REVIEW

Editorial Process: Submission:04/06/2024 Acceptance:08/18/2024

Impact of Serum Ferritin and Iron Overload on Acute Myeloid Leukemia Outcomes: A Systematic Review and Meta-Analysis

Sanambar Sadighi[1], Efe Sahinoglu[2], Ahmed Haider Kubba[2], Jhanvi Patel[2], Sayyideh Forough Hosseini[2], Mohammad Ali Shafiee[2]*, Bakhtavar Qureshi[3]

Abstract

Objective: To evaluate the iron overload among individuals with acute myeloid leukemia (AML) who have not received red blood cell transfusions. **Methods:** A comprehensive search was conducted in Embase, PubMed, PubMed Central, Web of Science, NIH, and Blood Library databases up to September 2023. The search strategy included keywords related to AML, iron overload, serum ferritin, survival, outcomes, and inflammation. Manual searches through included articles and relevant references were also performed. From 1650 initial articles, 16 studies involving 8752 patients met the inclusion criteria for systematic review. Statistical analysis used hazard ratios (HR) and confidence intervals (CI). **Results:** The systematic review and meta-analysis revealed a statistically significant association between high serum ferritin (SF) levels and poor outcomes in AML patients before starting chemotherapy. Elevated SF levels (>1000 mg/L) were associated with lower overall survival (OS) and event-free survival (EFS) (HR for OS: 1.99, 95% CI: 1.48-2.66; HR for EFS: 2.29, 95% CI: 1.73-3.05). Elevated SF levels were inversely correlated with the gradual onset of infections, indicating an increased risk of early mortality ($p<0.05$). **Conclusion:** Elevated serum ferritin levels are significantly associated with poor outcomes in AML patients before treatment initiation. These findings highlight the importance of monitoring iron levels in these patients to improve prognostic assessments and treatment strategies.

Keywords: Serum ferritin- iron overload- acute myeloid leukemia- survival

Asian Pac J Cancer Prev, **25 (8)**, 2951-2962

Introduction

Acute Myeloid Leukemia (AML) is characterized by the uncontrolled proliferation of early myeloid precursor cells, referred to as myeloblasts, resulting in impaired bone marrow function and involvement of the bloodstream and organs [1]. Leukemia was the leading cause of death for hematologic malignancies at the global and regional scales, followed by non-Hodgkin lymphoma, multiple myeloma, and Hodgkin lymphoma, accordingly for 45.8%, 34.9%, 15.5%, and 3.8% of total deaths in 2019, respectively [2].

Irrespective of Allogeneic Stem Cell Transplantation (Allo-SCT) Long-term survival in AML continues to pose a significant challenge, influenced by a range of prognostic factors associated with the disease, patient characteristics, and treatment strategies [3]. Ferritin's role as the primary intracellular iron storage protein has been established over many years [4]. Recent evidence shows the potential involvement of ferritin in proliferation, angiogenesis, immunosuppression, and iron delivery. Additionally, ferritin is highly expressed in tumor-associated macrophages and is recognized for its critical roles in tumor progression and therapy resistance [5]. These findings propose serum ferritin as a prognostic biomarker and a potential target for leukemia treatment [6].

Recent research has provided groundbreaking insights into the disease's mechanism, leading to the development of innovative approaches for combating AML [3]. A notable discovery includes the pivotal role of iron in the onset and progression of leukemia [4]. However, Information is scarce concerning the correlation between serum ferritin levels at diagnosis and treatment outcomes, particularly for patients with AML. While current evidence hints at the potential linkage between higher serum ferritin levels before transplantation and an adverse prognosis for the disease, our understanding is limited regarding AML patients who have yet to receive red blood cell transfusions.

Lebon et al. were the pioneers in reporting that heightened serum ferritin levels serve as unfavorable prognostic indicators for Overall Survival (OS) and Progression-Free Survival (PFS) in young AML patients with intermediate-risk karyotype [7]. Moreover, numerous studies have illustrated a notable correlation between elevated serum ferritin levels post-transplantation and an amplified risk of relapse, along with diminished overall

*[1]Hematology-Oncology Department, Cancer Institute of Iran, Tehran University of Medical Sciences, Tehran, Iran. [2]University of Toronto, Toronto, Canada. [3]Residency of Family Medicine, Toronto, Canada. *For Correspondence: mohammad.shafiee@uhn.ca*

survival [8-10]. The heightened ferritin levels observed in these scenarios primarily stem from iron overload due to transfusions, hemolysis, and ineffective hematopoiesis [11]. Additionally, these studies encompassed a diverse range of chronic benign and malignant hematologic diseases.

Intriguingly, many AML patients showcase elevated ferritin levels at the onset of the disease before undergoing any blood product transfusions [7], and initial heightened ferritin levels in AML patients are suggested as a marker of tumor burden, linked to predicting diminished event-free survival in the intermediate or high-risk group [12-14]. Additionally, for certain AML patients, where ferritin levels reach or exceed 5000 ng/ml—often associated with hemophagocytic lymph histiocytosis (HLH), or may be related to hereditary hemochromatosis, there is a markedly elevated risk of mortality [15].

Serum ferritin (SF) level threshold exceeding 1000 mg/l, which corresponds to the globally accepted range for cutoff values, signifies the requirement for therapeutic intervention in individuals with chronic hematologic diseases and iron overload [16]. Nevertheless, conflicting outcomes from various studies on this matter in Acute Myeloid Leukemia (AML) suggest that an elevated serum ferritin before transplantation may not function as a standalone prognostic indicator in individuals undergoing allogeneic hematopoietic stem cell transplantation (HSCT). Whether serum ferritin is independently associated with the survival of AML patients remains a subject of ongoing debate [17-20]. To our knowledge, there is no conclusive recommendation for administering iron chelation therapy based on serum ferritin levels in patients diagnosed with AML.

This systematic review and meta-analysis aimed to examine the association between high serum ferritin and the overall survival of adult AML patients. By finding a SF threshold for a significant poor outcome, study might provide insights into new therapeutic strategies in initial treatment of patients.

Materials and Methods

This systematic review adheres to the guidance of the Cochrane Collaboration and follows the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) statement. The research protocol was registered in PROSPERO with the assigned registration number CRD42023437260. The Embase, PubMed, PubMed Central, Web of Science, NIH, and Blood Library were searched using their respective database search engines up to September 2023.

The search strategy involved utilizing the following keywords: "AML or "acute myeloid leukemia" or Leukemia Myeloid Acute" And "Iron Overload" or "serum ferritin" or "ferritin" And "survival" or "outcomes" And "inflammation". Researchers also conducted manual searches through included articles and relevant references retrieved from the primary search results. These studies needed to provide data concerning serum ferritin levels at the time of AML diagnosis or before transplantation, with patients' survival as a primary outcome. Exclusions comprised studies involving animals, pregnant patients, and children, those primarily conducted in a laboratory setting, non-English articles, reviews, editorials, surveys, poster presentations, and abstracts retrieved from major journals. The researchers also excluded papers presenting research in specific settings, such as the Intensive Care Unit (ICU), or based on alternative iron overload indicators in place of serum ferritin.

In instances of uncertainties or diverging opinions among reviewers, a senior reviewer was approached to aid in reaching a definitive decision. Information from each incorporated study was systematically arranged and recorded in a predetermined data extraction spreadsheet. This spreadsheet encompassed details such as the primary author, publication year, study design, median or range of serum ferritin, cutoff values distinguishing low from high levels, inflammatory markers, follow-up duration, median survival, hazard ratio (HR), and 95% confidence interval (CI) for survival analysis based on the ferritin breakpoint.

Statistical Analysis

Two meta-analyses were conducted to calculate the overall risk ratio of the overall survival (OS) and event-free survival (EFS) of the patients with high and low serum ferritin. Only three studies acquired the criteria necessary for conducting meta-analysis based on effect homogeneity and the presence of two comparative groups. The chi-square test and I^2 statistics were used to assess the percentage of variability across studies attributable to heterogeneity beyond chance. The I^2 statistics indicate the percentage of systematic variability across studies (range: 0%–100%), with larger values depicting greater heterogeneity. The random effects model was used if the heterogeneity test showed statistical significance (I^2>50%, $p<0.05$); otherwise, we adopted a fixed effects model. As the number of included studies in the meta-analyses was insufficient (<10), potential publication bias was not assessed. The meta-analyses were performed using ReviewManager (RevMan) software (Version 5.4.1 Nordic Cochrane Centre, Cochrane Collaboration, 2011), with a significance level set at $p<0.05$.

Quality assessment

We employed the Newcastle-Ottawa Scale (NOS) for both cohort and case-control studies, allowing us to scrutinize multiple aspects, including study participant selection, performance, detection, attrition, reporting biases, and other study-specific biases [21]. Each study was assigned a quality score, representing the level of bias risk.

Results

Characteristics of the included studies

The comprehensive search across the specified databases initially identified a total of 1650 studies. After the removal of duplicates (n=111), 1539 studies remained. Further screening based on titles, abstracts, and scanning of the manuscripts led to 49 relevant articles undergoing dedicated full-text screening. In the final analysis, 16 studies met the inclusion criteria; among these, three were

deemed suitable for meta-analysis, as depicted in the PRISMA chart (Figure 1), aligning with recent guidelines [22]. The detailed characteristics of these studies are showcased in Table 1.

Among the included research, 12 retrospective cohort studies provided insights into the historical data regarding serum ferritin dynamics in leukemia treatment, highlighting past clinical practices and outcomes. Complementing these, three prospective cohort studies - Kong et al. [18], Tachibana et al. [23], and Penack et al. [24] offered forward-looking perspectives, shedding light on emerging trends and future considerations in this domain [18,23-24]. Moreover, an interventional clinical trial conducted by Armand et al. [25] embarked on a deep dive into the relationship between serum ferritin levels and leukemia outcomes, though its reach was limited to five cases due to slow accrual [25].

A closer examination of the selected studies reveals a broad age range among participants, from 16 to 71 years, reflecting the extensive demographic spectrum involved in leukemia treatment studies. Serum ferritin (SF) cut-offs exhibited significant variability, ranging from 400 ng/mL to 2515 ng/mL (Table 1). This diversity underscores the need for standardization in defining iron overload thresholds and points to the potential of SF as a prognostic marker, with several studies (Penack et al. [24], Armand et al. [25], and Wahlin et al. [26]) noting improved survival rates at lower SF levels [24-26].

Specifically, the contributions from Kong et al. [18] Tachibana et al. [23] and Penack et al. [24] highlight the proactive approach of recent research in addressing the complexities of serum ferritin's role in leukemia treatment. Collectively, these studies underscore the imperative of future research to refine methodological approaches and clinical guidelines, aiming for enhanced prognostic precision and improved treatment outcomes [18,23-24].

Initial Ferritin studies

Categorically, nine studies explored the association of serum ferritin with induction therapy, shedding light on its relevance in the initial phases of leukemia treatment. In a cohort study (Table 1) Tachibana et al. [23] found serum ferritin (SF) correlation with lactate dehydrogenase, C-reactive protein, and white blood cell count leading to poor performance status. The group with high ferritin levels (above 400 ng/mL) depicted a lower event-free survival (EFS) at the 5-year mark compared to the low ferritin group (30% vs. 40%; P = 0.033). Moreover, further analysis of the high-risk karyotype individuals indicated that elevated ferritin levels were predictive of worse EFS

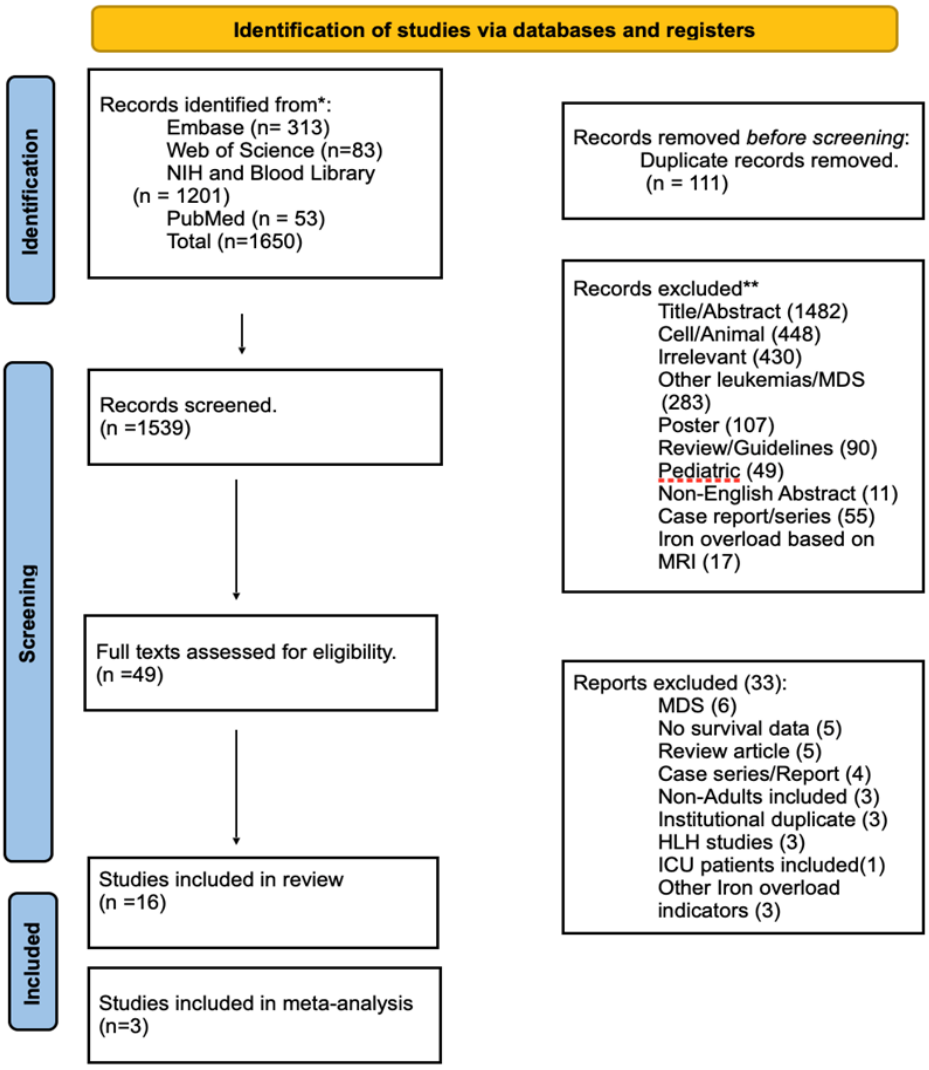

Figure 1. PRISMA Chart

Table 1A. Initial Ferritin Papers

First Author	Year of Publication	Study Period	Participant no	Median Age (Year)	Median SF	SF Cut-off	OS (Months)	EFS/DFS/PFS	Relapse
L. Dou	2022	2017-2020	212	Median age=49 (7-82)	439.7 (250.6-761.7)	NA	Median OS at 4 years: CRP ≤ 19.92 mg/L = ~62%, CRP > 19.92 mg/L = ~ 40%	Median EFS at 4 years: CRP ≤ 19.92 mg/L = ~ 48%, CRP > 19.92 mg/L = ~ 20%	NA
D. Dudok	2021	2017-2019	108	Average age = 51.9 (19-75)	NA	800	Average OS=14.8 months (11.5-18.8) / 3 year OS=6.4%	NA	NA
J. Ihlow	2018	2000-2015	137	Median age = 54.5 (44-63) for SF 750 mg/L N=88) and 53 (43–65) for SF > 750 mg/l (N=49)	769 ug/l	750	Median OS at 5 years: SF ≤ 750 = ~ 40%, SF > 750 = ~ 18%	NA	Risk of relapse at 5 years: SF ≤ 750 = ~ 62%, SF > 750 = ~ 82%
J. Ihlow	2021	2000-2017	590	Median age = 68 (63-74)	974 ug/L (509.6-1797.0)	1000	Median OS for entire cohort = 12.0 / 95% CI = 10.6 - 13.5	Median EFS for entire cohort = 8.3 / 95% CI = 7.1-9.6	NA
J. Hong	2015	2006-2013	110	Median age = 54.5 (20-80)	658.6 (47.3–7184.7)	290	Median OS=13.0 months / 95% CI=8.1-17.8	NA	NA
D. Lebon	2015	2007-2011	162	Median age = 49 (16-60)	633 ug/l (54–80,070 g/L)	4n	SF>4n: HR=4.12 / 95% CI=2.29-7.42 / p=<0.0001	NA	NA
T. Tachibana	2018	2000-2015	305	Median age = 50 (15-77)	512 ng/ml	400	Age >= 50 years: HR=1.97 / 95%CI=1.43-2.72 / P=<.001	Median EFS: Age >= 50 years: HR=1.53 / 95%CI=1.14-2.04 / P=.004	NA
P. Armand	2018	2013	5	Median = 49 (20-52)	Median SF level before HSCT = 3746 ng/mL (2879-7493)	1000	2-year OS = 100%	NA	0%
O. Yokus	2021	2015 - 2019	50	Mean ± SD = 57 ± 20,4	NA	1000	Mean OS, days ± SD: AML (n=32) 426,6 ± 450,6 [Median = 278 (29-2182)]Last status: 2(12.5%)in high ferritin, 2(28.6%)in low ferritin group with 42.5 and 23 blood transfusion respectively.	NA	NA

Table 1B. Pre-Transplant Serum Ferritin

First Author	Year of Publication	Study Period	Participant no	Median Age (Year)	Median SF	SF Cut-off	OS (Months)	EFS/PFS	Relapse	GVHD	CRP
S. G. Kong	2021	2003 - 2015	5395	Total mean = 35.9 ± 16.6	3746 ng/mL for 5 patients	1000	60-month OS: 54 ± 1% in the transplantation period of 2003–2009 (p = 0.270). 52 ± 1% in the transplantation period of 2010–2015 (p = 0.270).	NA	NA	GVHD accounted for 15% of the deaths. GVHD accounted for more than 50% of the deaths between 30 and 100 days.	NA
O. Penack	2020	2014 - 2018	298	52 (17.1-71.3) [38.1-60.2] for <= 1500 (N=153) / 53.2 19-70.9) [42.9-62.3] for >1500 (N=145)	1500	1500	36-month OS: ~ 60% for SF below cut off HR = 2.5, CI = 1.5–4.1, p = 0.0005). ~ 30% for SF above cut off HR = 2.5, CI = 1.5–4.1, p = 0.0005)	24- month PFS: ~ 65% for SF below cut off ~45% for SF above cut off (HR = 2.1, CI = 1.4–3.2, p = 0.00014	At 12 months: <1500 was ~ 20% and > 1500 was ~ 30%	Incidence of acute GVHD grades II–IV and grades III–IV in the whole population at 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	NA
P. Armand	2017	1997 - 2005	590	Median = 42 (18-68)	930 ng/mL	2515	60-month OS: Low risk group: 56% [95% CI(48–64)] High risk group: 5% [95% CI (0–12)]	60-month EFS: 27% (95% CI, 19%-36%) (P < .001).	Approx 30% at 8 years in ferritin highest quartile. / approx 38% for ferritin 1st-3rd quartile (p=.7)	NA	NA
R.S.Artz	2016	2008-2010	784	50 years (range 18–78 years)	Pre-T=1148 (51-14298)	2500	12-month OS: Ferritin >2500 HR:1.15, 95% CI (0.86-1.54), P=0.35	36-month PFS:Progression-free survival ranged from 57% (95%CI: 54%–61%) at one year to 45% (95%CI: 43%–49%) at three years.	None of the biomarkers significantly affected relapse or acute GvHD suggesting abnormal biomarkers represent a non-specific vulnerability to transplant toxicity.	The cumulative incidence of acute GvHD grades II–IV was 43% (95%CI: 39%–46%) and grade III–IV was 15% (95%CI: 13%–18%) at 100 days.	High CRP (>0.3 mg/dL, 28 patients) levels was significantly associated with the development of bacterial infection in a multivariate analysis (HR [95% CI]: ferritin, 4.00 [1.32–12.17]; CRP, 3.64 [1.44–9.20]). Bacterial infection at 30 days: CRP ≤0.3: 10.9% (5.4%-18.7%), CRP >0.3: 32.1% (16.1%-49.3%). OS at 3 years: CRP ≤0.3: 54.5% (95% CI, 39.1%-67.5%) CRP >0.3: 50.4% (95% CI, 26.5%-70.2%). TRM at 3 years: CRP ≤0.3: 12.2% (95% CI, 5.5%-21.6%) CRP >0.3: 22.4% (95% CI, 9.1%-39.3%). Hypoalbuminemia showed a stronger association with inferior survival (P=0.002) whereas the significance for CRP more than 10 mg/L was borderline (P=0.072).
S. C. Meyer	2012	2000 - 2009	290	Median = 44 (17-70)	Pretransplant SF level (ug/L) median (IQR) = 1332 (651-2283)	1000	60-month OS: FTN < median = ~100%. FTN > median = ~ 82%.	NA	NA	0-6 months: GVHD results in 7 (31%) and 12 (24%) deaths in patients below and above median SF respectively. 6-12 months: GVHD result in 0 and 2 (10%) death in patients below and above median SF respectively.	NA

Table 1B. Continued

First Author	Year of Publication	Study Period	Participant no	Median Age (Year)	Median SF	SF Cut-off	OS (Months)	EFS/PFS	Relapse	GVHD	CRP
J. Kanda	2011	2004 - 2009	112	Median = 47 (18-66)	Pretransplant SF level (ng/mL) median = 694.6 (34.7 - 12079.1)	700	36-month OS: FTN ≤700: 69.7% (95% CI, 51.1%-82.3%) FTN >700: 39.0% (95% CI, 22.1%-55.5%)	NA	Relapse >100 days after transplant: FTN ≤700 ng/mL = 9 (82%). FTN >700 ng/mL = 12 (75%).	GVHD was the cause of death in 2 (29%) in the first 100 days after transplant in the high ferritin group.	26 patients with a CRP value of >10 mg/l as an indicator of acute infections were excluded from the study
A. Wahlin	2010	1998 - 2005	309	Median = 47 (16-68)	Median pre-transplantation SF = 1,159 ug/l.	400	60-month OS: ~ 65% for normal ferritin (<=400 ug/l, N=74, HR=1) ~ 50% for elevated ferritin (>400 ug/l, N=186, HR=1.79, 95% CI =1.13–2.84, P=0.013)	NA	Normal (<=400 ug/l) N=64 (HR=1) Elevated (>400 ug/l) N=186 (HR=2.10, 95% CI =1.32-3.33, P=0.002). Prob of relapse at 10 years --> SF above cut off = ~ 40%, SF below cutoff = ~ 27%	Probability of cGVHD at 5 years: For elevated SF levels = ~ 53%, For normal SF levels = ~ 30%	Elevated CRP was associated with OS HR: 1.88 95% CI 1.27–2.78 P 0.002, RFS: HR 1.74 95% CI 1.18–2.58 P 0.005, NRM: HR 2.11 95% CI 1.23–3.60 P 0.006

(hazard ratio = 2.07; 95% confidence interval, 1.28-3.33; P =0.003), resulting in higher tumor burden and forecasting a poorer EFS for high-risk groups [23].

In Dou's study, findings revealed that AML patients with SF levels exceeding 800 ug/L faced heightened risks of early mortality and sepsis during induction therapy. These results underscore the detrimental effect of elevated SF on survival outcomes in AML patients undergoing therapy. Additionally, the study highlighted the prognostic significance of the C-reactive protein to albumin ratio (CAR) in AML patients, revealing a critical cut-off value of 1.015 determined via ROC curve analysis. Elevated CAR levels were associated with lower rates of achieving complete remission (CR) post-induction chemotherapy and increased risk of disease relapse [12].

Dudok and colleagues who included 108 patients with acute myeloid leukemia (AML) in their study, notably found that patients with SF levels above 800 µg/L experienced a significantly higher incidence of early death ($p = 0.020$) and sepsis during induction therapy ($p < 0.010$) compared to those with lower SF levels (Table 1). Furthermore, patients with lower SF levels demonstrated a higher rate of achieving complete remission (39.8%) compared to those with higher SF levels (26.9%), although without statistical significance ($p = 0.874$). Importantly, the study identified a critical SF cut-off value of 800 µg/L, beyond which disease-free survival was markedly shorter (12 months, 95%CI: 7.2 – 16.1) ($p = 0.048$). Univariate analysis further confirmed SF levels >800 µg/L as a significant predictor of poor overall survival ($p = 0.019$) and disease-free survival ($p = 0.040$) [27].

Lebon et al. conducted a comprehensive study (Table 1), focusing on the prognostic significance of serum ferritin (SF) levels. Through receiver operating characteristic (ROC) curve analysis, the study identified a cut-off value of >4 times the upper normal limit (>4n), which delineated patients at higher risk for adverse events. Patients with SF levels >4n exhibited distinct clinical characteristics, including higher white blood cell count and elevated c-reactive protein levels. Notably, ferritin >4n at diagnosis emerged as a poor prognostic factor for both disease-free survival (DFS) and overall survival (OS) in multivariate analysis (HR: 3.45, 95%CI: 1.98–6.04 for DFS; HR: 4.12, 95%CI: 2.29–7.42 for OS). Furthermore, patients with ferritin >4n had a significantly higher cumulative incidence of relapse compared to those with ferritin <4n, even among patients with favorable molecular prognosis (NPM1 mutation without FLT3-ITD) [7].

The study by Hong et al. involved 110 patients with AML undergoing induction chemotherapy. Their analysis revealed that elevated levels of CRP and ferritin were significantly associated with the incidence of systemic infection. Specifically, elevated CRP was related to infectious treatment-related mortality (TRM), while ferritin emerged as an independent risk factor for systemic infection. Furthermore, age and Eastern Cooperative Oncology Group (ECOG) performance status were also linked to an increased incidence of systemic infection [17].

In their investigation into iron overload during acute leukemia treatment, Yokus et al. examined a cohort of 50 patients, predominantly diagnosed with acute myeloid

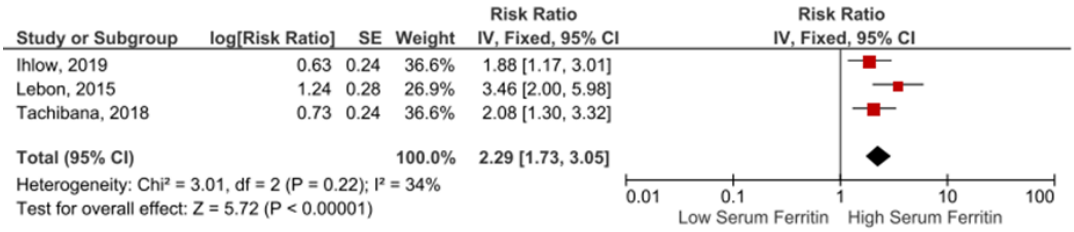

Figure 2. Meta Analysis- Serum Ferritin and Overall Survival

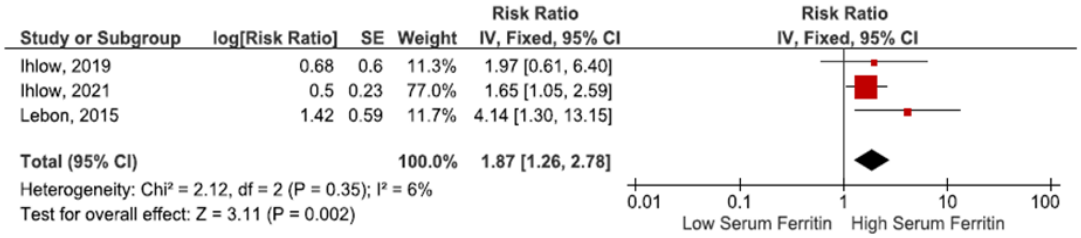

Figure 3. Meta Analysis Serum Ferritin and Event Free Survival

leukemia (AML) or acute lymphoblastic leukemia (ALL). Notably, AML patients demonstrated elevated serum ferritin levels, indicating a greater propensity for iron overload, particularly evident at the 6-month mark (mean ferritin level of 1500 µg/l). This finding correlated with a higher incidence of erythrocyte transfusions among AML patients, with a median total of 42.5 units received during the study period, compared to 23 units in ALL patients [28].

Results of the meta-analyses

Two meta-analyses were conducted to show the effect of initial high serum ferritin on overall survival (OS) and Event-Free Survival (EFS) survival in patients with high and low serum ferritin respectively. The Hazard Ratio (HR) was considered a measure of the effect. In three studies [7,14,26] consisting of 873 patients, the overall HR and 95% CI were 1.99 (1.48-2.66), showing that high serum ferritin is a predictor of poor OS. There was no evidence of heterogeneity across the studies (I2=40%, P-value=0.19) (Figure 2). In the second meta-analysis, totaling 588 patients, we compared event-free survival in patients with high and low serum ferritin [7,14,23]. The overall HR and 95% CI were 2.29 (1.73-3.05), showing

Table 2. The Newcastle-Ottawa Scale (NOS) for assessing the Quality of Serum Ferritin Studies

Studies	Selection				Comparability		Outcome		Total Quaity Score
Author, year	Representativeness of the exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Comparability of cases and controls	Assessment of outcome	Longetivity of follow-up for outcomes to occur	Adequacy of follow up for cohorts	
Dou et al, 2022	1	0	1	1	2	1	1	1	8
Dudok et al, 2021	1	0	1	1	1	1	1	1	7
Kong et al, 2021	1	1	1	1	1	1	1	1	8
Yokus et al, 2021	1	0	1	1	2	1	1	1	8
Ihlow et al, 2020	1	1	1	1	2	1	1	1	9
Penack et al, 2020	1	0	1	1	1	1	1	1	7
Ihlow et al, 2019	1	0	1	1	1	1	1	1	7
Tachibana et al, 2018	1	0	1	1	1	1	1	1	7
Artz et al, 2016	1	0	1	1	2	1	1	1	8
Hong et al, 2015	1	0	1	1	1	1	1	1	7
Lebon et al, 2015	1	0	1	1	1	1	1	1	7
Armand et al, 2013	1	0	1	1	2	1	0	1	7
Meyer et al, 2013	1	0	1	1	1	1	1	1	7
Kanda et al, 2011	1	0	1	1	2	1	1	1	8
Wahlin et al, 2010	1	0	1	1	1	1	1	1	7
Armand et al, 2007	1	0	1	1	2	1	1	1	8

Table 3. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Iron Chelator Studies

Studies	Selection				Comparability		Outcome		Total Quality Score
Author, Year	Representativeness of the exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Comparability of cases and controls	Assessment of outcome	Longetivity of follow-up for outcomes to occur	Adequacy of follow up for cohorts	
Argenziano et al, 2021	0	0	1	1	2	1	1	0	6
Kong et al, 2021	1	1	1	1	1	1	1	1	7
Tachibana et al, 2018	1	0	1	1	1	1	1	1	7
Taher et al, 2018	1	1	1	1	1	1	1	1	8
Vallejo et al, 2014	1	0	1	1	1	1	1	1	7
Armanda et al, 2013	1	0	1	1	2	1	0	1	7
Kennedy et al, 2013	1	0	1	1	1	1	1	1	8
Paubelle et al, 2013	1	0	1	1	1	1	1	1	7

that high serum ferritin is also a predictor of poor EFS. There was no evidence of heterogeneity across the studies (I^2=34%, P-value=0.22) (Figure 3).

Peritransplant studies

Seven studies focused on peritransplant serum ferritin (6998 patients), contributing to a nuanced understanding of its dynamics at different risk levels of the disease and therapeutic interventions [18, 24-25,29-32]. Research conducted by Kanda and colleagues on Allo-SCT examined individuals who experienced confirmed bacterial infections within 30 days following the transplantation procedure. The findings showed a 29.8% (17.6%-43.0%) infection rate in patients with serum ferritin (SF) levels above the cut-off (700), compared to 8.4% (2.7%-18.5%) in those below the cut-off. Furthermore, infection was identified as the cause of death in 29% of patients with high ferritin levels within the initial 100 days, as opposed to none in patients with ferritin levels below the cut-off [29]. Penack et al. [24] studied a cohort of 298 patients undergoing Allogeneic Stem Cell Transplantation (Allo-SCT). Specifically, the OS and the incidence of relapse were significantly higher in the high ferritin group. At the 12-month mark, the infection-related mortality rate was approximately 12% in patients with SF levels above the cut-off, in contrast to only 2% in those below the cut-off. The study also found that death after the last follow-up was attributed to infection in 10% of patients with SF levels above the cut-off, compared to 3% in patients below the cut-off after the last follow-up was attributed to infection in 10% of patients with SF levels above the cut-off, compared to 3% in patients below the cut-off [24]. Meyer et al. studied the impact of iron overload on the prognosis of patients undergoing Allo-HCT. Infection was found to be the cause of death in 5 (10%) of patients with SF levels above the median compared to 2 (9%) in patients with SF levels below the median in the first 6 months after transplant [30]. In a retrospective study, Tachibana et al. [23] explored the predictive value of serum ferritin levels and disease status for outcomes in Allo-SCT for patients with Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS), using a ferritin threshold of 1,000 ng/ml. During a median follow-up of 4.5 years, 61 patients remained alive and in remission, with primary causes of death including relapse, infection (in 10 cases), and graft-versus-Host Disease (GVHD) [23].

The study by Meyer et al., with a median follow-up of 5.3 years, meticulously documents the dynamics of iron metabolism post-allogeneic HSCT, highlighting the significant elevation of ferritin levels pre-HSCT (median of 1,322 mg/L), which further peaks between 1 to 3 months post-transplant (medians of 2,660 and 2,337 mg/L, respectively). This peak is followed by a gradual normalization, reaching near-normal levels at 5 years (224 mg/L). This trajectory is mirrored by transferrin saturation and iron, which also peak early post-transplant and subsequently decrease. Interestingly, a significant proportion of patients exhibited ferritin levels indicative of relevant iron overload (>1,000 mg/L) across various post-transplantation timelines, underscoring the persistence of iron overload in the post-transplantation phase. The study aligns with previously published data, confirming the detrimental impact of elevated pre-transplantation ferritin levels on survival (P = .04), with landmark analysis further elucidating the persistently negative prognostic effect of high ferritin levels across all post-transplant periods analyzed [30]. In contrast, Armand et al. [25] despite not finding a direct correlation between serum ferritin (SF) and relapse in acute leukemia, identified elevated SF levels (>2,500 mg/L) as significantly associated with lower overall survival (HR of 1.7, P = 0.007), highlighting the nuanced impact of iron parameters on post-transplant outcomes [25].

Multiple studies have explored iron chelation therapy's role in leukemia treatment and post-transplant iron overload. Cho et al. found longer survival in AML patients treated with deferasirox despite dose reductions due to adverse effects [31]. Vallejo et al. observed reduced serum ferritin levels with deferasirox but noted adverse events. High post-transplant serum ferritin levels were linked to reduced survival, emphasizing the importance of iron removal therapies [32]. Additionally, combining deferasirox with vitamin D prolonged survival in AML patients unresponsive to other therapies [33-34]. Kong et al. [18] found lower transplant-related mortality in patients undergoing iron chelation pre-transplant [18]. A clinical trial testing peri-transplant iron chelation faced recruitment challenges [25].

Risk of bias in included studies

The Newcastle-Ottawa Scale (NOS) was employed to assess the quality of included studies, focusing on selection, comparability, and outcome measures to evaluate the overall risk of bias, as presented in Table 2 [21]. The analysis revealed that, while the majority of studies exhibited strong selection criteria, ensuring the robust representation of study populations, specifically, the selection of non-exposed cohorts was often lacking, as evidenced by several studies scoring zero in this area. Furthermore, while ascertainment of exposure was generally well-addressed, the comparability of cases and controls varied, with some studies receiving lower scores due to insufficient adjustment for key variables. These variations highlight the necessity for methodological refinement. In terms of outcome measures, most studies adhered to objective and reliable outcome measurement practices. The total quality scores of the studies ranged from 7 to 9 (one 6 in Table 3), indicating a generally high level of methodological quality across the board. Despite these areas for improvement, the studies predominantly adhered to objective and reliable outcome measurement practices.

Discussion

This study has demonstrated a statistically significant association between unadjusted serum ferritin levels above 1000 mg/L or adjusted by CRP levels above 750 mg/L and both overall survival (OS) and event-free survival (EFS) among AML patients before initiating treatment. Elevated serum ferritin levels are inversely correlated with the gradual onset of infections. In such cases, heightened serum ferritin levels are associated with an increased risk of early mortality, with infection being the primary contributing factor [31]. This investigation could open up promising possibilities for personalized treatment approaches for AML patients with iron overload at diagnosis.

The majority of participants in the meta-analysis, the systematic review, had acute myeloid leukemia (AML) without concurrent hematological malignancies and underwent standard induction chemotherapy. An unadjusted threshold of >1000 mg/l for serum ferritin (SF) level aligns with the internationally accepted range for cutoff values, indicating the need for therapeutic intervention in patients with hematologic diseases and iron overload. However, there is currently no widely acknowledged algorithm for quantitatively adjusting elevated serum ferritin (SF) levels based on an individual's (subclinical) inflammation status. Nevertheless, the algorithm employed in the two studies is sourced from comprehensive published research and relies on serum CRP values [13-14]. One study excluded patients based on CRP levels above normal values [28].

The connection between excess iron levels and the results of various types of leukemias, particularly in the context of transplantation, has been assessed in a few meta-analyses [8,35]. Yet, as far as we know, there hasn't been a systematic review examining the distinct impact of serum ferritin specifically on the survival of individuals with AML. Elevated ferritin levels identified in this systematic review have been linked to unfavorable outcomes, establishing a connection between iron metabolism and critical aspects of acute myeloid leukemia (AML) development, including cell proliferation and inflammation. The investigations involved the assessment of patients exhibiting diminished overall survival (OS) and disease-free survival (DFS), associating heightened serum ferritin (SF) levels with excessive growth of bone marrow cells. The primary emphasis is on the observation that AML patients without pre-existing conditions mostly do not necessitate transfusions before treatment, and ferritin could serve as an indicator of disease burden and inflammation. Nearly all the studies integrated into this systematic review revealed a noteworthy correlation between serum ferritin and well-known inflammatory biomarkers such as C-reactive protein (CRP), albumin, and fibrinogen [1, 36-37]. Furthermore, the three studies by Tachibana et al, Wahlin et al. [26] and Kanda et al. [23, 26, 29], employing SF cutoff points below the iron overload threshold (<1000 mg/L or adjusted <750 mg/L), demonstrated a substantial hyperferritinemia impact on the OS of AML patients. This effect was attributed to immunosuppressive effects leading to increased rates of relapse [7, 8, 30] and mortality related to infections [8,24, 29-30] or chemotherapy-related toxicity [31].

Ihlow et al. and Dudok et al. [14,27] found that with adjusting serum ferritin levels based on elevated C-reactive protein (CRP) patients with higher baseline serum ferritin levels (>750 mg/l) experienced higher non-relapse mortality (NRM). This increased mortality is primarily attributed to iron-related toxicity during chemotherapy. Research has shown that elevated levels of C-reactive protein (CRP) and ferritin in the bloodstream are associated with a higher risk of systemic infection, regardless of white blood cell count [14]. In a study focusing on elderly AML patients, the same research team found a significant correlation between non-adjusted serum ferritin (SF) levels exceeding 1000 and elevated mortality rates in individuals undergoing intensive induction chemotherapy [38]. This suggests that SF could serve as a biomarker that is concerning in terms of guidance for therapeutic decisions for older AML patients, whose long-term survival is only 10%-15% [14, 38]. When addressing elderly patients with acute myeloid leukemia (AML), retrospective studies indicate that iron chelator plus Vitamin D therapy is associated with a heightened overall survival rate [33-34].

As per guidelines set by the European Leukemia Net (ELN), a significant proportion of acute myeloid leukemia (AML) patients who achieve initial complete remission (CR) are at risk of relapse unless they undergo post-remission therapy [1]. The objective of such therapy is to eliminate residual, undetectable diseases to ensure sustained disease control and a potential cure. Allogeneic stem cell transplantation (Allo-SCT) is considered among the available options for post-remission therapy. Notably, in all studies within this domain, serum ferritin (SF) levels have served as a surrogate marker for iron overload. Additionally, pre-transplant serum ferritin levels could serve as a useful indicator for predicting the risk

of early bacterial complications and mortality after Allo-SCT. In the context of transplantation, existing literature underscores the reverse relationship between relapse and graft-versus-host disease (GVHD), underscoring the immunosuppressive impacts of iron overload and elevated ferritin levels [20, 31]. In our comprehensive review, we observed an association between pre-transplant serum ferritin levels and the susceptibility to relapse. Some of the studies we examined indicated a positive and straightforward correlation, indicating that increased post-transplant ferritin levels were associated with a higher probability of mortality due to relapse, although this connection was not consistently observed in all studies.

Meyer et al. focused on the timing of peak serum ferritin levels in the context of allogeneic stem cell transplantation (Allo-SCT), determining that this peak typically occurs within one to six months post-transplantation. They underscored iron overload as the leading cause of hyperferritinemia during this period [30]. In the Yokus et al study, it was revealed that within six months, patients with iron overload received a median total of 42.5 units of erythrocyte transfusion, whereas those without iron overload received only 23 units. The research concludes that, especially in diseases like acute leukemias, the main cause of iron overload stems from multiple blood transfusions [28]. Meyer et al. also concluded that over five years, iron overload significantly impacts post-transplantation mortality, highlighting the potential benefits of efforts to reduce iron overload both before and after transplantation [30]. These risks are primarily associated with immune suppression, organ failure, and infection rates, which are major contributors to mortality and ultimately influence the overall survival of transplant recipients [31].

Iron chelator therapy, recognized for its dual efficacy in treating leukemia and preventing complications, has been employed in clinical trials and case studies for patients with the disease and transfusion-related iron overload. Iron chelators such as deferoxamine (DFO) and deferasirox (DFX) have been demonstrated the ability to inhibit the generation of deoxyribonucleotides, resulting in G1/S cell cycle arrest in leukemia cells, inducing apoptosis in leukemia cells, and impede various signaling pathways [37, 39-40]. This sequence of events leads to an increase in platelet production, the suppression of leukemia cell growth, and the promotion of their differentiation [41]. Moreover, when utilized in combination with conventional chemotherapy medications, iron chelators exhibit synergistic effects, enhancing the responsiveness of leukemia cells to treatment [42]. Nevertheless, it is essential to acknowledge that the effectiveness of iron chelators may vary based on the specific chemotherapy drug employed. In a phase I trial involving 31 patients, primarily those with refractory acute leukemia, it was observed that four achieved complete remission (CR) and a longer median survival after receiving a combination of 3-AP and Ara-C. However, the study documented the occurrence of dose-limiting toxicities, including mucositis, neutropenic colitis, neuropathy, and hyperbilirubinemia. Other phase I trials reported a similar pattern of dose-related toxicities (DLTs) with a 3-AP and Ara-C combination. [43-45]. The prognosis for older individuals (aged 65 years or more) diagnosed with acute myeloid leukemia (AML) is generally grim, particularly for those who are not eligible for intensive therapies. In such situations, promoting blast differentiation is similar to the mechanism seen with all-trans-retinoic acid (ATRA) in treating promyelocytic leukemia (APL), a specific subtype of AML, could represent a promising strategy.

One strength of this systematic review lies in its examination of serum ferritin (SF) levels both at the initiation of treatment and during the transplantation phase. Additionally, by comparing outcomes based on SF cutoff values across various studies, we aimed to identify differences in SF as an inflammatory and iron overload surrogate biomarker. The diversity in study designs including both retrospective and prospective studies enhances the comprehensiveness of our analysis, incorporating data from various research methodologies. Furthermore, it is worth mentioning that we specifically delved into the effects of iron chelator therapy in AML. This aspect contributes a valuable perspective to our examination of serum ferritin dynamics within the realm of AML treatment. However, our review has several limitations. inconsistencies arose among studies due to researchers using varying ferritin levels (ranging from 400 to 2500 mg/l) for statistical analysis. This variation in serum ferritin cut-off points across studies limits the extent of meta-analysis. Certain studies, particularly in the peri-transplant group, included cases of myelodysplastic syndrome (MDS) and acute lymphoblastic leukemia (ALL) alongside acute myeloid leukemia (AML) patients, but we tried to use just AML data. Importantly, the study only considered literature in English, potentially excluding relevant studies in other languages. Despite conducting an extensive search for recent prospective and retrospective studies, the heterogeneity in therapeutic strategies, which encompass criteria for allogeneic stem cell transplantation (Allo-SCT), transplant source, graft-versus-host disease (GVHD) prevention, infection prophylaxis, and differences in follow-up durations among studies, poses a challenge. Future research should aim to address these sources of heterogeneity by employing standardized methodologies and clearly defined inclusion criteria to enhance comparability across studies in this field. Additionally, in the context of iron chelators, there is a recognized need for advanced clinical trials and large prospective cohorts that include validation studies on less toxic medications [45].

In conclusion currently, the main clinical approaches for managing AML involve chemotherapy and bone marrow transplantation. However, a potential shift in the treatment paradigm for AML, especially in medically unfit patients, may emerge by focusing on iron metabolism. This systematic review and meta-analyses have revealed that hyperferritinemia impacts the overall survival and event-free survival of AML patients, with iron chelators showing potential to improve patients' outcomes. Nevertheless, the toxicity associated with current iron chelators underscores the importance of exploring new, less toxic options with multiple effects which has the off-label potential to reshape the landscape of AML treatment.

Further research and extensive clinical trials are essential to gain a deeper understanding of the optimal utilization of these treatments and their wide spectrum of benefits.

Author Contribution Statement

All authors contributed equally in this study.

Acknowledgements

None.

References

1. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et al. Diagnosis and management of aml in adults: 2022 recommendations from an international expert panel on behalf of the eln. Blood. 2022;140(12):1345-77. https://doi.org/10.1182/blood.2022016867.
2. Zhang N, Wu J, Wang Q, Liang Y, Li X, Chen G, et al. Global burden of hematologic malignancies and evolution patterns over the past 30 years. Blood Cancer J. 2023;13(1):82. https://doi.org/10.1038/s41408-023-00853-3.
3. Sasaki K, Ravandi F, Kadia TM, DiNardo CD, Short NJ, Borthakur G, et al. De novo acute myeloid leukemia: A population-based study of outcome in the united states based on the surveillance, epidemiology, and end results (seer) database, 1980 to 2017. Cancer. 2021;127(12):2049-61. https://doi.org/10.1002/cncr.33458.
4. Jensen PD. Evaluation of iron overload. Br J Haematol. 2004;124(6):697-711. https://doi.org/10.1111/j.1365-2141.2004.04838.x.
5. Alkhateeb AA, Connor JR. The significance of ferritin in cancer: Anti-oxidation, inflammation and tumorigenesis. Biochim Biophys Acta. 2013;1836(2):245-54. https://doi.org/10.1016/j.bbcan.2013.07.002.
6. Wang F, Lv H, Zhao B, Zhou L, Wang S, Luo J, et al. Iron and leukemia: New insights for future treatments. J Exp Clin Cancer Res. 2019;38(1):406. https://doi.org/10.1186/s13046-019-1397-3.
7. Lebon D, Vergez F, Bertoli S, Harrivel V, De Botton S, Micol JB, et al. Hyperferritinemia at diagnosis predicts relapse and overall survival in younger aml patients with intermediate-risk cytogenetics. Leuk Res. 2015;39(8):818-21. https://doi.org/10.1016/j.leukres.2015.05.001.
8. Yan Z, Chen X, Wang H, Chen Y, Chen L, Wu P, 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. https://doi.org/10.1097/md.0000000000010310.
9. Mahindra A, Bolwell B, Sobecks R, Rybicki L, Pohlman B, Dean R, et al. Elevated pretransplant ferritin is associated with a lower incidence of chronic graft-versus-host disease and inferior survival after myeloablative allogeneic haematopoietic stem cell transplantation. Br J Haematol. 2009;146(3):310-6. https://doi.org/10.1111/j.1365-2141.2009.07774.x.
10. Bazuaye GN, Buser A, Gerull S, Tichelli A, Stern M. Prognostic impact of iron parameters in patients undergoing allo-sct. Bone Marrow Transplant. 2012;47(1):60-4. https://doi.org/10.1038/bmt.2011.13.
11. Armand P, Sainvil MM, Kim HT, Rhodes J, Cutler C, Ho VT, et al. Does iron overload really matter in stem cell transplantation? Am J Hematol. 2012;87(6):569-72. https://doi.org/10.1002/ajh.23188.
12. Dou L, Shi M, Song J, Niu X, Niu J, Wei S, et al. The prognostic significance of c-reactive protein to albumin ratio in newly diagnosed acute myeloid leukaemia patients. Cancer Manag Res. 2022;14:303-16. https://doi.org/10.2147/cmar.S343580.
13. Bertoli S, Paubelle E, Bérard E, Saland E, Thomas X, Tavitian S, et al. Ferritin heavy/light chain (fth1/ftl) expression, serum ferritin levels, and their functional as well as prognostic roles in acute myeloid leukemia. Eur J Haematol. 2019;102(2):131-42. https://doi.org/10.1111/ejh.13183.
14. Ihlow J, Gross S, Sick A, Schneider T, Flörcken A, Burmeister T, et al. Aml: High serum ferritin at initial diagnosis has a negative impact on long-term survival. Leuk Lymphoma. 2019;60(1):69-77. https://doi.org/10.1080/10428194.2018.1461860.
15. Delavigne K, Bérard E, Bertoli S, Corre J, Duchayne E, Demur C, et al. Hemophagocytic syndrome in patients with acute myeloid leukemia undergoing intensive chemotherapy. Haematologica. 2014;99(3):474-80. https://doi.org/10.3324/haematol.2013.097394.
16. Zeidan AM, Giri S, DeVeaux M, Ballas SK, Duong VH. Systematic review and meta-analysis of the effect of iron chelation therapy on overall survival and disease progression in patients with lower-risk myelodysplastic syndromes. Ann Hematol. 2019;98(2):339-50. https://doi.org/10.1007/s00277-018-3539-7.
17. Hong J, Woo HS, Ahn HK, Sym SJ, Park J, Cho EK, et al. Pre-treatment blood inflammatory markers as predictors of systemic infection during induction chemotherapy: Results of an exploratory study in patients with acute myeloid leukemia. Support Care Cancer. 2016;24(1):187-94. https://doi.org/10.1007/s00520-015-2762-1.
18. Kong SG, Jeong S, Lee S, Jeong JY, Kim DJ, Lee HS. Early transplantation-related mortality after allogeneic hematopoietic cell transplantation in patients with acute leukemia. BMC Cancer. 2021;21(1):177. https://doi.org/10.1186/s12885-021-07897-3.
19. Akı Ş Z, Suyanı E, Bildacı Y, Çakar MK, Baysal NA, Sucak GT. Prognostic role of pre-transplantation serum c-reactive protein levels in patients with acute leukemia undergoing myeloablative allogeneic stem cell transplantation. Clin Transplant. 2012;26(5):E513-21. https://doi.org/10.1111/ctr.12028.
20. Artz AS, Logan B, Zhu X, Akpek G, Bufarull RM, Gupta V, 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):1426-33. https://doi.org/10.3324/haematol.2016.145847.
21. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
22. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The prisma 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71.
23. Tachibana T, Andou T, Tanaka M, Ito S, Miyazaki T, Ishii Y, et al. Clinical significance of serum ferritin at diagnosis in patients with acute myeloid leukemia: A yacht multicenter retrospective study. Clin Lymphoma Myeloma Leuk. 2018;18(6):415-21. https://doi.org/10.1016/j.clml.2018.03.009.
24. Penack O, Peczynski C, van der Werf S, Finke J, Ganser A, Schoemans H, et al. 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. Front Immunol. 2020;11:586. https://doi.org/10.3389/fimmu.2020.00586.
25. Armand P, Kim HT, Cutler CS, Ho VT, Koreth J, Ritz J, et al. A prognostic score for patients with acute leukemia or myelodysplastic syndromes undergoing allogeneic stem cell transplantation. Biol Blood Marrow Transplant. 2008;14(1):28-35. https://doi.org/10.1016/j.bbmt.2007.07.016.
26. Wahlin A, Lorenz F, Fredriksson M, Remberger M, Wahlin BE, Hägglund H. Hyperferritinemia is associated with low incidence of graft versus host disease, high relapse rate, and impaired survival in patients with blood disorders receiving allogeneic hematopoietic stem cell grafts. Med Oncol. 2011;28(2):552-8. https://doi.org/10.1007/s12032-010-9496-1.
27. Dudok D, Virijević M. Prognostic significance of serum ferritin levels on initial diagnosis in patients with acute myeloid leukemia. Serbian medical journal of the Medical Chamber. 2021;2(4):362-70.
28. Yokus O, Herek C, Cinli TA, Goze H, Serin I. Iron overload during the treatment of acute leukemia: Pretransplant transfusion experience. Int J Hematol Oncol. 2021;10(3):Ijh36. https://doi.org/10.2217/ijh-2021-0005.
29. Kanda J, Mizumoto C, Ichinohe T, Kawabata H, Saito T, Yamashita K, et al. Pretransplant serum ferritin and c-reactive protein as predictive factors for early bacterial infection after allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2011;46(2):208-16. https://doi.org/10.1038/bmt.2010.108.
30. Meyer SC, O'Meara A, Buser AS, Tichelli A, Passweg JR, Stern M. Prognostic impact of posttransplantation iron overload after allogeneic stem cell transplantation. Biol Blood Marrow Transplant. 2013;19(3):440-4. https://doi.org/10.1016/j.bbmt.2012.10.012.
31. Cho BS, Jeon YW, Hahn AR, Lee TH, Park SS, Yoon JH, et al. Improved survival outcomes and restoration of graft-vs-leukemia effect by deferasirox after allogeneic stem cell transplantation in acute myeloid leukemia. Cancer Med. 2019;8(2):501-14. https://doi.org/10.1002/cam4.1928.
32. Vallejo C, Batlle M, Vázquez L, Solano C, Sampol A, Duarte R, et al. Phase iv open-label study of the efficacy and safety of deferasirox after allogeneic stem cell transplantation. Haematologica. 2014;99(10):1632-7. https://doi.org/10.3324/haematol.2014.105908.
33. Hughes PJ, Marcinkowska E, Gocek E, Studzinski GP, Brown G. Vitamin d3-driven signals for myeloid cell differentiation--implications for differentiation therapy. Leuk Res. 2010;34(5):553-65. https://doi.org/10.1016/j.leukres.2009.09.010.
34. Paubelle E, Zylbersztejn F, Alkhaeir S, Suarez F, Callens C, Dussiot M, et al. Deferasirox and vitamin d improves overall survival in elderly patients with acute myeloid leukemia after demethylating agents failure. PLoS One. 2013;8(6):e65998. https://doi.org/10.1371/journal.pone.0065998.
35. Yang Y, Tang Z, An T, Zhao L. The impact of iron chelation therapy on patients with lower/intermediate ipss mds and the prognostic role of elevated serum ferritin in patients with mds and aml: A meta-analysis. Medicine (Baltimore). 2019;98(40):e17406. https://doi.org/10.1097/md.0000000000017406.
36. Zhou L, Zhao B, Zhang L, Wang S, Dong D, Lv H, et al. Alterations in cellular iron metabolism provide more therapeutic opportunities for cancer. Int J Mol Sci. 2018;19(5). https://doi.org/10.3390/ijms19051545.
37. Callens C, Coulon S, Naudin J, Radford-Weiss I, Boissel N, Raffoux E, et al. Targeting iron homeostasis induces cellular differentiation and synergizes with differentiating agents in acute myeloid leukemia. J Exp Med. 2010;207(4):731-50. https://doi.org/10.1084/jem.20091488.
38. Ihlow J, Gross S, Neuendorff NR, Busack L, Herneth A, Singh A, et al. Clinical outcome of older adults with acute myeloid leukemia: An analysis of a large tertiary referral center over two decades. J Geriatr Oncol. 2021;12(4):540-9. https://doi.org/10.1016/j.jgo.2020.11.001.
39. Jeon SR, Lee JW, Jang PS, Chung NG, Cho B, Jeong DC. Anti-leukemic properties of deferasirox via apoptosis in murine leukemia cell lines. Blood Res. 2015;50(1):33-9. https://doi.org/10.5045/br.2015.50.1.33.
40. Isidori A, Loscocco F, Visani G, Chiarucci M, Musto P, Kubasch AS, et al. Iron toxicity and chelation therapy in hematopoietic stem cell transplant. Transplant Cell Ther. 2021;27(5):371-9. https://doi.org/10.1016/j.jtct.2020.11.007.
41. Fujisawa K, Takami T, Matsumoto T, Yamamoto N, Yamasaki T, Sakaida I. An iron chelation-based combinatorial anticancer therapy comprising deferoxamine and a lactate excretion inhibitor inhibits the proliferation of cancer cells. Cancer Metab. 2022;10(1):8. https://doi.org/10.1186/s40170-022-00284-x.
42. Gharagozloo M, Khoshdel Z, Amirghofran Z. The effect of an iron (iii) chelator, silybin, on the proliferation and cell cycle of jurkat cells: A comparison with desferrioxamine. Eur J Pharmacol. 2008;589(1-3):1-7. https://doi.org/10.1016/j.ejphar.2008.03.059.
43. Zeidner JF, Karp JE, Blackford AL, Smith BD, Gojo I, Gore SD, et al. A phase ii trial of sequential ribonucleotide reductase inhibition in aggressive myeloproliferative neoplasms. Haematologica. 2014;99(4):672-8. https://doi.org/10.3324/haematol.2013.097246.
44. Tarantini F, Cumbo C, Anelli L, Zagaria A, Conserva MR, Redavid I, et al. Exploring the potential of eltrombopag: Room for more? Front Pharmacol. 2022;13:906036. https://doi.org/10.3389/fphar.2022.906036.
45. Frey N, Jang JH, Szer J, Illés Á, Kim HJ, Ram R, et al. Eltrombopag treatment during induction chemotherapy for acute myeloid leukaemia: A randomised, double-blind, phase 2 study. Lancet Haematol. 2019;6(3):e122-e31. https://doi.org/10.1016/s2352-3026(18)30231-x.