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Adverse Prognostic Impact of Pretransplant Serum Ferritin and Hepcidin on Survival Outcomes After Allogeneic Hematopoietic Stem Cell Transplantation

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To the Editor,

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains limited by significant morbidity and mortality. Scoring systems, such as the Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) have been introduced to estimate the risk of transplant-related mortality. Serum ferritin (SF) is frequently elevated in transplant candidates [1, 2] and further peaks around day 42 posttransplant, reflecting iron overload (IO) due to red blood cell (RBC) transfusions and conditioning-induced erythropoietic suppression [3]. High SF has been associated with inferior overall survival (OS) or progression-free survival (PFS) and higher non-relapse mortality (NRM) [4], but a meta-analysis combining four studies investigating more specifically liver iron concentration (LIC) found no significant association between LIC and OS, relapse or NRM [5]. This indicates that high SF might not be an accurate IO marker but may also be influenced by inflammation, hepatic cytolysis, and renal failure. This multifaceted significance of SF and its association with transplant outcomes has never been addressed comprehensively. Hepcidin, the key regulator of systemic iron balance, increases with IO and inflammation and decreases with anemia or erythropoiesis. We demonstrated that hepcidin strongly increased early after allo-HSCT, paralleling the kinetics of SF and transferrin saturation (Tsats), contrarywise that of erythroferrone (ERFE) and soluble transferrin receptor (sTfR), reflecting the respective impact of IO, inflammation and myelosuppression [3, 6]. The only four hepcidin studies reported conflicting

results on outcomes [7]. In this study, we investigated in 502 allo-HSCT patients the determinants of pretransplant SF and hepcidin, and their impact on OS, PFS, relapse and NRM with at least 5 years of follow-up.

Materials and methods are provided as [Supporting Information](#).

Significance of pre-conditioning serum ferritin and hepcidin. Pretransplant characteristics of the 502 patients according to hepcidin and SF quartiles are described in Table S1 and Table S2, respectively. Median pre-conditioning hepcidin and SF were 25.13 ng/mL (0.4–345.1) and 1083 ng/mL (6–21 466), respectively, and correlated strongly (Figure 1A). Patients were divided into quartiles (Q1–Q4). Patients in Q4-hepcidin had higher PS and HCT-CI, more treatment lines and transfusions, and more frequently acute leukemias (AL), NMA conditioning, and HLA-mismatched donors (Table S1). Similar differences were observed between SF quartiles, except for HCT-CI and donor relationships (Table S2). Q4-SF included more high-risk Disease-Risk Index (DRI), and Q1-SF had larger use of MMF rather than MTX and longer time between diagnosis and transplantation. Among patients in Q1-, Q2-, Q3-, and Q4-SF quartiles, 60%, 37%, 35%, and 53% were in the same hepcidin quartile. Pretransplant biological characteristics are described in Table S3. Multivariate analyses (MV) of clinical and biological parameters associated with hepcidin and SF or posttransplant SF peak are displayed in Table 1.

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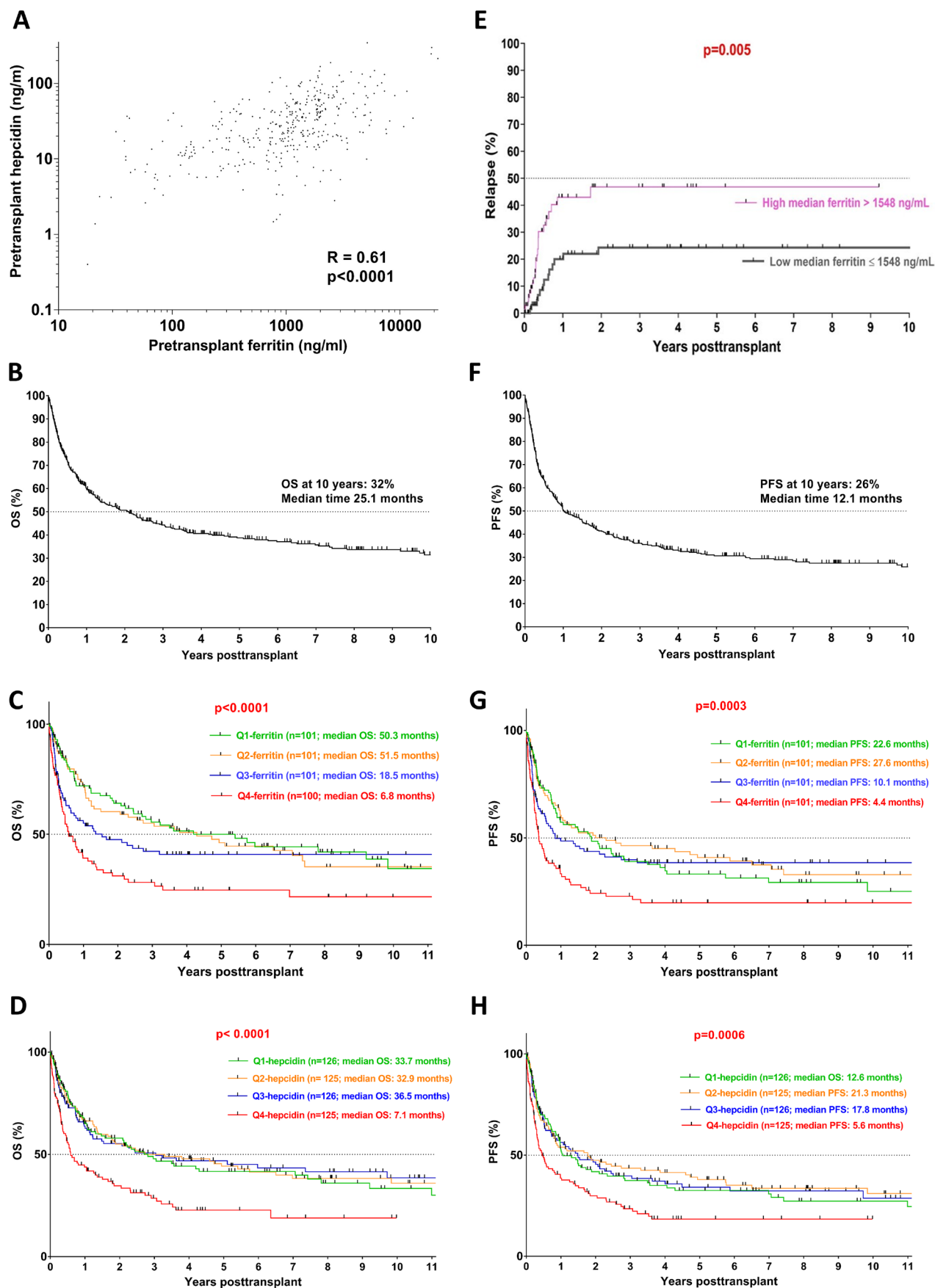


FIGURE 1 | Legend on next page.

FIGURE 1 | (A) Correlation between same-day pre-conditioning serum hepcidin and serum ferritin in the whole group of patients ($n=401$; $r=0.61$, $p<0.0001$). (B–D) OS after allogeneic HSCT: Long-term OS in all patients (B), in patients stratified by pretransplant serum ferritin quartiles (C) and pretransplant serum hepcidin quartiles (D). (E) Relapse of acute leukemia after allogeneic HSCT in patients stratified by pretransplant serum ferritin above or below the median. (F–H) PFS after allogeneic HSCT: Long-term PFS in all patients (F), in patients stratified by pretransplant serum ferritin quartiles (G) and pretransplant serum hepcidin quartiles (H). [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

OS, PFS and NRM. After median follow-up of 9.3years, OS was 81% at 100days, 60% at 1% and 32% at 10years (median 25.1 months; Figure 1B). Patients in Q3–Q4 SF and Q4-hepcidin groups had significantly lower OS (Figure 1C,D). In univariate analyses (UV), high hepcidin and SF were associated with decreased long-term OS (Table S4a). In bivariate analyses, SF was a significantly stronger predictor (Table S4b). In MV, hepcidin lost significance, whereas SF remained associated with poor long-term OS (Table S4c). PFS was 75% at 100days, 50% at 1% and 26% at 10years (median 12.1 months; Figure 1F). Patients in Q4-SF and Q4-hepcidin groups had inferior PFS (Figure 1G,H). In UV, high hepcidin and SF were associated with reduced PFS (Table S5a). In bivariate analyses, SF remained the best predictor (Table S5b). In MV, both hepcidin and ferritin lost significance for long-term PFS (Table S5c). Relapse incidence at 100days, 1 and 10years was 10%, 30%, and 44%, respectively, with no correlation with SF or hepcidin. In MV, DRI (HR 2.88, $p<0.0001$), age (HR 1.02, $p=0.006$), treatment lines (HR 1.11, $p=0.03$), and total bilirubin (HR 1.44, $p=0.046$) were significantly associated with long-term relapses. Among 185 AL patients, median pretransplant hepcidin was 36 ng/mL (63% in Q3–4) and SF 1548 ng/mL (73% in Q3–4). While hepcidin did not correlate with relapse, higher SF did (30% vs. 18%; Figure 1E). In MV, only DRI remained predictive. NRM was 14% at 100days, 22% at 1% and 34% at 10years, and higher in Q4 hepcidin ($p=0.02$) and Q3–4 SF groups ($p=0.03$). In UV, only pretransplant SF was significantly associated with long-term NRM, whereas hepcidin was not (Table S6a), hence no bivariate model was constructed. Neither of them emerged in MV as significant risk factor of NRM (Table S6b).

Determinants of SF and hepcidin and their combined prognostic impact on outcomes remained underexplored. Previous studies exploring hepcidin were limited by small patient numbers (16–166), use of less reliable ELISA, and lack of MV analyses. Our study, the largest with 502 patients, confirmed elevated hepcidin by mass spectrometry and its strong positive correlation with SF [7], and in MV demonstrated its dependence on RBC transfusions, HCT-CI, PS, and inflammation, SF also remaining an independent predictor. This confirms our previous finding that the stimulating impact of IO dominates the inhibitory effect of erythropoiesis on hepcidin [3, 6]. Many studies reported elevated SF pretransplant, often linked to LIC, serum iron or Tsat, CRP or interleukin-6, ALAT, anemia, male sex, age, AL, previous treatment lines, advanced disease, RBC transfusions, high HCT-CI, or poor PS. None included MV analyses. We performed comprehensive MV, and SF correlated with anemia, Tsat, liver and renal dysfunction, previous RBC and platelet transfusions, AL, and PS, hepcidin being also associated with it. Hence, pre-conditioning SF reflects not only transfusional IO but also the cumulative burden of comorbidities, organ dysfunction, and disease severity that shapes transplant outcomes.

TABLE 1 | Multiple linear regression of parameters (that had a p -value <0.15 in univariate analyses) influencing pretransplant serum hepcidin ($R^2=0.44$, $p<0.0001$) and ferritin ($R^2=0.67$, $p<0.0001$), as well as posttransplant ferritin peak ($R^2=0.72$, $p<0.0001$).

	β -coefficient	SE	p
1.a Multivariate analysis of pretransplant serum hepcidin			
Pretransplant serum CRP (mg/L)	0.13	0.04	0.0003
Pretransplant neutrophils ($10^9/L$)	−0.14	0.06	0.01
Pretransplant RBC transfusions (N)	0.18	0.02	<0.0001
Comorbidity score (HCT-CI)	0.09	0.03	0.0008
PS score	0.24	0.08	0.02
1.b Multivariate analysis of pretransplant serum ferritin			
Pretransplant transferrin saturation (%)	0.47	0.08	<0.0001
Pretransplant hemoglobin (g/dL)	−1.25	0.28	<0.0001
Pretransplant ALAT (U/L)	0.23	0.06	0.0003
Pretransplant creatinine (mg/dL)	0.37	0.11	0.0006
Pretransplant lymphocytes ($10^9/L$)	−0.20	0.09	0.02
Pretransplant RBC transfusions (N)	0.16	0.03	<0.0001
Pretransplant platelet transfusions (N)	0.06	0.03	0.046
Myeloproliferative neoplasm (vs acute leukemia)	−0.75	0.17	<0.0001
Lymphoid malignancy (vs acute leukemia)	−0.44	0.11	<0.0001
PS score	0.23	0.08	0.006
1.c Multivariate analysis of posttransplant ferritin peak			
Pretransplant serum hepcidin (ng/mL)	0.15	0.04	<0.0001
Transferrin saturation peak (%) before day 100	0.59	0.12	<0.0001

(Continues)

TABLE 1 | (Continued)

	β -coefficient	SE	<i>p</i>
Platelet nadir ($10^9/L$) before day 100	−0.04	0.02	0.007
Neutrophil nadir ($10^9/L$) before day 100	−0.29	0.09	0.003
CRP peak (mg/L) before day 100	0.13	0.04	0.0005
ALAT peak (U/L) before day 100	0.19	0.04	<0.0001
Creatinine peak (mg/dL) before day 100	0.16	0.08	0.04
Serum albumin nadir (g/L) before day 100	−0.04	0.01	<0.0001
Pretransplant RBC transfusions (N)	0.08	0.02	<0.0001
HLA-mismatched unrelated vs HLA identical sibling donor	0.22	0.07	0.002
ABO compatibility (minor + major mismatch vs identical)	−0.46	0.15	0.003
2nd or 3rd transplant (vs first transplant)	−0.19	0.07	0.01

Note: Other parameters were included into the model but were found not significant in multivariate analyses: For pretransplant hepcidin (1.a): Diagnosis, DRI score, pretransplant platelet transfusions, serum iron, hemoglobin, platelets, lymphocytes, total bilirubin, ALAT, creatinine, and uric acid. For pretransplant ferritin (1.b): Age, sex, BMI, number of previous treatment lines, transplant number, DRI score, HTC-CI score, serum iron, platelets, neutrophils, CRP, total bilirubin, and uric acid. For ferritin peak (1.c): Age, BMI, performance status, HCT-CI, DRI score, diagnosis, delay between diagnosis and transplant, number of treatment lines, pretransplant platelet transfusions, conditioning, use of ATG, donor age, graft manipulations, GVHD prophylaxis, antibiotic prophylaxis, CMV status, CD34+ cell dose; serum iron peak, hemoglobin nadir, lymphocyte nadir, peak of total bilirubin and nadir of uric acid before day 100.

Abbreviations: ALAT, alanine aminotransferase; ATG, anti-thymocyte globulin; BMI, body mass index; CMV, cytomegalovirus; CRP, C reactive protein; DRI, disease risk index; GVHD, graft-versus-host disease; HCT-CI, comorbidity score; HLA, human leucocyte antigen; PS, performance status; RBC, red blood cells; SE, standard error.

Our next objective was to evaluate the influence of SF and hepcidin on survival outcomes, the literature reporting conflicting results [1, 2, 4]. High hepcidin and SF were significantly associated with poorer OS and PFS or increased NRM in UV. However, only SF retained predictive value in MV for OS, whereas neither was predictive of PFS or NRM, consistent with previous studies. Although our study is by far the largest, only Sakamoto observed a significant relationship between high hepcidin, but not SF, and poor OS in UV and MV [7]. Conversely, our results align with others, supporting the negative impact of SF on OS, PFS and NRM [8]. A meta-analysis of 25 studies (4545 patients) found pretransplant SF strongly associated with poor OS (HR 1.82; $p < 0.001$) and PFS (HR 1.72; $p < 0.001$) and increased NRM (HR 2.28; $p < 0.001$) [1].

Relapse rates were not influenced by SF or hepcidin overall but, in AL patients, higher SF correlated with relapse, agreeing with other reports, although this was not confirmed in MV. Elevated

hepcidin and SF in AL likely reflect disease-related iron dysregulation, while the potential contribution of HFE mutations warrants further investigation.

The array of parameters analyzed in our study unveiled predictors rarely considered by others. The literature shows that limiting analyzed factors to a few known predictors in addition to SF itself may result in SF being incorporated too often while ignoring potentially better clinical or biological markers. We took a less restrictive approach for selecting potential outcome predictors. Pretransplant RBC transfusions probably excluded SF from MV of NRM (Table S6b).

Other studies identified DRI or similar parameters (diagnosis, disease status, treatment lines, advanced disease, prior transplant) alongside SF as powerful predictors of relapse, PFS, or OS [7]. Prognostic score proposed by Vaughn [9], based on age, disease type and stage, cytogenetics, and SF, resulted in three groups with 5-year OS of 56%, 22%, and 5%. Artz constructed a score based on SF, CRP, and albumin in 784 patients, leading to three groups with 1-year OS of 74%, 67%, and 56% [8].

As SF reflects multiple determinants, the role of iron overload per se remains uncertain. A meta-analysis of four MRI-based studies of LIC (276 patients) before allo-HSCT showed no significant impact of liver iron stores on OS or NRM, except for higher NRM among RIC-conditioned patients [5]. However, two of the four studies showed that high LIC was associated with higher NRM and poorer OS.

In conclusion, our study shows that pretransplant SF and hepcidin are influenced by multiple factors, affect allo-HSCT outcomes, and require comprehensive assessment for accurate prediction, highlighting the complexity of iron metabolism and the need for further research [10].

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Ethics Statement

The study was approved by the Ethics Committee of the Faculty and the University Hospital at the University of Liège under # 2016-119.

Consent

Patients (or their guardian if of minor age) signed an Ethics Committee-approved informed consent form for the collection of clinical data as well as blood samples for research purposes.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Z. Yan, X. Chen, H. Wang, et al., "Effect of Pre-Transplantation Serum Ferritin on Outcomes in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation: A Meta-Analysis," *Medicine (Baltimore)* 97, no. 27 (2018): e10310.
2. W. Fingrut, A. Law, W. Lam, et al., "Post-Transplant Ferritin Level Predicts Outcomes After Allogeneic Hematopoietic Stem Cell Transplant, Independent From Pre-Transplant Ferritin Level," *Annals of Hematology* 100, no. 3 (2021): 789–798.
3. M. Pirotte, M. Fillet, L. Seidel, A. Jaspers, F. Baron, and Y. Beguin, "Erythroferrone and Heparin as Mediators Between Erythropoiesis and Iron Metabolism During Allogeneic Hematopoietic Stem Cell Transplant," *American Journal of Hematology* 96, no. 10 (2021): 1275–1286.
4. P. Armand, H. T. Kim, C. S. Cutler, et al., "Prognostic Impact of Elevated Pretransplantation Serum Ferritin in Patients Undergoing Myeloablative Stem Cell Transplantation," *Blood* 109, no. 10 (2007): 4586–4588.
5. P. Armand, H. T. Kim, J. M. Virtanen, et al., "Iron Overload in Allogeneic Hematopoietic Cell Transplantation Outcome: A Meta-Analysis," *Biology of Blood and Marrow Transplantation* 20, no. 8 (2014): 1248–1251.
6. A. Jaspers, F. Baron, E. Willems, et al., "Serum Heparin Following Autologous Hematopoietic Cell Transplantation: An Illustration of the Interplay of Iron Status, Erythropoiesis and Inflammation," *Haematologica* 99, no. 3 (2014): e35–e37.
7. S. Sakamoto, H. Kawabata, J. Kanda, et al., "High Pretransplant Heparin Levels Are Associated With Poor Overall Survival and Delayed Platelet Engraftment After Allogeneic Hematopoietic Stem Cell Transplantation," *Cancer Medicine* 6, no. 1 (2017): 120–128.
8. A. S. Artz, B. Logan, X. Zhu, 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* 101, no. 11 (2016): 1426–1433.
9. J. E. Vaughn, B. E. Storer, P. Armand, et al., "Design and Validation of an Augmented Hematopoietic Cell Transplantation-Comorbidity Index Comprising Pretransplant Ferritin, Albumin, and Platelet Count for Prediction of Outcomes After Allogeneic Transplantation," *Biology of Blood and Marrow Transplantation* 21, no. 8 (2015): 1418–1424.
10. M. Pirotte, "Detailed Investigation of Erythropoiesis and Iron Metabolism in the Context of Allogeneic Hematopoietic Stem Cell Transplantation," (PhD thesis, University of Liège, defended on March 6, 2024).

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** ajh70272-sup-0001-Supinfo.docx.