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# Pretransplant serum ferritin level may be a predictive marker for outcomes in patients having undergone allogeneic hematopoietic stem cell transplantation

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Iron overload increases the risk of infections, veno-occlusive disease and hepatic dysfunction in post-transplant period. Our objective was to investigate the association of pre-transplant ferritin levels with complications and survival after allogeneic hematopoietic stem cell transplantation (alloHSCT).

We retrospectively analysed 84 patients' data who had undergone allogeneic HSCT into two groups: patients with a serum ferritin level≥1000ng/ml, and patients with <1000 ng/ml at the time of HSCT.

Cox-regression analysis showed that pre-transplant serum ferritin levels were significantly higher in patients who had at least one infectious event compared with those who had no any infectious event in the post-transplant 100 days ($p<0.023$). Overall survival (OS) and disease-free survival (DFS) rates were significantly higher in patients with a time-to-tx interval <12 months compared with group time-to-tx interval>12 months ($p=0.002$ and $p=0.008$ respectively). A higher risk of death was observed in high-ferritin group (hazard ratio=2.27, CI:1.01-5.09, $p=0.023$ for OS and hazard ratio=2.49, CI:1.12-5.53 $p=0.039$ for DFS). No significant effect on OS and DFS among groups was observed for variables conditioning regimen, gender and diagnosis. Acute GVHD was more common in patients with a ferritin level ≥1000 ng /mL, but this was not statistically significant ($p>0.05$). There was no statistical significance in both groups (ferritin≥1000ng /mL and ferritin<1000ng/mL) for relapse rates ($p>0.05$). Platelet and neutrophil engaftment day was not found statistically significant compared with both groups ($p=0.273$ and $p=0.882$, respectively).

Pre-transplant ferritin levels may predict poor outcomes in patients who had undergone allogeneic hematopoietic stem cell transplantation.

*Key words: allogeneic hematopoietic stem cell transplantation, ferritin, graft-versus-host disease, iron overload, survival*

Allogeneic hematopoietic stem cell transplantation (alloHSCT) is considered a curative treatment for various hematologic malignancies. Although improvement of the outcome has been achieved in recent decades via advances in many procedures, such as the prevention of graft-versus-host disease (GVHD), infectious complications remain an important contributor to transplant-related mortality [1,2]. It has recently been reported that iron overload increases the risk of veno-occlusive disease, hepatic dysfunction, and infections after transplantation [3]. It has also been shown that elevated serum levels of pre-transplant ferritin, which is a reliable marker of iron overload, are associated with increased nonrelapse mortality in patients having undergone allo-HSCT [4-6]. The pathogenetic mechanisms for iron overload in hematological malignancies are: prolonged dyserythropoiesis, hemolysis, increased intestinal iron absorption, and multiple red blood cell transfusions [7]. Free iron causes increased sensitivity for infections by inhibiting chemotaxis and phagocytosis and also impaires cellular immunity [8]. Excessive amounts of iron can cause tissue damage, resulting in protein oxidation, membrane lipid peroxidation, and nucleic acid modification, with conversion of hydrogen peroxide to reactive oxygen species [9]. Due to the fact that ferritin is an acute phase reactant, it may not always show total iron body stores reliably. However, it is the most common and cost-effective commercial method for measuring the total body iron. Stem cell transplant patients are at risk of excess accumulation of iron resulting from repeated blood transfusions both before and during transplantation

[10]. In this study we aimed to evaluate the influence of pre-transplantation ferritin levels on the outcomes of alloHSCT recipients, including graft-versus-host disease (GVHD), infections and survival.

## Patients and Methods

A total of 211 patients who had undergone alloHSCT between April 2004 and June 2010 at Dedeman Stem Cell Transplantation Hospital, Faculty of Medicine, Erciyes University, Kayseri, Turkey; were analysed retrospectively. The data was obtained from the patients' records. A pretransplantation serum ferritin level (drawn within 100 days prior to transplantation) was available for 84 patients. The patients were divided into two groups; patients with a pre-transplant ferritin level lower than 1000ng/ml (ferritin<1000ng/ml) and higher than 1000ng/ml (ferritin≥1000ng/ml). Graft-vs-host disease (GvHD) was graded according to European Blood and Marrow Transplantation criteria [11]. Engraftment was defined, for platelet engrafment, as the day on which platelet count exceeds 20000/$mm^3$ and the day on which neutrophil count exceeds 500/$mm^3$ for at least 3 days consecutively for neutrophil engraftment. This study was approved by the local ethic committee of Erciyes University.

**Statistical analysis.** Continuous variables between the 2 groups were compared using the Mann-Whitney test. Categorical variables were compared using the $\chi^2$ test. Overall survival (OS) and disease free-survival (DFS) were calculated using the Kaplan-Meier method. Possible risk factors were tested using the log rank test and the Cox regression model. The calculations were performed using commercially available software (SPSS version 18.0; SPSS Inc, Chicago, Illinois). Numerical variables are summarized by their medians and ranges, categorical variables by counts and relative frequencies. The primary end-points were overall survival (OS) and disease-free survival (DFS). OS was defined as the time between transplantation and death (from any cause) or last follow-up. Univariate and multivariate survival analyses were performed using Cox proportional hazards regression to identify the most significant independent prognostic factors.

## Results

A total of 84 patients who underwent alloHSCT were retrospectively investigated. 41 (48.8%) of the patients were female, and 43 (51.2%) were male. The majority of the patients was diagnosed with AML (37, 44.1%), while the others were ALL (16, 19.1%), aplastic anemia (16, 19.1%), non-Hodgkin lymphoma (5, 5.8%), chronic myelogenous leukemia (2, 2.3%), and others (8, 9.6%). The median age was found to be 28 years (min-max:15-56). The patient characteristics are shown in Table 1. The conditioning regimen was Bu / Cy in 43 (51.1%) of the patients, Cy / TBI in 13 (15.4%), ATG/Flu/Cy in 13 (15.4%), ATG/Flu/Bu in 7 (8.4%) and Flu / Bu in 2 ( 2.3%) of the patients. The median number of RBC transfusions in the pre-transplant period was 6 (2 - 13). The iron parameters and albumin levels of the patients are shown in Table 2.

**GVHD and relapse.** A total of 44 patients were diagnosed with GVHD. Of these patients, 18 had acute GVHD (21.4%) and 26 had chronic GVHD (30.9%). The site of acute GVHD was the liver in 7 patients (38.8%), skin in 5 patients (27.7%) and gastrointestinal tract in 6 patients (33.3%). The distrubution of sites of chronic GVHD were liver in 12 patients (46.1%), skin in 9 patients (34.6%) and GI tract in 5 patients (19.2%). Acute GVHD was more common in patients with a ferritin level >1000 ng /mL, but this was not statistically significant ($p>0.05$). There was no statistical significance between groups ferritin>1000 ng /mL and ferritin≥1000 ng/mL for chronic GVHD ($p>0.05$).

In relapse analysis, a total of 18 (21.4%) patients relapsed after transplantation. Of the patients who relapsed, 13 had acute leukemia (72.2%), 3 non-Hodgkin lymphoma (16.6%), one patient multiple myeloma (5.6 %) and one aplastic anemia (5.6%). There was no statistical significance in both ferritin groups (ferritin≥1000ng /mL and ferritin<1000ng/mL) for relapse rates ($p>0.05$).

**Infectious events.** In our study, cox-regression analysis showed that pre-transplant serum ferritin levels were significantly higher in patients who had had at least one infectious event, as was the case in 51 patients (60.7%), compared with those who had not had any infectious event in the 100 post-transplant days ($p<0.023$). Most of these infectious events were pneumonia (29 patients, 56.8%), diarrhea (7, 13.7%), bacteremia (14, 27.4%), mucositis (11, 21.5%), perianal abscess (5, 9.8%) and zona zoster in one (1.9%). Fungal pneumonia was diagnosed in 23 of 29 patients (79.3%) in the post-transplant period, with the remaining cases (6 patients, 20.7%) having a bacterial origin. Pre-transplant serum ferritin levels were found to be significantly higher in patients who had experienced an infectious event ($p<0.05$). In patients with fungal pneumonia, median ferritin level was found to be 1815 ng/ml (min-max: 20-6418), while in patients without a history of fungal pneumonia median level was found to be 905 ng/ml (min-max: 18-9513). The difference between groups with and without pneumonia was statistically significant ( $p<0.005$).

**Effect of ferritin on peritransplant mortality.** Peritransplant mortality was defined as death within 3 months of transplant. A total of 6 of the 84 patients (7.1%) died within 100 days of alloHSCT. Univariate analysis showed that all of deaths occurred from among the high-ferritin (≥1000ng/mL) group. In the high-ferritin group, 6 of 51 patients died (11.7%), but no death was observed from among the 33 patients of the low-ferritin group (<1000ng/mL, 0%). Though all deaths were from among high-ferritin group, the difference between groups was not statistically significant ($p=0.077$) for peritransplant mortality. In our study, we showed that elevated pre-transplantation serum ferritin levels were significantly associated with increased rates of infectious events, including pneumonia, decreased

**Table 1. Patient characteristics**

| | Ferritin<1000ng/mL (33) N % | Ferritin≥1000ng/mL (51) N % | Total (84) N % |
|---|---|---|---|
| Age | | | |
| **Median (min-max)** | 29 (15-56) | 27 (18-59) | 28 (15-56) |
| **mean** | 45 | 40 | 29 |
| Gender | | | |
| ***male*** | 17 (51.5) | 26 (50.9) | 43 (51.2) |
| ***female*** | 16 (48.5) | 25 (49.1) | 41 (48.8) |
| Diagnosis | | | |
| ***AML*** | 11 (33.3) | 26 (50.9) | 37 (44.1) |
| ***ALL*** | 3 (9.1) | 13 (25.6) | 16 (19.1) |
| ***CML*** | 2 (6.0) | 0 | 2 (2.3) |
| ***AA*** | 6 (18.1) | 10 (19.7) | 16 (19.1) |
| ***NHL*** | 4 (12.1) | 1 (1.9) | 5 (5.8) |
| ***Others*** | 7 (21.2) | 1 (1.9) | 8 (9.6) |
| Median interval to tx (months) | | | |
| **<12 months** | 23 (69.7) | 35 (68.7) | 58 (69.1) |
| **>12 months** | 10 (30.3) | 16 (31.3) | 26 (30.9) |
| Graft source | | | |
| ***PBSC*** | 33 (100) | 51 (100) | 84 (100) |
| ***BM*** | 0 | 0 | 0 |
| Donor status | | | |
| ***Sibling*** | 31 (93.9) | 50 (98.2) | 81 (96.4) |
| ***Haploidentical*** | 2 (6.1) | 1 (1.8) | 3 (3.6) |
| ***Unrelated*** | 0 | 0 | 0 |
| **$CD34^+$ ($10^6$/kg)** | 6.7 (4-19) | 6.4 (3-14) | |
| Preparative regimen | | | |
| ***Cy/Bu*** | 15 (45.5) | 26 (50.9) | 41 (48.8) |
| ***Cy/TBI*** | 3 (9.1) | 10 (19.7) | 13 (15.4) |
| ***ATG/Flu/Cy*** | 7 (21.2) | 7 (13.8) | 14 (16.7) |
| ***Others*** | 8 (24.2)) | 8 (15.6) | 16 (19.1) |
| **HLA match** | | | |
| *full-match* | 27 (81.8) | 44 (86.2) | 71 (84.5) |
| *≥ 1 miss-match* | 6 (18.2) | 7 (13.8) | 13 (15.5) |

**Table 2. Serum iron status and albumin**

| Variables | Ferritin (<1000 ng/mL) N= 33 (39.2 %) median (min-max) | Ferritin (≥1000 ng/mL) N= 51 (60.8 %) median (min-max) | P |
|---|---|---|---|
| Ferritin (ng/ml) | 388.6 (18-905) | 1705.0 (1021-9513) | **<0.001** |
| Serum iron (μg/dL) | 95.0 (30-303) | 172.0 (30-396) | **0.004** |
| Total iron binding capacity (μg/dL) | 264.0 (111-401) | 270.0 (18-692) | 0.916 |
| Transferrin saturation (%) | 40.4 (13.8-97.5) | 75.4 (5.9-100) | 0.052 |
| Albumin (g/dl) | 3.9 (2-4.8) | 3.7 (1.6-4.8) | 0.353 |

disease-free survival (DFS) and overall survival (OS), as shown in Figures 1 and 2.

**Effect of time-to-transplant interval on survival.** The patients were divided into two groups according to time interval from diagnosis to transplantation (tx). One group comprised patients who had undergone alloHSCT before or within 12 months from diagnosis (<12 months; early tx) and the other group of those who had undergone alloHSCT more than 12 months from diagnosis (>12 months; late tx). The results of cox regression analysis showed that both overall survival (OS) and disease-free survival (DFS) rates were significantly higher in patients with a time-to-tx interval <12 months compared with the group time-to-tx interval>12 months (p=0.002 and p=0.008 respectively). The median survival in early transplant group was found to be 68 months (min-max; 34-101 months) and in late tx group 26 months ( min-max; 12-52 months).

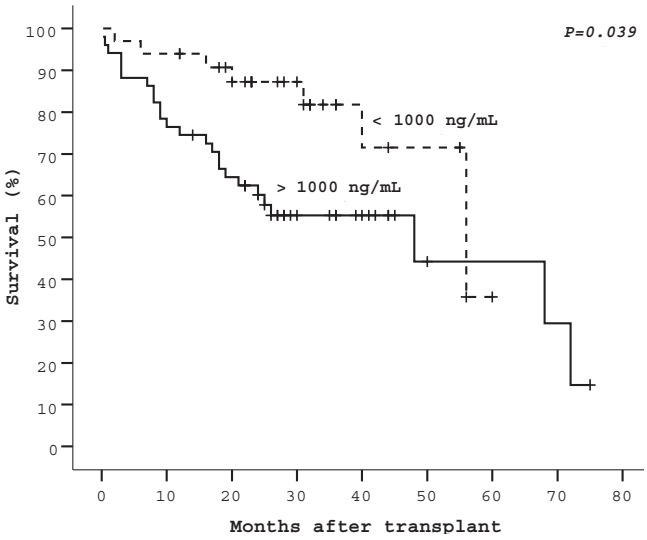


**Figure 1. Disease-free survival (DFS) analysis for ferritin levels**

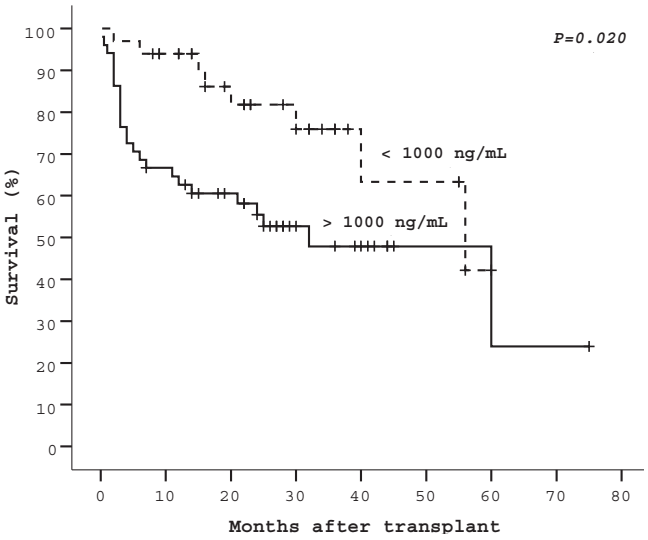


**Figure 2. Overall survival (OS) analysis for ferritin levels**

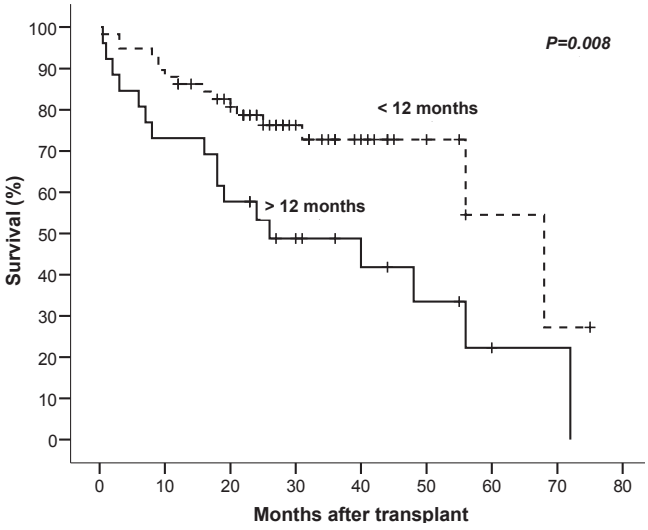


**Figure 3. Disease-free survival (DFS) analysis for time-to-transplant intervals**

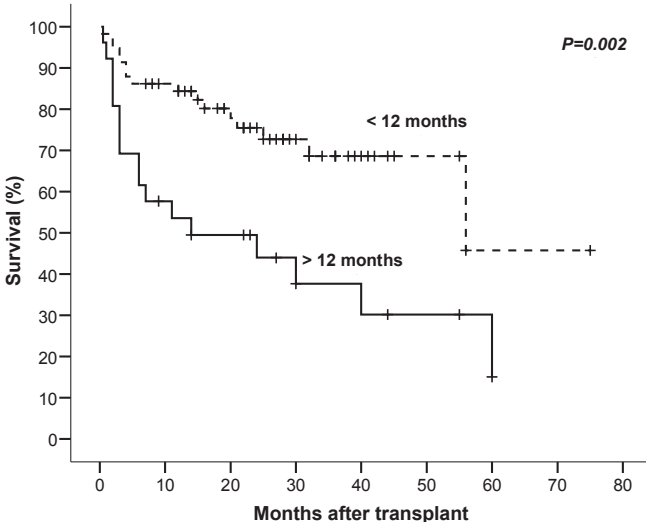


**Figure 4. Overall survival (OS) analysis for time-to-transplant intervals**

There was a strong association between survival rates and time-to-tx interval. Patients who underwent alloHSCT before or within 12 months from diagnosis, OS and DFS were found to be longer than patients whom underwent alloHSCT longer than 12 months from diagnosis (Figures 3 and 4) .

**Engraftment.** The median day for platelet engraftment was found to be 10.5 days (min-max: 8.0-39.0) in group ferritin<1000ng/ml and 11.5 days (7.0-30.0) in group ferritin≥1000 ng/ml. The difference was not statistically significant (p=0.273). The median day for neutrophil engraftment was found to be 14.5 days (8.0-39.0) in group ferritin<1000 ng/ml and 14.0 days (9.0-30.0) in group ferritin≥1000ng/ml. This difference was not statistically significant (p=0.882). In general estimation, ferritin levels had no effect on both platelet and neutrophil engraftment.The data are shown in Table 3.

**Overall survival (OS) and Disease-free survival (DFS) relation with ferritin.** A total of 6 patients (18.1%) died in the first 100 days of transplantation and 27 patients (81.9%) died after completing 100 days. Univariate and multivariate analysis showed that high pre-transplant ferritin levels (≥1000ng /mL) were correlated with decreased overall survival (OS) and disease-free survival (DFS) rates compared with lower pre-transplant ferritin levels (<1000ng /ml) (p=0.03 and p=0.02 respectively). A higher risk of death

**Table 3. Comparison of parameters affecting post-transplant outcomes in alloHSCT recipients**

| Variables | Ferritin (<1000 ng/mL) median (min-max) | Ferritin (≥1000 ng/mL) median (min-max) | P |
|---|---|---|---|
| **Platelet engraftment (day)** | 10.5 (8.0-39.0) | 11.5 (7.0-30.0) | 0.273 |
| **Neutrophil engraftment (day)** | 14.5 (8.0-39.0) | 14.0 (9.0-30.0) | 0.882 |
| | **N (%)** | **N (%)** | |
| **Infection** | | | |
| No | 15 (71.4) | 6 (28.6) | **0.001** |
| Yes | 18 (28.6) | 45 (71.4) | |
| **Acute GVHD** | | | |
| No | 28 (42.4) | 38 (57.6) | 0.291 |
| Yes | 5 (27.8) | 13 (72.2) | |
| **Chronic GVHD** | | | |
| No | 20 (35.7) | 36 (64.3) | 0.355 |
| Yes | 13 (46.4) | 15 (53.6) | |
| **Relapse** | | | |
| No | 28 (42.4) | 38 (57.6) | 0.291 |
| Yes | 5 (27.8) | 13 (72.2) | |
| **Exitus** | | | |
| No | 25 (49.0) | 26 (51.0) | **0.039** |
| Yes | 8 (24.2) | 25 (75.8) | |

Bold values are statistically significant

was observed in high-ferritin group (hazard ratio=2.27, CI:1.01-5.09, p=0.023 for OS and hazard ratio=2.49, CI:1.12-5.53 p=0.039 for DFS), among patients with a time –to-tx interval longer than 12 months (hazard ratio=2.45, CI:1.23-4.87, p=0.02 for OS and hazard ratio=2.78, CI:1.39-5.54, p=0.008 for DFS), in patients with ≥1 mismatch (hazard ratio =2.48, CI: 1.10-5.58, p=0.023 for OS and hazard ratio:2.61, CI:1.16-5.88, p=0.021 for DFS) and patients with infection (hazard ratio:2.92, p=0.046 for OS and hazard ratio:2.88, CI: 1.02-8.36, p=0.049 for DFS). No significant effect on OS and DFS among groups was observed for variables conditioning regimen, number of $CD34^+$ ($10^6$/kg), gender and diagnosis. The results are shown in Table 4.

## Discussion

This study was mainly focused on the predictive role of pre-transplantation serum ferritin levels on outcomes of patients having undergone alloHSCT in the post-transplant period.

Recent studies have suggested a marked relationship between iron overload and toxic and infectious complications in the early post-HSCT period in alloHSCT recipients, which indicates the effect of iron burden on mucositis, bacteremia, and fever [12,13]. Iron overload has been associated with increased susceptibility to organ damage and increased risk of infection [14,15]. Patients undergoing HSCT often have received multiple blood transfusions prior to transplantation, which probably contribute to elevated ferritin levels. Recently, iron overload has been shown to increase the toxic effects of conditioning regimens in HSCT recipients.

Elevated levels of pre-transplant ferritin were found to be associated with increased rates of fungal infections in alloHSCT recipients [16,17]. In our patients, there was a remarkable association between serum ferritin levels and infectious events, including pneumonia, of which the majority had a fungal origin. In iron overload states, increased availability of iron provides an important nutrient for both bacterial and fungal growth, and this may impair the host defense. There is a positive correlation between iron overload and infectious events in both allogeneic and autologous hematopoietic stem cell transplantation. Among these infections, bacteremia, invasive aspergillosis and mucormycosis are the most prevalent [18].

Kataoka et al [19] showed in a study of 264 patients who underwent alloHSCT that patients with high levels of ferritin prior to the transplantation had lower overall survival, and higher nonrelapse mortality. Also, these patients were found to be more likely to die due to infections and organ failure.

Patients who undergo alloHSCT often have history of multiple red blood cell (RBC) transfusions during chemotherapy prior to transplantation. This may give rise to elevated levels of ferritin in body stores. In our patients, it was not possible to obtain clear information about transfusions. Increased amounts of ferritin in body stores severely damage or abolish normal bactericidal mechanisms, leading to overwhelming growth of bacteria and fungi [20]. Iron does not only adversely affect the phagocytic, chemotactic, and bactericidal capacity of neutrophils and monocytes, but also inhibits the activity of natural killer cells and macrophages [21].

The data suggest that, in patients with thalassemia, iron overload causes deaths which are mainly due to cardiomyopa-

**Table 4. Univariate and multivariate prognostic factors for overall survival (OS) and disease-free survival (DFS) in alloHSCT recipients**

| Variable | OS | | DFS | |
|---|---|---|---|---|
| | Univariate | Multivariate | Univariate | Multivariate |
| | HR (%95 CI) | HR (%95 CI) | HR (%95 CI) | HR (%95 CI) |
| **Ferritin** | | | | |
| <1000 | 1.00 | 1.00 | 1.00 | 1.00 |
| ≥1000 | 2.27 (1.01-5.09) | 2.46 (1.10-5.52) | 2.49 (1.12-5.53) | 2.96 (1.32-6.62) |
| **Age** | 1.01 (0.97-1.04) | NS | 1.00 (0.97-1.04) | - NS |
| **Gender** | | | | |
| Male | 1.00 | - NS | 1.00 | - NS |
| Female | 1.00 (0.50-1.99) | - NS | 1.07 (0.54-2.13) | - NS |
| **Infection** | | | | |
| Yes | 1.00 | - NS | 1.00 | - NS |
| No | 2.92 (1.02-8.36) | - NS | 2.88 (1.00-8.26) | - |
| **Donor status** | | | | |
| Gender match | 1.00 | - NS | 1.00 | - |
| Gender mismatch | 0.85 (0.41-1.77) | - NS | 0.99 (0.48-2.04) | - |
| **Diagnosis** | | | | |
| 1 | 1.00 | - NS | 1.00 | - |
| 2 | 1.81 (0.77-4.25) | - NS | 1.76 (0.75-4.10) | - |
| 3 | 1.93 (0.69-5.41) | - NS | 1.37 (0.51-3.71) | - |
| 4 | 2.41 (0.66-8.87) | - NS | 2.09 (0.58-7.51) | - |
| **Time –to-tx interval (months)** | | | | |
| <12 | 1.00 | 1.00 | 1.00 | 1.00 |
| >12 | 2.45 (1.23-4.87) | 2.51 (1.27-4.99) | 2.78 (1.39-5.54) | 2.80 (1.39-5.63) |
| **Conditioning regimen** | | | | |
| Myeloablative | 1.00 | - NS | 1.00 | - |
| Nonmyeloablative | 1.04 (0.50-2.15) | - NS | 1.02 (0.50-2.11) | - |
| **HLA match** | | | | |
| Full match | 1.00 | 1.00 | 1.00 | 1.00 |
| ≥1 mismatch | 2.48 (1.10-5.58) | 2.69 (1.19-6.04) | 2.61 (1.16-5.88) | 2.81 (1.22-6.44) |
| **$CD34^+$ ($10^6$/kg)** | 0.96 (0.80-1.15) | - NS | 0.97 (0.81-1.15) | - |

thy and liver fibrosis before the introduction of iron chelation therapy [22]. Nevertheless, in our patients, the major cause of death in the high-ferritin group (ferritin≥1000ng/mL) was infection, the most prevalent form of which was pneumonia. It should be emphasized that patients who undergo alloHSCT are more susceptible to infections than patients receiving transfusions. This is because of prolonged neutropenia and breaks in the mucocutaneous barrier as a result of conditioning regimens, immunity defects and dysfunctions in the reticuloendothelial system [23].

Estimating the role of iron overload on GVHD, our results showed that the difference among groups for acute or chronic GVHD was not statistically significant. This was consistent with the findings of Armand et al [24]. Nevertheless; in a study performed by Mahindra et al [25], in patients with alloHSCT, it was shown that patients with a ferritin level>1910ng/ml had a lower incidence of acute and chronic GVHD. This may be explained by the immunosuppressive role of iron overload as a result of reduced $CD8^+$ T-cell counts [26]. Contrary to these findings, a study by Pullarkat et al.[27] found that the patients in high-ferritin group (ferritin>1000 ng/ ml) had an increased risk of acute GVHD in patients with HSCT.

In our study, time-to-transplant interval was found to be an important predictor of overall survival (OS) and disease-free survival (DFS). This may be due to earlier remission of some patients as a result of first or second-line chemotherapy regimens. It should be noted that chemoresistant patients underwent alloHSCT later than patients who achieved remission in first-line regimens. Patients who underwent alloHSCT in the early group (<12months) survived longer than patients in the late group (>12 months). This difference was statistically significant for both OS and DFS (p=0.002 and p=0.008 respectively).

Our study had several limitations. 1) This study was performed retrospectively in a single-center university hospital. It was difficult to determine the causes of death, infections and some other parameters such as albumin and ferritin. Therefore, further multicenter studies may provide further data regarding the association between iron status and transplant outcomes. 2) It is well known that serum ferritin is an acute phase reactant and is not a reliable indicator of total body iron

stores in patients with inflammation or infections. Therefore, albumin, which is a negative acute phase reactant, was included in the analysis [28,29] and there was no statistical significance between ferritin groups. However, serum ferritin level remains the most cost-effective, inexpensive and noninvasive measure for iron overload available worldwide [30,31]. It is important to estimate the significance of iron overload in patients who underwent alloHSCT using non-invasive imaging like liver-specific MRI.

This study showed that patients with elevated ferritin levels in the pretransplant period had poor survival due to especially infections in alloHSCT. It seems very important for physicians to take iron status into account for probable adverse effects on survival and prognosis in patients candidate for alloHSCT. This hyperferritinemia status may be treated with iron chelation and/or phlebotomy to achieve beter survival and outcomes in alloHSCT. We recently showed that oral deferasirox treatment in the posttransplant period for alloHSCT recipients is safe and effective way of iron chelation [32]. Such further studies will be helpful to confirm our findings.

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