et al analyzed 119 patients with AML or MDS who underwent allogeneic HSCT. High ferritin level and disease risk were independently associated with worse 5-year OS. The cumulative incidence of relapse as well as non relapse mortality was higher in patients with elevated ferritin levels.[28] On contrary, Konuma et al did not find any significant impact of hyperferritinemia either on OS, relapse and TRM, or grades II-IV acute graft-vs-host disease (GVHD), extensive chronic GVHD and neutrophil engraftment.[29] Based on the cumulative data regarding the potential prognostic impact of ferritin on transplant outcome, a scoring system was developed for patients with acute leukemia and MDS undergoing HSCT, which depends on age, disease, stage at HSCT, cytogenetics and pre-HSCT ferritin.[30,31]

Ferritin, a predictor of IO and ineffective erythropoiesis in MDS, has a considerable role in a variety of conditions including inflammation, infection and oxidative stress. Thus, it seems reasonable to consider the potential prognostic impact of ferritin in a multifactorial manner. Nevertheless, based on the available data, the prognostic role of ferritin should be confirmed in larger prospective studies in order to include this feasible candidate in standard prognostic scoring scales of MDS. Despite the limitations of our study including small sample size and retrospective design, representation of a novel population from a genetic area with low prevalence of iron metabolism disorders including hemachromatosis, may be considered as the novelty and contribution of this study.

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Conflict of Interest

Authors declared no conflict of interest or financial support.

Authorship Contributions

Creation of Hypothesis, Consultancy, Study Design, Analysis and Evaluation, Reference Screening, Article Writing, Critical Examination: *Zeynep Arzu Yegin;* ***Data Collection and Processing, Responsibility for Study Materials, Source/FundSupply:*** *Mutlu Hızal;* ***Data Collection andProcessing, Responsibility for Study Materials, Source/FundSupply:*** *Rezzan Eren Sadioğlu;* ***Analysis and Evaluation:*** *Zübeyde Nur Özkurt; Creation of Hypothesis, Consultancy, Critical Examination:* ***Gülsan Türköz Sucak.***

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