

Pretransplant Serum Ferritin Levels and Outcomes after Myeloablative Allogeneic HSCT

Burcu Aslan Candir^{1*}, Sema Seçilmiş², Samet Yaman³, Ersin Bozan¹, Bahar Uncu Ulu¹, Dicle Iskender¹, Tuğçe Nur Yiğenoğlu¹, Merih Kızıl Çakar², Turgay Ulas¹, Mehmet Sinan Dal¹, Fevzi Altuntas^{1,4}

¹Department of Hematology and Bone Marrow Transplantation Center, Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, University of Health Sciences, Ankara, Turkey

²Department of Hematology, Etlik City Hospital, Ankara, Turkey

³Department of Hematology, Erol Olcok Training and Research Hospital, Çorum, Turkey

⁴School of Medicine, Department of Internal Medicine, Division of Hematology, Ankara Yıldırım Beyazıt University, Ankara, Turkey

ABSTRACT

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative treatment for hematologic malignancies. Serum ferritin, an indicator of iron overload and systemic inflammation, has been suggested as a prognostic biomarker for post-transplant outcomes.

The association between pre-transplant serum ferritin levels and post-transplant outcomes, particularly 100-day transplant-related mortality (TRM), was evaluated in acute leukemia patients who underwent their first allo-HSCT.

We conducted a retrospective analysis of 170 adult patients with acute leukemia who received their initial myeloablative allo-HSCT during complete remission from 2015 to 2021 at a single institution. Patients were divided into two groups based on their ferritin levels before the transplant: $<1500 \mu\text{g/L}$ and $\geq 1500 \mu\text{g/L}$. The primary endpoint was 100-day TRM. The mean age of the cohort was 39 years, and 60.6% had acute myeloid leukemia. The median level of ferritin was $1595 \mu\text{g/L}$. The high-ferritin group exhibited significantly higher 100-day mortality (10.8% vs. 1.3%, $p = 0.013$) and 100-day TRM (8.6% vs. 1.3%, $p=0.041$) than the low-ferritin group. Invasive fungal infections were more frequent in the high-ferritin group (11.8% vs. 3.9%, $p=0.091$). There were no notable differences in engraftment kinetics, cytomegalovirus reactivation, or graft-versus-host disease rates between the two groups.

High pre-transplant serum ferritin correlates with elevated early TRM and a tendency toward increased rates of invasive fungal infections post-allo-HSCT. Ferritin may be used as a simple and accessible biomarker for initial risk stratification, facilitating enhanced infectious monitoring and possible iron-reducing interventions in high-risk patients. Future multicenter studies are necessary to confirm these results.

Keywords: ferritin, allogeneic stem cell transplantation, acute leukemia, transplant-related mortality, invasive fungal infection

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains a curative treatment for several malignant and benign hematological diseases (1, 2). Despite significant advances in donor screening, preconditioning regimens, graft manipulation, and supportive care, allo-HSCT is associated with considerable transplant-related morbidity and mortality (1, 2) due to infections, organ failure, disease relapse, and graft-versus-host disease (GVHD) [1-3]. As a result, there is an increasing demand for easily measurable pretransplant biomarkers that can stratify

patients based on risk and customize transplant strategies.

Serum ferritin, a readily accessible indicator of iron levels, also functions as an acute-phase reactant, which may confound its interpretation in the context of malignancies and inflammatory disorders (4, 5). Nevertheless, elevated ferritin levels prior to a transplant may serve as a valuable prognostic indicator. Numerous studies indicate that elevated ferritin levels correlate with worse overall survival (OS), increased non-relapse mortality (NRM), delayed engraftment, and an elevated risk of infections in

*Corresponding Author: Dr. Burcu Aslan Candir, Department of Hematology and Bone Marrow Transplantation Center, Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, University of Health Sciences, Ankara, Turkey
Email: drburcuaslanandir@gmail.com, Tel.: +90 506 571 8516

ORCID ID: Burcu Aslan Candir: 0000-0003-3386-8984, Sema Seçilmiş: 0000-0003-2957-2339, Samet Yaman: 0000-0003-4081-1070, Ersin Bozan: 0000-0002-3307-3121, Bahar Uncu Ulu: 0000-0002-6230-9519, Dicle Iskender: 0000-0002-6062-6422, Tuğçe Nur Yiğenoğlu: 0000-0001-9962-8882, Merih Kızıl Çakar: 0000-0003-0978-0923, Turgay Ulas: 0000-0001-9332-663X, Mehmet Sinan Dal: 0000-0002-5994-2735, Fevzi Altuntas: 0000-0001-6872-3780

Received: 03.01.2026, Accepted: 31.08.2026

patients after undergoing allo-HSCT (6–8). A recent meta-analysis conducted by Pan et al. identified a correlation between elevated pre-transplant ferritin levels and reduced OS, progression-free survival (PFS), and NRM rates. Nonetheless, the role of ferritin in the risk of GVHD remains ambiguous (9). Magnetic resonance imaging (MRI) and other imaging modalities have demonstrated that elevated iron levels in the liver are associated with worse transplant outcomes (10). Recent studies indicate that free iron contributes to the onset of GVHD and veno-occlusive disease (VOD) through oxidative damage to the endothelium (11). In addition, there is evidence of an increased risk of GVHD in patients with elevated ferritin levels (7, 12), although recent prospective analyses, do not corroborate this association (6, 8, 9).

Free iron also causes oxidative tissue damage, impairs immune regulation, and increased risk of infections. A recent study showed that bone marrow iron levels did not increase the likelihood of fungal infections in patients with newly diagnosed acute leukemia [13]. Likewise, Sivgin et al., have reported an association between elevated pre-transplant iron levels and increased risk of invasive fungal pneumonia following HSCT (14). Additionally, post-transplant ferritin levels can also predict HSCT outcomes. Fingrut et al. demonstrated that elevated ferritin levels post-HSCT correlated with worse OS and increased NRM, even after adjusting for baseline ferritin levels (15). Furthermore, ferritin has been identified as an oncological biomarker in certain malignancies, especially in critically ill patients (16, 17).

Nevertheless, the prognostic value of pre-transplant ferritin remains controversial. Previous studies have reported inconsistent associations between pre-transplant ferritin levels and transplant-related mortality, GVHD, infections, and survival, largely due to heterogeneous patient populations, different conditioning regimens, variable ferritin cutoff values, and diverse transplantation settings. Furthermore, evidence derived from homogeneous cohorts of patients with acute leukemia undergoing first myeloablative allo-HSCT remains limited. Therefore, we hypothesized that high pre-transplant serum ferritin levels would be associated with increased early transplant-related mortality and infections. To test this hypothesis, we performed a retrospective single-center study to evaluate the association between pre-transplant ferritin levels and 100-day transplant-related mortality (TRM), engraftment, acute GVHD, cytomegalovirus (CMV) reactivation and invasive fungal infections in adult acute leukemia patients undergoing their first myeloablative allo-HSCT in complete remission (CR).

Materials and Methods

Subjects: This single-center retrospective non-randomized study included 170 patients who underwent their first transplantation for acute leukemias, specifically acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), while in CR from 2015 to 2021. All participants in the study were aged 18 years and above. Patients without comprehensive or essential information, including therapy specifics, engraftment data, GVHD status, relapse information, or survival results were excluded. Other exclusion criteria were hematological or non-hematological malignancies not meeting the study criteria, previous allo-HSCT, active disease at transplantation, and haploidentical transplantation. Additionally, patients who received stem cells from unspecified sources were also excluded.

Ethics approval and consent: Ethical approval was obtained from the relevant institutional ethics committee in accordance with the Declaration of Helsinki (Approval number: 2022-19/1591). Written informed consent was obtained from all patients authorizing the use of their data for research purposes prior to the transplantation.

Donor selection: Matched related, one mismatched related, matched unrelated, and one mismatched unrelated donors were selected for the patients. The patients underwent transplantation if they had a matched or one mismatched related donor; if there were no matched or one mismatched related donor, donor search was initiated from TURKOK, the national donor pool operated by the Ministry of Health. Unrelated donors were selected if a matched unrelated or one mismatched unrelated donor was found from the TURKOK pool.

Conditioning Regimens and Transplantation

Procedures: All laboratory values were obtained prior to the initiation of the conditioning regimen. The patients received myeloablative conditioning regimens according to the EBMT definitions; fludarabine 150 mg/m², busulfan 12.8 mg/kg, treosulfan 42 g/m², and fractionated 12 Gray total body irradiation (TBI). Fludarabine/busulfan ± ATLG ± post-transplant cyclophosphamide (PTCy), fludarabine/treosulfan ± ATLG ± PTCy were used for AML patients, and fludarabine/TBI ± ATLG ± PTCy combinations were used for ALL patients. For ATLG-containing regimens, ATLG (Grafalon) was given from day -5 (pre-transplantation) to day -3 at the total dose of 7.5 mg/kg (2.5 mg/kg/day) for matched related donors and at the total dose of 15

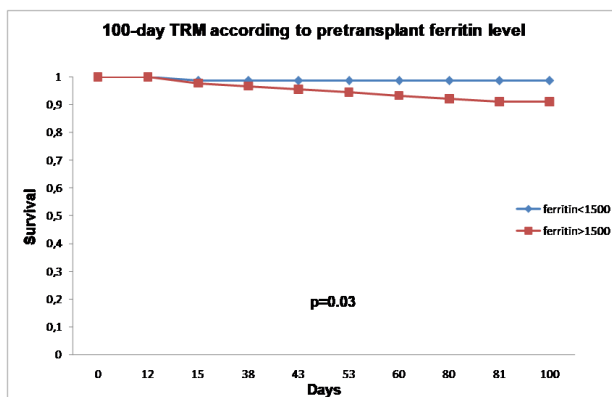


Fig. 1. Kaplan–Meier analysis of 100-day Transplant-Related Mortality Stratified By Pre-Transplant Serum Ferritin Levels

mg/kg (5 mg/kg/day) for unrelated donors based on our standard operating procedures. Stem cells enriched from peripheral blood and bone marrow were used for transplantation. Cyclophosphamide was administered on days 3 and 4 post-HSCT at the dose of 50 mg/kg/day. G-CSF was given to all patients starting on day +5 at the dose of 5 µg/kg/day until absolute neutrophil count recovery.

Definitions: Neutrophil engraftment was defined as a measurable neutrophil count $>0.5 \times 10^9/L$ for 3 consecutive days. Primary graft failure was defined as failure to recover neutrophil count by day +28 post-HSCT without evidence of relapsed disease. Secondary graft failure was defined as graft failure occurring after either initial partial or complete engraftment, and manifesting as a recurrent pancytopenia with a neutrophil count $<0.5 \times 10^9/L$ without evidence of relapsed disease.

TRM was defined as deaths related to treatment complications. The physician confirmed the diagnosis of acute GVHD based on clinical, radiological, and laboratory results. The Mount Sinai Acute GVHD International Consortium (MAGIC) standards were used to assess the staging and grading of acute GVHD. National Institutes of Health (NIH) consensus criteria were used for the diagnosis and staging/grading of chronic GVHD.

Endpoints: The primary endpoint was TRM at 100 days. Secondary endpoints included incidence of acute GVHD, CMV reactivation, and invasive fungal infections.

Statistical analysis: Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Normally distributed continuous variables are presented as mean $\pm$ standard deviation (SD), whereas non-normally distributed variables are presented as median

(interquartile range, IQR). Categorical variables are expressed as number and percentage.

Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal ferritin cutoff for predicting 100-day TRM. However, no statistically significant optimal threshold was identified (AUC = 0.649, 95% CI 0.462–0.837; $p = 0.132$). Moreover, no universally accepted ferritin cutoff has been established for patients undergoing allo-HSCT, and previous studies have reported thresholds ranging from 1000 to 2500 µg/L. Given the lack of a statistically significant ROC-derived cutoff, the median pre-transplant ferritin level of our cohort (1595 µg/L), and the previously reported threshold of 1500 µg/L in transplantation studies was selected as the predefined cutoff for the present analysis. Patients were accordingly classified into a high-ferritin group (≥ 1500 µg/L) and a low-ferritin group (< 1500 µg/L). None of the patients received iron chelation therapy before allogeneic HSCT.

The baseline demographic, disease-related, transplant-related, and post-transplant characteristics were compared between the low- and high-ferritin groups. Continuous variables were analyzed using the Independent Samples t test or the Mann-Whitney U test according to data distribution. Categorical variables were compared using the Pearson chi-square test or Fisher's exact test, as appropriate. The 100-day TRM of both groups was compared by Kaplan-Meier survival analysis with the log-rank test. Patients who died because of transplant-related causes within the first 100 days after transplantation were considered events. Patients who were alive at day +100 or died from relapse before day +100 were censored at the time of last follow-up or day +100 as appropriate.

Univariate Cox proportional hazards regression analysis was performed to identify variables associated with 100-day TRM. Variables included age, sex, diagnosis (AML/ALL), pre-transplant ferritin level, pre-transplant C-reactive protein (CRP) level, TBI-containing conditioning, ATLG-containing conditioning, PTCy, acute GVHD, CMV infection, and invasive fungal infection. Variables with a p value <0.10 in the univariate analysis were incorporated into the multivariate Cox proportional hazards regression model. Hazard ratios (HRs) are reported with their corresponding 95% confidence intervals (CIs). All statistical tests were two-sided and p values <0.05 were considered statistically significant.

Because of the retrospective observational design of this study, no a priori sample size calculation was performed. All consecutive eligible patients who underwent allo-HSCT during the study period and met the predefined inclusion criteria were included in the analysis.

Results

Baseline Patient Characteristics: A total of 170 patients were included in the study, with a mean age of 39 ± 13.6 years, 58.2% of the patients were male. AML was the predominant diagnosis (60.6%). The median number of prior treatment lines was 2 (Q1-Q3, 1-3). The median pre-transplant ferritin level was 1595 $\mu\text{g/L}$ (Q1-Q3, 986–2362), and median transferrin saturation (TS) was 50.4% (Q1-Q3, 29.4–126.4). Peripheral blood stem cells were used as the graft source in the majority of patients (96.5%). Most patients had a related donor (68.2%) and a fully matched donor (81.2%). Conditioning regimens included TBI in 39.4% and ATLG in 72.9% of the patients. GVHD prophylaxis regimen primarily consisted of PTCy and cyclosporine A (CsA) in 71.8% of cases. Table 1 summarizes the baseline demographic and transplant-related characteristics of the cohort.

Post-transplant Clinical Outcomes: Following allo-HSCT, the median time to neutrophil engraftment was 15 days (Q1-Q3, 14-16), and the median time to platelet engraftment was 14 days (Q1-Q3, 12-19). Seven patients (4.1%) experienced engraftment failure, while 4.1% of the cohort experienced VOD. Acute GVHD of any grade developed in 33 patients (19.4%), whereas grade III-IV acute GVHD occurred in 12 patients (7.1%). Chronic GVHD was reported in 24 patients (14%), with extensive/severe chronic GVHD observed in 5 patients (2.9%). CMV reactivation occurred in 69 patients (40.5%), with a median onset of 34 days (Q1-Q3, 16-43). Invasive fungal infections were diagnosed in 14 patients (8.2%), with a median time to diagnosis of 16 days (Q1-Q3, 13-22). Table 2 summarizes the post-transplant clinical outcomes of the study cohort.

Comparison By Pre-Transplant Ferritin Level: ROC analysis demonstrated limited discriminatory ability of pre-transplant serum ferritin for predicting 100-day TRM (AUC = 0.649, 95% CI 0.462–0.837; $p = 0.132$) (Supplementary Figure S1). Patients were divided into two groups based on pre-transplant ferritin levels: $<1500 \mu\text{g/L}$ ($n=77$) and $\geq 1500 \mu\text{g/L}$ ($n=93$). The proportion of patients with AML was significantly higher in the high-ferritin group (67.7% vs. 51.9%, $p=0.036$). Likewise, the pre-transplant CRP levels (median 11.5 vs. 4.4 mg/L, $p=0.001$) were also significantly elevated in the high-ferritin group. Furthermore, TBI-based conditioning was more frequent in the low ferritin group (48.1% vs. 32.3%, $p=0.036$), while other transplant-related variables including stem cell source, donor type, HLA matching, and use of ATLG did not differ significantly between the two groups. The times to

neutrophil or platelet engraftment were also similar in both groups. VOD (6.5% vs. 1.3%, $p=0.129$) and engraftment failure (6.5% vs. 1.3%, $p=0.129$) were numerically higher in the high-ferritin group, although the association did not reach statistical significance. The incidence of acute GVHD, grade III-IV acute GVHD, and chronic GVHD was comparable between the two groups, there was no significant difference in CMV reactivation rates as well (38.7% vs. 42.9%, $p=0.584$). However, invasive fungal infections were more common in the high-ferritin group (11.8% vs. 3.9%), although the difference did not reach statistical significance ($p=0.091$). The baseline characteristics and post-transplant outcomes stratified by pre-transplant ferritin level are summarized in Table 3.

The 100-day TRM

The overall 100-day mortality and 100-day TRM rates for the entire cohort were 6.4% and 5.3% respectively. When stratified by pre-transplant ferritin level, patients with ferritin $\geq 1500 \mu\text{g/L}$ had significantly higher 100-day mortality than those with ferritin $<1500 \mu\text{g/L}$ (10.8% vs. 1.3%, $p=0.013$). Similarly, the incidence of 100-day TRM was significantly higher in the high ferritin group (8.6% vs. 1.3%, $p=0.041$). Kaplan–Meier analysis further showed that patients with pre-transplant ferritin levels $\geq 1500 \mu\text{g/L}$ had significantly inferior 100-day TRM-free survival compared with those with ferritin $<1500 \mu\text{g/L}$ (log-rank $p=0.03$). The Kaplan–Meier curves are shown in Figure 1.

In the univariate Cox regression analysis, pre-transplant ferritin $\geq 1500 \mu\text{g/L}$ showed a trend toward an increased risk of 100-day TRM (HR= 6.978, 95% CI: 0.873–55.806, $p = 0.067$). Invasive fungal infections were significantly associated with increased TRM (HR: 7.130, 95% CI: 1.780–28.558, $p = 0.006$), while the use of PTCy-based regimens was significantly associated with a reduced risk of 100-day TRM (HR = 0.191, 95% CI: 0.048-0.763, $p= 0.019$). In the multivariate Cox regression analysis, PTCy-based regimens were significantly associated with a reduced risk of 100-day TRM (HR = 0.149, 95% CI: 0.036–0.621 $p = 0.009$). On the other hand, having fungal infections was independently associated with increased risk of 100-day TRM (HR=7.717, 95% CI: 1.828-32.574, $p=0.005$). Although not statistically significant, higher ferritin levels showed a strong trend toward increased 100-day TRM (HR = 7.713, 95% CI: 0.947–62.847, $p = 0.056$). Other variables, including age, sex, primary disease, pre-transplant CRP levels, TBI or ATLG conditioning regimen, acute GVHD, and CMV infections did not show a significant correlation to 100-day TRM in univariate

Table 1: Baseline Characteristics of the Study Cohort (N = 170)

Variable	Value
Age, Mean $\pm$ SD, years	39 $\pm$ 13.6
Sex, Female/Male, n (%)	71 (41.8) / 99 (58.2)
Diagnosis, n (%)	
AML	103 (60.6)
ALL	67 (39.4)
Prior treatment lines, median (Q1-Q3)	2 (1-3)
Pre-transplant ferritin, median (Q1-Q3), μ g/L	1595 (986–2362)
Pre-transplant transferrin saturation, median (Q1-Q3), %	50.4 (29.4–126.4)
Pre-transplant ferritin group, n (%)	
<1500 μ g/L	77 (45.6)
$\geq$ 1500 μ g/L	93 (54.4)
Pre-transplant CRP, median (Q1-Q3), mg/L	7.1 (2.6-20.1)
EBMT risk score, median (Q1-Q3),	2 (1–3)
Related donor, n (%)	116 (68.2)
HLA full match (10/10), n (%)	138 (81.2)
Peripheral blood stem cell source, n (%)	164 (96.5)
TBI, n (%)	67 (39.4)
ATLG, n (%)	124 (72.9)
GVHD prophylaxis regimen, n (%)	
PTCy + CsA	122 (71.8)
CsA alone	26 (15.3)
CsA + MTX	14 (8.2)
Others	8 (4.7)

Abbreviations: SD, standard deviation; **Q1–Q3**, first quartile to third quartile (25th–75th percentiles); AML: Acute Myeloid Leukemia; ALL: Acute Lymphoblastic Leukemia; TS: transferrin Saturation; CRP: C-reactive protein; EBMT: European Society for Blood and Marrow Transplantation; HLA: Human Leukocyte Antigen; TBI: Total Body Irradiation; ATLG: Anti-T Lymphocyte Globulin; PTCy: Post-transplant Cyclophosphamide; GVHD: Graft-versus-Host Disease; CsA: Cyclosporine A; MTX: Methotrexate. Continuous variables are presented as mean $\pm$ SD or median (Q1–Q3), as appropriate; categorical variables are presented as n (%)

analyses. The results of univariate and multivariate analyses have been summarized in Table 4.

The median follow-up duration was 27 months (range, 0.7–83.0). During the follow-up, relapse occurred in 39 patients (22.8%), and overall mortality rate was 31.6%. The leading cause of death was disease progression (57.4%), followed by TRM (31.5%). Although relapse (26.9% vs. 18.2%, $p=0.179$) and overall mortality (37.6% vs. 24.7%, $p=0.071$) were numerically higher in the high-ferritin group than in the low-ferritin group, the differences did not reach statistical significance.

Discussion

The prognostic significance of ferritin levels in patients undergoing HSCT has garnered considerable attention in recent years. Ferritin is an indicator of iron overload as well as systemic

inflammation (17-19). Thus, elevated ferritin levels may be associated with a predisposition to infections, organ toxicity, and immune dysregulation. In this retrospective study, we investigated the impact of pre-transplant serum ferritin levels on transplant outcomes in patients who underwent allo-HSCT with a MAC regimen during their first remission of acute leukemia. Our findings show that high serum ferritin levels ($\geq 1500 \mu\text{g/L}$) were linked to an increased risk of 100-day TRM ($p=0.03$, log-rank). Furthermore, invasive fungal infections were more common in patients with high ferritin levels ($p=0.091$). On the other hand, pre-transplant ferritin levels had no significant impact on the days to engraftment, and the rates of VOD, CMV infection and acute GVHD.

In our study, the 100-day TRM rate was significantly higher in patients with pre-transplant

Table 2: Post-transplant Clinical Outcomes of the Study Cohort (N=170)

Neutrophil engraftment, median (Q1-Q3), days	15 (14–16)
Platelet engraftment, median (Q1-Q3), days	14 (12–19)
VOD, n (%)	7 (4.1)
Engraftment failure, n (%)	7 (4.1)
Acute GVHD (<i>any grade</i>), n (%)	33 (19.4)
Liver involvement	18 (10.5)
Skin involvement	19 (11.2)
Gastrointestinal involvement	9 (5.3)
Grade III-IV acute GVHD, n (%)	12 (7.1)
Chronic GVHD, n (%)	24 (14)
Liver involvement	16 (9.4)
Skin involvement	11 (6.5)
Gastrointestinal involvement	2 (1.2)
Extensive/severe chronic GVHD, n (%)	5 (2.9)
CMV infection, n (%)	69 (40.5)
Time to CMV infection, median (Q1–Q3), days	34 (16–43)
Invasive fungal infection, n (%)	14 (8.2)
Time to invasive fungal infection, median (Q1–Q3), days	16 (13–22)
100-day mortality, n (%)	11 (6.4)
100-day TRM, n (%)	9 (5.3)
Relapse, n (%)	39 (22.8)
Overall mortality, n (%)	54 (31.6)
Causes of death, (n=54)	
Disease progression	31 (57.4)
TRM	17 (31.5)
Other causes	6 (11.1)

Abbreviations: VOD: Veno-Occlusive Disease; GVHD: Graft-versus-Host Disease; CMV: Cytomegalovirus; TRM: Transplant-Related Mortality, SD, standard deviation; Q1–Q3, first quartile to third quartile (25th–75th percentiles). Continuous variables are presented as mean $\pm$ SD or median (Q1–Q3), as appropriate; categorical variables are presented as n (%)

ferritin levels of ≥ 1500 $\mu\text{g/L}$ (8.6% vs. 1.3%, $p=0.041$). A large case series based on CIBMTR data demonstrated that biomarkers such as elevated CRP, increased ferritin, and low albumin were associated with post-transplant mortality (19). Similarly, Mahindra et al. (20) and Oakes et al. (21) reported that elevated ferritin levels negatively affected survival not only after MAC but also non-MAC and RIC regimens. A 2017 meta-analysis suggested that high ferritin levels were associated with inferior OS and PFS but had no significant impact on acute GVHD and might even reduce the incidence of chronic GVHD (12). In our cohort as well, there was no significant relationship between ferritin levels and acute GVHD or grade III-IV acute GVHD.

Previous studies have correlated elevated ferritin with mucositis, GVHD, and hepatic toxicity in

both pediatric and adult populations (22, 23). We did not systematically evaluate different organ toxicities according to the pre-transplant ferritin levels, which should be considered a limitation. Nevertheless, our results support the negative impact of elevated ferritin levels on survival and TRM as reported in previous studies. For example, Pullarkat et al. demonstrated that ferritin levels above 1000 $\mu\text{g/L}$ increased NRM and decreased survival (7). Likewise, Armand et al. identified a significant relationship between logarithmic increases in ferritin and early mortality (8). In patients with myelofibrosis, ferritin levels ≥ 4000 $\mu\text{g/L}$ were associated with increased NRM and incidence of acute GVHD (24).

We identified invasive fungal infection as a strong predictor of early TRM. Consistent with previous studies, our findings suggest that high ferritin

Table 3: Baseline Characteristics and Transplant

Variable	Low Ferritin (n=77)	High Ferritin (n=93)	p-value
Age, Mean $\pm$ SD, years	36.8 $\pm$ 13.5	40.9 $\pm$ 13.4	0.053
Sex, n (%)			0.565
Female/ Male	34 (44.2)/ 43 (55.8)	37 (39.8)/ 56 (60.2)	
Diagnosis, n (%)			0.036
AML	40 (51.9)	63 (67.7)	
ALL	37 (48.1)	30 (32.3)	
Prior treatment lines, median (Q1-Q3)	2 (2-3)	2 (2-3)	0.080
Pre-transplant CRP, median (Q1-Q3), mg/L	4.4 (1.5-9.7)	11.5 (5.3-28.2)	<0.001
Peripheral blood stem cell source, n (%)	74 (96.1)	90 (96.8)	1.000
Related donor, n (%)	53 (68.8)	63 (67.7)	0.879
HLA full match, n (%)	62 (80.5)	76 (81.7)	0.842
TBI-based conditioning, n (%)	37 (48.1)	30 (32.3)	0.036
ATLG, n (%)	51 (66.2)	73 (78.3)	0.073
PTCy, n (%)	55 (71.4)	67 (72.0)	0.929
Neutrophil engraftment, median (Q1-Q3), days	14 (13-15)	15 (14-16)	0.290
Platelet engraftment, median (Q1-Q3), days	13 (12-17)	14 (13-20)	0.170
VOD, n (%)	1 (1.3)	6 (6.5)	0.129
Engraftment failure, n (%)	1 (1.3)	6 (6.5)	0.129
Acute GVHD (any grade), n (%)	16 (20.8)	16 (17.2)	0.553
Grade III-IV acute GVHD, n (%)	5 (6.5)	7 (7.5)	0.465
CMV infection, n (%)	33 (42.9)	36 (38.7)	0.584
Invasive fungal infection, n (%)	3 (3.9)	11 (11.8)	0.091
100-day mortality, n (%)	1 (1.3)	10 (10.8)	0.013
100-day TRM, n (%)	1 (1.3)	8 (8.6)	0.041
Relapse, n (%)	14 (18.2)	25 (26.9)	0.179
Overall mortality, n (%)	19 (24.7)	35 (37.6)	0.071

Outcomes Stratified by Pretransplant Ferritin Level

Abbreviations: SD, standard deviation; Q1–Q3, first quartile to third quartile (25th–75th percentiles); AML: Acute Myeloid Leukemia; ALL: Acute Lymphoblastic Leukemia; HLA: Human Leukocyte Antigen; TBI: Total Body Irradiation; ATLG: Anti-T Lymphocyte Globulin; VOD: Veno-Occlusive Disease; GVHD: Graft-versus-Host Disease; CMV: Cytomegalovirus; TRM: Transplant-Related Mortality; ECOG: Eastern Cooperative Oncology Group; CRP: C-reactive protein; EBMT: European Society for Blood and Marrow Transplantation; PTCy: Post-transplant Cyclophosphamide.

Continuous variables are presented as mean $\pm$ SD or median (Q1–Q3), as appropriate. Categorical variables are presented as number (%). Continuous variables were compared using the independent samples t test or the Mann–Whitney U test, as appropriate. Categorical variables were compared using the Pearson chi-square test or Fisher's exact test, as appropriate

levels are associated with an increased risk of fungal infections, particularly in the early post-transplant period (14, 25).

In our study, patients receiving PTCy demonstrated a decreased incidence of TRM, and the use of a PTCy-based regimen was independently associated with reduced TRM. This aligns with existing literature that supports the role of PTCy in reducing GVHD and consequently TRM (3, 26). Therefore, pre-transplant ferritin levels also hold promise as biomarkers to

guide treatment decisions, and should be considered when choosing a strategy for GVHD prophylaxis.

However, our results contradict those of Uysal et al., who did not find a significant association between pre-transplant ferritin levels with post-transplant outcomes, such as engraftment, GVHD, TRM, and OS in a real-life Turkish cohort of 69 allo-HSCT recipients. While both studies evaluated the prognostic role of pre-transplant ferritin, methodological differences have to be taken into

Table 4: Univariate and Multivariate Cox Regression Analysis of Factors Associated with 100-day TRM

	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	P
Ferritin ≥ 1500 $\mu\text{g/L}$	6.978 (0.873-55.806)	0.067	7.713 (0.947-62.847)	0.056
Invasive fungal infections	7.130 (1.780-28.558)	0.006	7.717 (1.828-32.574)	0.005
PTCy-containing regimen	0.191 (0.048-0.763)	0.019	0.149 (0.036-0.621)	0.009
Age	1.035 (0.985-1.088)	0.175		
Sex	0.353 (0.088-1.410)	0.141		
Primary disease	0.792 (0.198-3.165)	0.741		
Pre-transplant CRP	1.005 (0.978-1.033)	0.727		
TBI-containing conditioning	0.446 (0.093-2.145)	0.313		
ATLG-containing conditioning	1.353 (0.281-6.513)	0.706		
Acute GVHD	0.511 (0.064-4.089)	0.527		
CMV infections	0.708 (0.177-2.830)	0.625		

Abbreviations: HR: Hazard Ratio; CI: Confidence Interval; GVHD: Graft-versus-host disease; CMV: Cytomegalovirus; TBI: Total body irradiation; ATLG: Anti-T Lymphocyte Globulin; TRM: Transplant-Related Mortality; CRP: C reactive protein.

Only variables with $p < 0.10$ in the univariate analysis were included in the multivariate Cox regression model

account when interpreting these apparently contradictory findings (27). The population studied by Uysal et al. was heterogeneous in terms of hematological diagnoses, donor types, and myeloablative and reduced-intensity conditioning regimens. Conversely, our study was confined to a larger and clinically more homogeneous cohort of patients with acute leukemia who underwent their first allo-HSCT in CR, and received myeloablative conditioning. The homogeneity of our cohort may have allowed a clearer assessment of the independent prognostic value of ferritin in the early post-transplant period by reducing disease and treatment-related heterogeneity. Moreover, Uysal et al. used a ferritin cutoff of $1000 \mu\text{g/L}$, while we used a pre-specified cutoff of $1500 \mu\text{g/L}$ determined by the median ferritin level in our cohort ($1595 \mu\text{g/L}$), previous transplantation studies, and the lack of a statistically significant ROC-derived threshold. Notably, our primary endpoint was 100-day TRM, which is a clinically meaningful measure of early transplantation toxicity, while Uysal et al. focused mainly on OS. These differences in study population, transplant characteristics, ferritin distribution and endpoint selection may explain the discordant results. Nevertheless, both studies consistently demonstrated that pre-transplant ferritin was not associated with engraftment kinetics or the incidence of acute and chronic GVHD, indicating that its prognostic value may be more closely associated with early transplant-related complications than transplantation outcomes in general.

This study has several limitations. First, its retrospective single-center design limits the

generalizability of the findings, and may have introduced selection bias. Second, although the study included a relatively homogeneous cohort of patients with acute leukemia undergoing their first myeloablative allo-HSCT, the overall sample size and the limited number of 100-day TRM events may have reduced the statistical power and the stability of the multivariate Cox regression model, as reflected by the wide CIs. Third, since the ROC analysis did not identify a statistically significant optimal ferritin cutoff, the threshold of $1500 \mu\text{g/L}$ was selected based on previous literature and the median ferritin level of our cohort. In addition, serum ferritin is an acute-phase reactant that reflects not only iron overload but also systemic inflammation; therefore, residual confounding related to inflammatory status cannot be completely excluded despite adjusting for pre-transplant CRP levels. Finally, ferritin was measured at a single pre-transplant time point, and longitudinal changes in ferritin levels or direct measures of tissue iron overload, such as MRI data, were not available. Therefore, prospective multicenter studies with larger cohorts and a greater number of clinical events are warranted to validate these findings and further define the prognostic role of pre-transplant ferritin in allo-HSCT.

In conclusion, pre-transplant serum ferritin level is a promising marker for post-HSCT prognosis, particularly for TRM. Elevated ferritin levels are associated with a higher susceptibility to invasive fungal infections and potential immune dysregulation. Patients with ferritin levels ≥ 1500

µg/L should be considered high risk, and may benefit from closer monitoring, and optimized supportive care. Prospective studies will have to be conducted to determine whether iron-reducing interventions could improve transplant outcomes.

References

- Balassa K, Danby R, Rocha V. Haematopoietic stem cell transplants: principles and indications. *Br J Hosp Med (Lond)*. 2019;80(1):33-39.
- Simpson E, Dazzi F. Bone Marrow Transplantation 1957-2019. *Front Immunol*. 2019;10:1246.
- Namdaroglu S, Kaya AH, Batgi H, et al. Impacts of post-transplantation cyclophosphamide treatment after allogeneic hematopoietic stem cell transplantation in acute myeloid leukemia. *Sci Rep*. 2019;9(1):2046.
- Girelli D, Nemeth E, Swinkels DW. Hepcidin in the diagnosis of iron disorders. *Blood*. 2016;127(23):2809-2813.
- Weiss G. Anemia of Chronic Disorders: New Diagnostic Tools and New Treatment Strategies. *Semin Hematol*. 2015;52(4):313-320.
- Wermke M, Schmidt A, Middeke JM, et al. MRI-based liver iron content predicts for nonrelapse mortality in MDS and AML patients undergoing allogeneic stem cell transplantation. *Clin Cancer Res*. 2012;18(23):6460-6468.
- Pullarkat V, Blanchard S, Tegtmeier B, et al. Iron overload adversely affects outcome of allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2008;42(12):799-805.
- Armand P, Kim HT, Cutler CS, et al. Prognostic impact of elevated pretransplantation serum ferritin in patients undergoing myeloablative stem cell transplantation. *Blood*. 2007;109(10):4586-4588.
- Pan W, Teng Q, Chen H, et al. Association between the pre-transplantation serum ferritin level and outcomes of hematopoietic stem cell transplantation: A systematic review and meta-analysis. *Heliyon*. 2024;10(18):e37436.
- Majhail NS, Lazarus HM, Burns LJ. Iron overload in hematopoietic cell transplantation. *Bone Marrow Transplant*. 2008;41(12):997-1003.
- Hilken A, Langebrake C, Wolschke C, et al. Impact of non-transferrin-bound iron (NTBI) in comparison to serum ferritin on outcome after allogeneic stem cell transplantation (ASCT). *Ann Hematol*. 2017;96(8):1379-1388.
- Yan Z, Chen X, Wang H, et al. Effect of pre-transplantation serum ferritin on outcomes in patients undergoing allogeneic hematopoietic stem cell transplantation: A meta-analysis. *Medicine (Baltimore)*. 2018;97(27):e10310.
- Apostolidi EA, Gamaletsou MN, Arapaki M, et al. Bone Marrow Iron Stores Are Not Associated with Increased Risk for Invasive Fungal Infections in Patients with Newly Diagnosed Acute Leukemia or Myelodysplastic Syndrome in Transformation: Is There a Relationship?. *J Fungi (Basel)*. 2023;9(7):748.
- Sivgin S, Baldane S, Kaynar L, et al. Pretransplant iron overload may be associated with increased risk of invasive fungal pneumonia (IFP) in patients that underwent allogeneic hematopoietic stem cell transplantation (alloHSCT). *Transfus Apher Sci*. 2013;48(1):103-108.
- Fingrut W, Law A, Lam W, et al. Post-transplant ferritin level predicts outcomes after allogeneic hematopoietic stem cell transplant, independent from pre-transplant ferritin level. *Ann Hematol*. 2021;100(3):789-798.
- Ramírez-Carmona W, Díaz-Fabregat B, Yuri Yoshigae A, et al. Are Serum Ferritin Levels a Reliable Cancer Biomarker? A Systematic Review and Meta-Analysis. *Nutr Cancer*. 2022;74(6):1917-1926.
- Hsu CC, Senussi NH, Fertrin KY, Kowdley KV. Iron overload disorders. *Hepatol Commun*. 2022;6(8):1842-1854.
- Eisfeld AK, Westerman M, Krahel R, et al. Highly Elevated Serum Hepcidin in Patients with Acute Myeloid Leukemia prior to and after Allogeneic Hematopoietic Cell Transplantation: Does This Protect from Excessive Parenchymal Iron Loading?. *Adv Hematol*. 2011;2011:491058.
- Artz AS, Logan B, Zhu X, et al. The prognostic value of serum C-reactive protein, ferritin, and albumin prior to allogeneic transplantation for acute myeloid leukemia and myelodysplastic syndromes. *Haematologica*. 2016;101(11):1426-1433.
- Mahindra A, Sobecks R, Rybicki L, et al. Elevated pretransplant serum ferritin is associated with inferior survival following nonmyeloablative allogeneic transplantation. *Bone Marrow Transplant*. 2009;44(11):767-768.
- Oakes R, Sood N, Pearce R, Swirsky D, Cook G, Gillece M. Prognostic impact of serum ferritin concentration on survival following reduced-intensity conditioned allogeneic haemopoietic SCT. *Bone Marrow Transplant*. 2010;45(12):1754-1755.

22. Sucak GT, Yegin ZA, Ozkurt ZN, Aki SZ, Yağci M. Iron overload: predictor of adverse outcome in hematopoietic stem cell transplantation. *Transplant Proc.* 2010;42(5):1841-1848.
23. Küpesiz FT, Hazar V, Eker N, et al. Retrospective Evaluation of Relationship Between Iron Overload and Transplantation Complications in Pediatric Patient Who Underwent Allogeneic Stem Cell Transplantation Due to Acute Leukemia and Myelodysplastic Syndrome. *J Pediatr Hematol Oncol.* 2020;42(5):e315-e320.
24. Yoon JH, Min GJ, Park SS, et al. HLA-mismatched donor and high ferritin level showed poor clinical outcomes after allogeneic hematopoietic cell transplantation in patients with advanced myelofibrosis. *Ther Adv Hematol.* 2020;11:2040620720936935.
25. Choi JK, Cho SY, Yoon SS, et al. Epidemiology and Risk Factors for Invasive Fungal Diseases among Allogeneic Hematopoietic Stem Cell Transplant Recipients in Korea: Results of "RISK" Study. *Biol Blood Marrow Transplant.* 2017;23(10):1773-1779.
26. Jin X, Yang Y, Chen X. Post-transplant cyclophosphamide versus anti-thymocyte globulin in haploidentical stem cell transplantation: a systematic review and meta-analysis. *Ann Hematol.* 2025;104(3):1317-1328
27. Uysal A, Erkurt MA, Kuku I, et al. The Impact of Ferritin Levels on Outcomes of Allogeneic Hematopoietic Stem Cell Transplantation: Real-Life Data. *Selcuk Medical Journal.* 2026;42(2): 168–174.