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Association of Serum Ferritin Levels Before Start of Conditioning With Mortality After alloSCT – A Prospective, Non-interventional Study of the EBMT Transplant Complications Working Party

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Elevated serum ferritin levels occur due to iron overload or during inflammation and macrophage activation. A correlation of high serum ferritin levels with increased mortality after alloSCT has been suggested by several retrospective analyses as well as by two smaller prospective studies. This prospective multicentric study aimed to study the association of ferritin serum levels before start of conditioning with alloSCT outcome. Patients with acute leukemia, lymphoma or MDS receiving a matched sibling alloSCT for the first time were considered for inclusion, regardless of conditioning. A comparison of outcomes between patients with high and low ferritin level was performed using univariate analysis and multivariate analysis using cause-specific Cox model. Twenty centers reported data on 298 alloSCT recipients. The ferritin cut off point was determined at 1500 μg/l (median of measured ferritin levels). In alloSCT recipients with ferritin levels above cut off measured before the start of conditioning, overall survival (HR = 2.5, CI = 1.5–4.1, $p = 0.0005$) and progression-free survival (HR = 2.4, CI = 1.6–3.8, $p < 0.0001$) were inferior. Excess mortality in the high ferritin group was due to both higher relapse incidence (HR = 2.2, CI = 1.2–3.8, $p = 0.007$) and increased non-relapse mortality (NRM) (HR = 3.1, CI = 1.5–6.4, $p = 0.002$). NRM was driven by significantly

higher infection-related mortality in the high ferritin group (HR = 3.9, CI = 1.6–9.7, $p = 0.003$). Acute and chronic GVHD incidence or severity were not associated to serum ferritin levels. We conclude that ferritin levels can serve as routine laboratory biomarker for mortality risk assessment before alloSCT.

Keywords: transplantation, stem cell, immunology, biomarker, iron metabolism, ferritin

INTRODUCTION

Allogeneic stem cell transplantation (alloSCT) is a curative treatment option for patients suffering from hematological malignancies and some other diseases. High treatment-associated mortality is a major difficulty of this procedure and predicting mortality is a clinical challenge. The current standard for alloSCT risk assessment is the use of clinical scores, such as the European Society for Blood and Marrow Transplantation (EBMT)-score (1), the Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) (2), the Dana-Farber Cancer Institute (DFCI)-score (3), and a combination of such scores (4).

The use of biomarkers to further improve alloSCT risk assessment is an attractive option (5). Mortality in the first months/years after alloSCT is mainly due to leukemia relapse, infections or graft-versus-host disease (GVHD). In all these clinical situations serum ferritin, an acute phase and iron binding protein, has been demonstrated to be elevated (6–13). Based on this background results, several retrospective studies and meta-analyses have suggested that serum ferritin may be of use as a biomarker during alloSCT (7, 14–18).

Based on these preliminary results and on the fact that ferritin is a routine laboratory parameter assessed in patients undergoing alloSCT, we saw a strong rationale for investigating serum ferritin as a biomarker. The Transplant Complications Working Party (TCWP) of the EBMT performed a prospective, multicenter and non-interventional study to test whether the ferritin level evaluated prior to the start of conditioning therapy is an independent risk factor for increased mortality after alloSCT.

MATERIALS AND METHODS

Data Source, Study Design, and Data Collection

We asked EBMT centers performing more than 50 alloSCT per year if they were willing to participate in this prospective study. Twenty centers in ten countries agreed to participate. Data collection for the EBMT registry was approved by the European Society for Blood and Marrow Transplantation and by the IRB of Charité Universitätsmedizin Berlin as well as by IRBs of the participating centers. Data were prospectively collected between 8/2014 and 2/2018. Consecutive alloSCT recipients with acute leukemia, lymphoma or myelodysplastic syndrome (MDS) receiving a first matched sibling alloSCT from peripheral blood, regardless of conditioning, were eligible, provided they had signed an informed consent document that permitted sharing of clinical data according to national rules. Basic data on patient and disease characteristics as well as longer term follow up was taken from minimal essential data (MED-A) forms, which are submitted from all consecutive patients to the central EBMT registry. In addition, we designed registration and MED-B/C forms that were prospectively collected and specific to this study. Treatment teams completed specific forms (MED-B/C) forms at the time of registration and at day + 100 after alloSCT. The MED-B/C form contained detailed information on ferritin serum levels prior to alloSCT, patient characteristics, infectious- as well as non-infectious complications, GVHD staging, morbidity and mortality. Ferritin levels were determined at time of hospital admission for alloSCT directly before start of conditioning therapy.

ENDPOINTS AND STATISTICAL ANALYSES

Patient, disease, and transplant-related characteristics for the two cohorts (ferritin levels prior to alloSCT above median/ferritin levels below median) were compared by using $\chi 2$ statistics for categorical variables and the Mann-Whitney test for continuous variables. Primary endpoint was the incidence of acute GVHD. Acute GVHD was picked as a primary endpoint because of our previous observation on a correlation of maximum Ferritin levels after alloSCT with acute GVHD severity (12). Secondary endpoints were relapse incidence (RI), non-relapse mortality (NRM), overall survival (OS), progression free survival (PFS), and the incidence of chronic GVHD. PFS was defined as survival with no evidence of relapse or progression. RI was defined as the probability of having had a relapse during follow up time. Death without experiencing a relapse was a competing event. NRM was defined as death without evidence of relapse or progression. OS was defined as the time from alloSCT to death, regardless of the cause. To define acute GVHD during the consensus process, we used the criteria established by the MAGIC group (19–21). To define chronic GVHD, we used the NIH 2014 criteria (20–22). Cumulative incidence was used to estimate the endpoints of NRM, RI, acute, and chronic GVHD to accommodate for competing risks. To study acute and chronic GVHD, we considered relapse and death to be competing events. Probabilities of OS and PFS were calculated using the Kaplan–Meier method. Univariate analyses were done using the Gray test for cumulative incidence functions and the log rank test for OS and PFS. A Cox proportional hazards model was used for multivariate regression. All variables differing significantly between the 2 groups or factors associated with one outcome in univariate analysis were included in the Cox model. The following variables entered the multivariate

models as possible confounders: age, sex mismatch between recipient and donor, diagnosis, disease status, Karnofsky score, number of CD34 cells given, intensity of conditioning (EBMT definition: myeloablative conditioning (MAC) was defined as TBI > 6 gray or oral busulfan > 8 mg/kg or intravenous busulfan > 6.4 mg/kg), type of GVHD prophylaxis, ATG use, time from diagnosis to transplant, year of transplant and CMV status. As the number of variables was too high regarding the number of events, a stepwise selection using Akaike information criterion (AIC) was run for all the confounding factors. The difference between the two cohorts was then assessed in the final selected model.

Results were expressed as the hazard ratio (HR) with the 95% confidence interval (95% CI). Proportional hazards assumptions were checked systematically for all proposed models using the Grambsch-Therneau residual-based test. All tests were 2-sided. The type I error rate was fixed at 0.05 for the determination of factors associated with time-to-event outcomes. Statistical analyses were performed in November 2018 with R 3.4.2 (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria[1]).

RESULTS

Patients and Transplant Characteristics

The entry criteria for analysis of OS were fulfilled in 298 patients. The main patients and transplant characteristics that were included in the analysis of OS are described in **Table 1**. Most parameters were balanced between the two cohorts. However, a higher percentage of sex mismatch transplants in the direction of female to male were observed in the group of patients with ferritin above cut off before alloSCT. The ferritin cut off point was determined at 1500 μg/l (median of measured ferritin levels).

Endpoints

In the present study, the incidence of acute GVHD grades II–IV and grades III–IV in the whole population at

[1]https://www.R-project.org/

TABLE 1 | Population characteristics.

	Ferritin <=1500 μ G/L (*N* = 153)	Ferritin > 1500 μ G/L (*N* = 145)	*P*-value
Year of transplant median (range) [IQR]	2016 (2014–2018)[2015–2017]	2015 (2014–2018)[2015–2016]	0.6
Patient age (years) Median (range) [IQR]	52 (17.1–71.3) [38.1–60.2]	53.2 (19–70.9) [42.9–62.3]	0.3
Time from diagnosis to transplant (months) median (range) [IQR]	5 (1–71) [3–8]	4 (1–61) [3–6]	0.05
Number of CD34 + cells infused (E + 06) median (range) [IQR]	5.9 (0.9–10.7) [4.5–7.2]	5.5 (0.6–10.2) [4.2–6.7]	0.1
Sex mismatch			0.012
Female to male	27 (18%)	43 (30%)	
Other combination	123 (82%)	98 (70%)	
Diagnosis			0.058
Acute leukemia	93 (61%)	107 (74%)	
Lymphoma	19 (12%)	12 (8%)	
MDS	41 (27%)	26 (18%)	
Disease status			0.2
CR	94 (64%)	98 (70%)	
Not in CR	54 (36%)	42 (30%)	
ATG			0.5
No	77 (50%)	79 (54%)	
Yes	76 (50%)	66 (46%)	
Conditioning intensity			0.9
MAC/CHEMO	30 (20%)	32 (22%)	
MAC/TBI	26 (17%)	25 (17%)	
RIC	95 (63%)	87 (61%)	
Karnovsky Score			0.8
< = 80	23 (16%)	21 (15%)	
90–100	125 (85%)	122 (85%)	
Missing	5	2	
Disease risk index			0.8
Low	6 (4%)	4 (3%)	
Intermediate	86 (59%)	88 (65%)	
High	48 (33%)	39 (29%)	
Very high	5 (3%)	5 (4%)	
Missing	8	9	

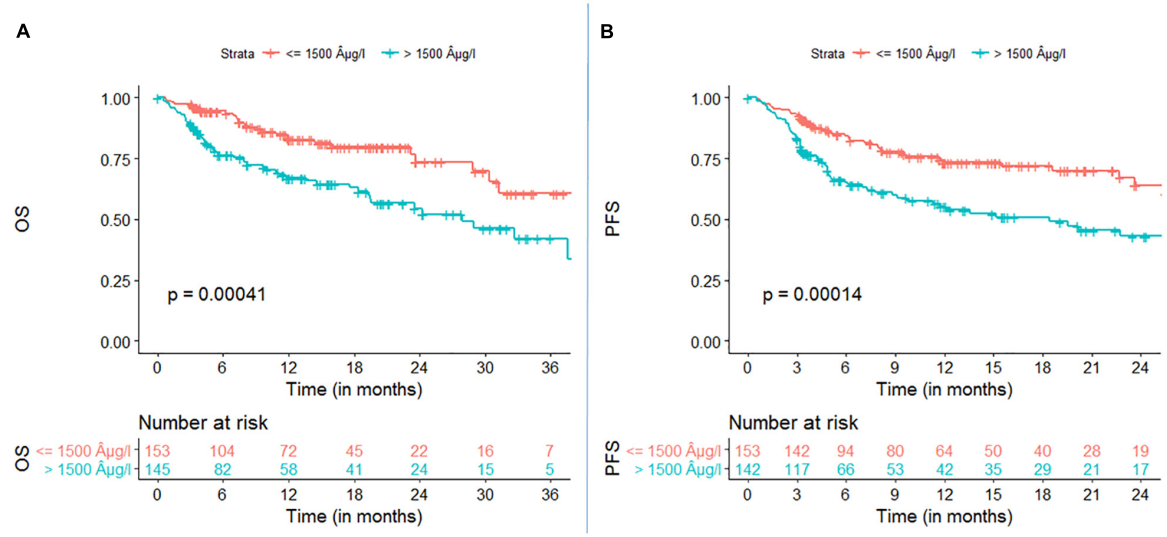

FIGURE 1 | Survival after alloSCT in both cohorts according to ferritin serum levels prior to alloSCT. Overall survival (OS) **(A)** as well as progression free survival (PFS) **(B)** were significantly inferior in patients with high ferritin serum levels (blue line) as compared to patients with low ferritin levels (red line).

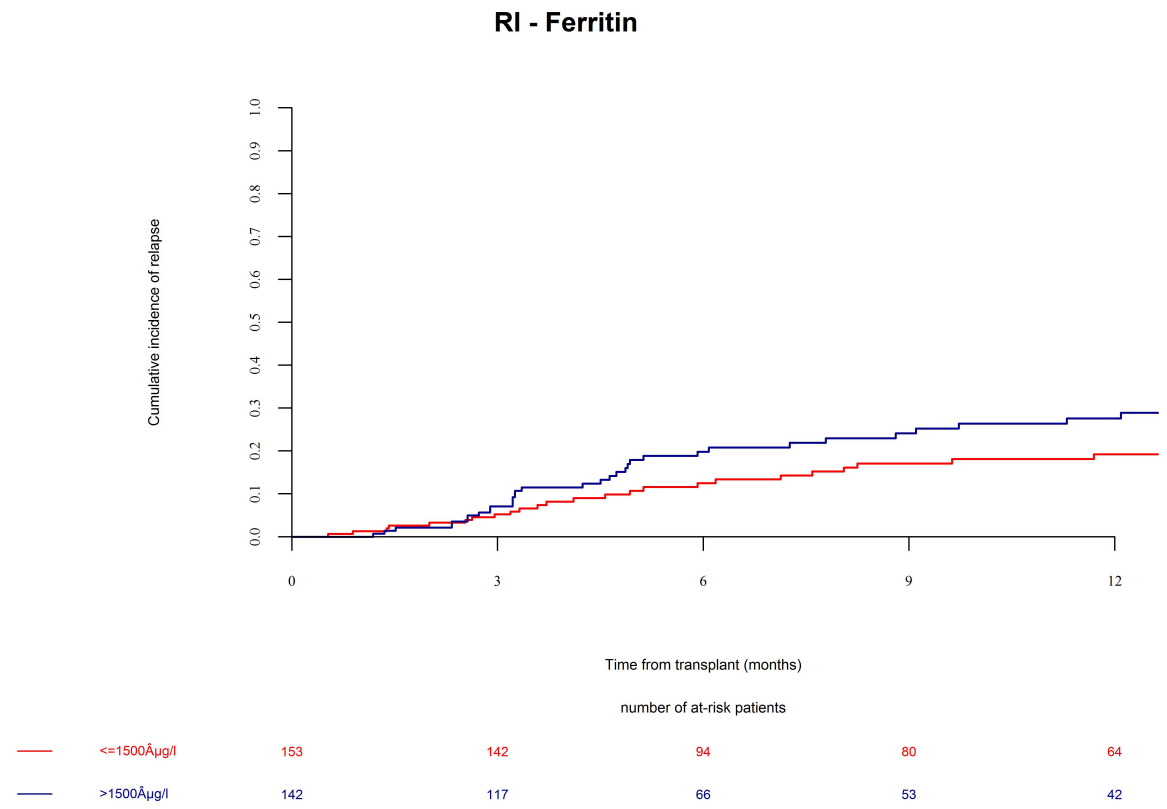

FIGURE 2 | Relapse incidence (RI) after alloSCT in both cohorts according to ferritin serum levels prior to alloSCT. Relapse incidence was increased in patients with high ferritin serum levels (blue line) as compared to patients with low ferritin levels (red line).

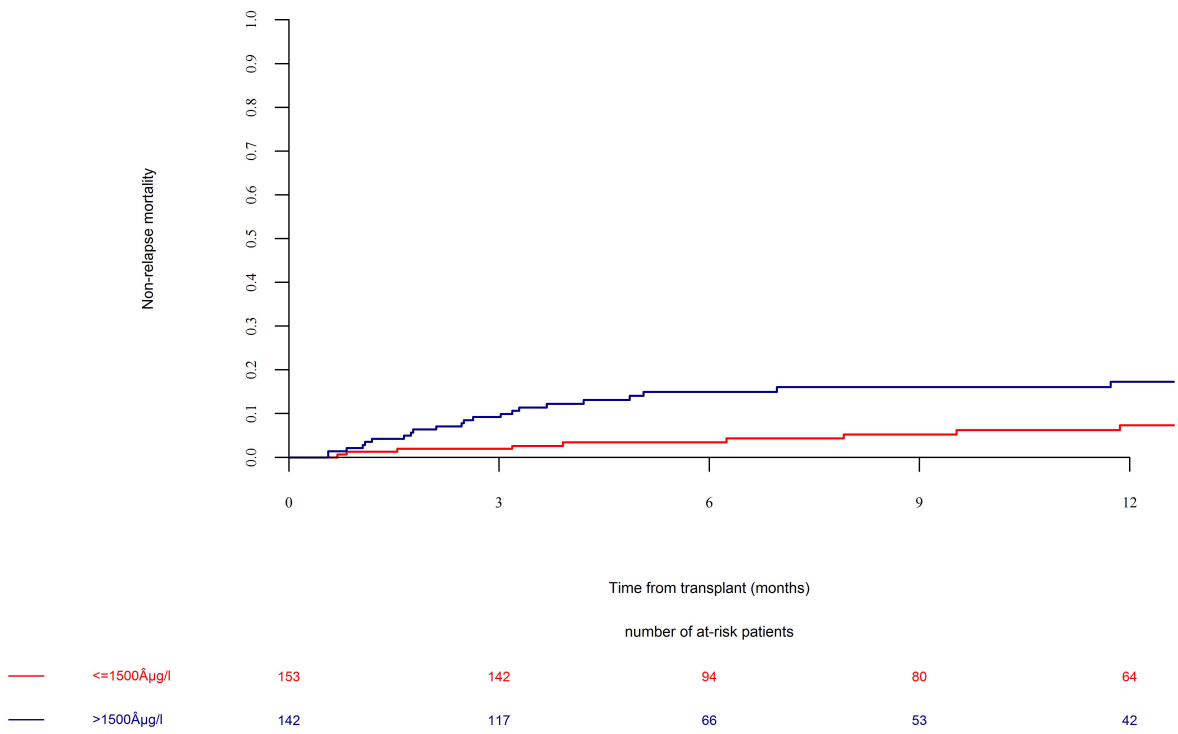

FIGURE 3 | Non-relapse mortality (NRM) after alloSCT in both cohorts according to ferritin serum levels prior to alloSCT. NRM was increased in patients with high ferritin serum levels (blue line) as compared to patients with low ferritin levels (red line).

100 days was 25% and 11%, respectively. The incidence of chronic GVHD and severe chronic GVHD at last follow up was 25.8% and 15.1%, respectively. We observed no differences in incidence and severity of acute GVHD as well as chronic GVHD in between the two cohorts. As expected, chronic GVHD incidence was significantly lower in alloSCT recipients receiving anti-T-cell globulin as part of the conditioning regimen (ATG, HR = 0.25, CI = 0.13–0.5, $p < 0.0001$).

We found that OS and PFS of alloSCT recipients with ferritin levels above cut off measured before start of conditioning were significantly shorter as compared with the low ferritin cohort (**Figure 1A**, OS univariate HR = 2.3, CI = 1.4–3.6, $p = 0.00041$; multivariate HR = 2.5, CI = 1.5–4.1, $p = 0.0005$) (**Figure 1B**, PFS univariate HR = 2.1, CI = 1.4–3.2, $p = 0.00014$; multivariate HR = 2.4, CI = 1.6–3.8, $p < 0.0001$).

Mortality was 29% at last follow up and with distribution of 15.0% relapse/progression as well as 14% NRM. Excess mortality in the high ferritin group was driven by higher relapse incidence as well as by higher NRM. We found that the incidence of relapse after alloSCT was 24.2% till the end of follow up. AlloSCT recipients with ferritin levels above cut off had significantly more relapses as compared with the low ferritin group (**Figure 2**, univariate HR = 1.7, CI = 1–2.8, $p = 0.03$; multivariate HR = 2.2, CI = 1.2–3.8, $p = 0.007$).

Patients in the ferritin high group had significantly more NRM (**Figure 3**, univariate HR = 3.1, CI = 1.5–6.3, $p = 0.002$; multivariate HR = 3.1, CI = 1.5–6.4, $p = 0.002$). NRM was driven by significantly higher infection-related mortality in the high ferritin group (**Figure 4**, univariate HR = 3.9, CI = 1.6–9.7, $p = 0.003$; multivariate HR = 3.9, CI = 1.6–9.7, $p = 0.003$). A descriptive analysis of causes of death is given in **Table 2**.

We conclude that serum ferritin levels prior to alloSCT are an independent risk factor for OS, relapse, and NRM at one year.

DISCUSSION

Our results from this prospective study indicate that serum ferritin prior to alloSCT is associated to mortality after alloSCT. This trial served as confirmation of previous retrospective studies, which delivered preliminary results pointing in the same direction (7, 14–18). Of note, the Center for International Blood and Marrow Transplantation Research (CIBMTR) published an evaluation on different biomarkers and found that ferritin levels above 2500µg/ml were not associated with inferior alloSCT outcome (23) contrasting previously published studies (7, 14–18) and our results.

A limitation of our clinical study is the lack of mechanistic insight on the role of ferritin in development of complications

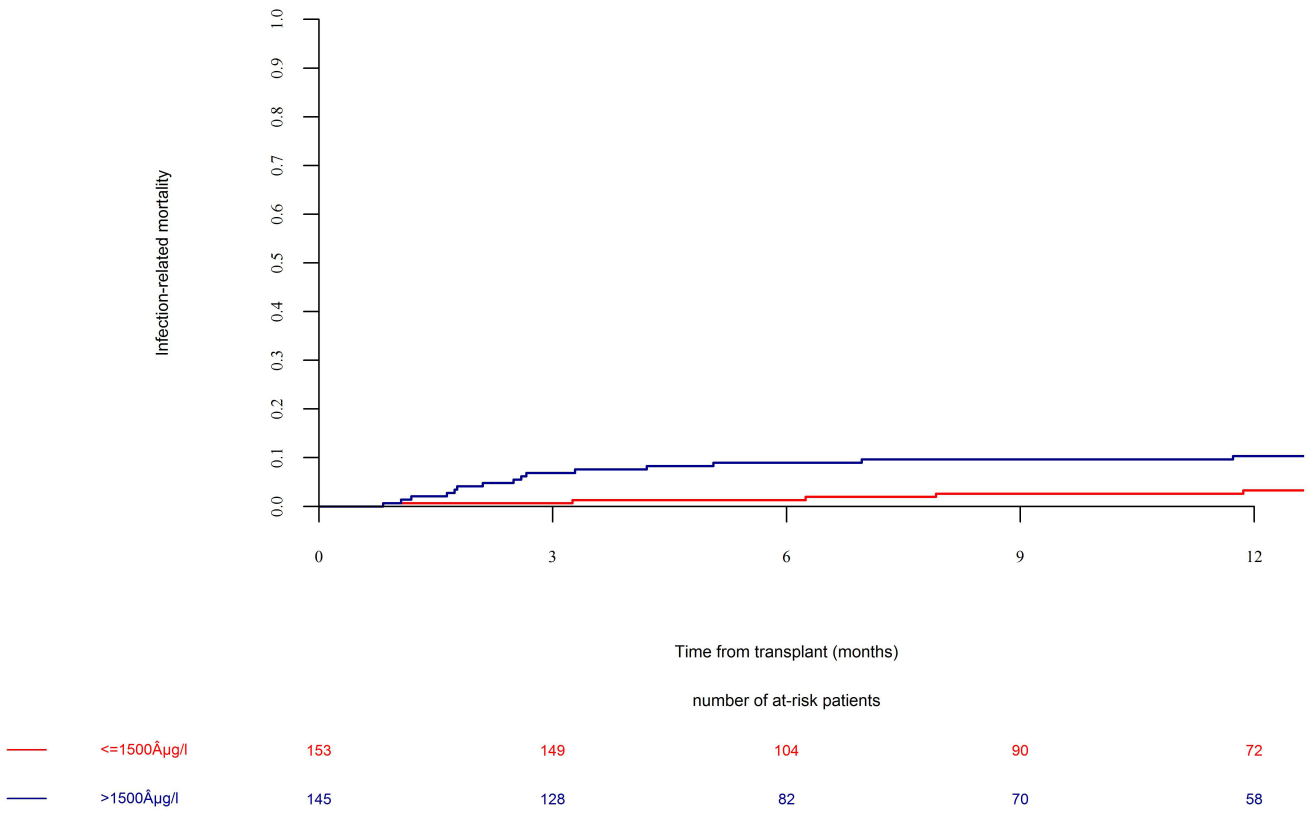

FIGURE 4 | Infection-related mortality after alloSCT in both cohorts according to ferritin serum levels prior to alloSCT. Infection-related mortality was increased in patients with high ferritin serum levels (blue line) as compared to patients with low ferritin levels (red line).

TABLE 2 | Mortality and cause of death in both cohorts.

Status at last follow up	Ferritin <= 1500 µ G/L (*N* = 153)	Ferritin > 1500 µ G/L (*N* = 145)
Alive	126 (82%)	92 (63%)
Dead	26 (18%)	53 (37%)
Death due to relapse or progression	15 (10%)	27 (19%)
Death without relapse	11 (7%)	26 (18%)
NRM infection related	5 (3%)	14 (10%)
NRM due to other causes	6 (4%)	12 (8%)

after alloSCT. In addition, our patient population was restricted to alloSCT from HLA-identical sibling donors. We are therefore unable to draw definite conclusions from these results regarding the association of ferritin levels with outcome in matched unrelated donor alloSCT or in haploidentical alloSCT, which are increasingly used.

An attractive feature of using ferritin as a biomarker for alloSCT outcome is that many severe clinical conditions occurring in the peri-transplant period are associated to high ferritin levels. First, high ferritin is related to iron overload although those factors are not always closely associated (10). Iron overload due to multiple pre-transplant red blood cell transfusion has been described to have negative impact on alloSCT outcome (7, 8, 11, 13). Second, ferritin levels are very high during severe graft-versus-host disease and during macrophage activation syndromes after alloSCT (12). Third, ferritin is an acute phase protein that is regularly elevated during acute and chronic infections (24, 25). Ferritin has been implicated in fungal growth and high ferritin levels have previously been suggested to be a risk factor for infections after alloSCT (26–28). In line with these data, our results indicated increased infection-related mortality in the group with higher ferritin levels. Fourth, ferritin levels have been associated with increased growth of acute myeloid leukemia (AML) (9, 16). So, taken together ferritin is elevated during tumor relapse and major infectious as well as non-infectious complications after alloSCT. Based on these considerations, ferritin might be a surrogate marker for organ dysfunction and it is understandable that it can serve as a biomarker for alloSCT mortality with significant prediction of tumor relapses as well as NRM.

In our study ferritin levels were not associated to a higher disease stage (CR/non-CR) or a longer time between diagnosis and alloSCT. In line with these findings, high ferritin levels were not associated to the diagnosis of MDS, where patients often receive multiple blood transfusions prior to alloSCT. There are two likely explanations: (1) Patients with multiple blood transfusions often receive drug treatment to reduce iron overload, and (2) The ferritin levels may not primarily reflect iron overload as discussed in the previous paragraph. Interestingly, a recent prospective study in patients with MDS and CMML undergoing alloSCT reported that administration of iron chelation therapy prior to HSCT was not associated to outcome. However, early iron reduction after alloSCT (started before d + 180) was associated to improved relapse free survival (29).

In conclusion, we found that high serum ferritin is an independent risk factor for increased mortality after alloSCT. The perspective of the future use of ferritin as biomarker will be likely a combination with clinical parameters such as the EBMT-score or the HCT-CI. However, to investigate such a combination or a combination with alternative biomarkers was not within the scope of our study and remains to be analyzed in the future.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

OP wrote the manuscript. CP analyzed the data. All authors read, edited, and approved the manuscript.

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