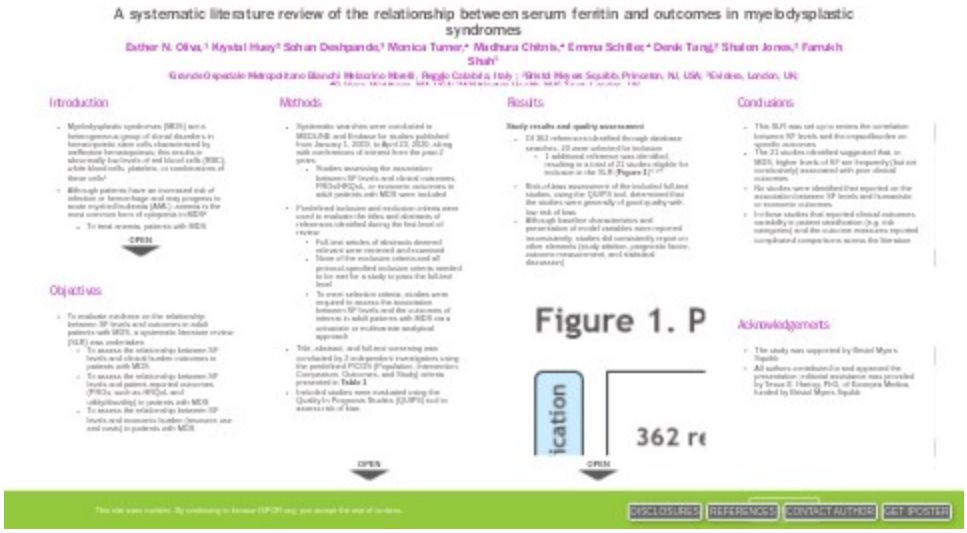
A systematic literature review of the relationship between serum ferritin and outcomes in myelodysplastic syndromes



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INTRODUCTION

- Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal disorders in hematopoietic stem cells characterized by ineffective hematopoiesis; this results in abnormally low levels of red blood cells (RBC), white blood cells, platelets, or combinations of these cells[1]

- Although patients have an increased risk of infection or hemorrhage and may progress to acute myeloid leukemia (AML), anemia is the most common form of cytopenia in MDS[2]
    - To treat anemia, patients with MDS frequently require regular RBC transfusions[3]

- Because iron overload is represented by high serum ferritin (SF) levels, the SF level marker is especially important[4]
- However, the impact of SF levels on clinical, health-related quality of life (HRQoL), and economic outcomes remains largely unknown

OBJECTIVES

- To evaluate evidence on the relationship between SF levels and outcomes in adult patients with MDS, a systematic literature review (SLR) was undertaken
  - To assess the relationship between SF levels and clinical burden outcomes in patients with MDS
  - To assess the relationship between SF levels and patient-reported outcomes (PROs; such as HRQoL and utility/disutility) in patients with MDS
  - To assess the relationship between SF levels and economic burden (resource use and costs) in patients with MDS

METHODS

- Systematic searches were conducted in MEDLINE and Embase for studies published from January 1, 2009, to April 23, 2020, along with conferences of interest from the past 2 years
  - Studies assessing the association between SF levels and clinical outcomes, PROs/HRQoL, or economic outcomes in adult patients with MDS were included
- Predefined inclusion and exclusion criteria were used to evaluate the titles and abstracts of references identified during the first level of review
  - Full-text articles of abstracts deemed relevant were retrieved and examined
  - None of the exclusion criteria and all protocol-specified inclusion criteria needed to be met for a study to pass the full-text level
  - To meet selection criteria, studies were required to assess the association between SF levels and the outcomes of interest in adult patients with MDS via a univariate or multivariate analytical approach
- Title, abstract, and full-text screening was conducted by 2 independent investigators using the predefined PICOS (Population, Intervention, Comparison, Outcomes, and Study) criteria presented in **Table 1**
- Included studies were evaluated using the Quality In Prognosis Studies (QUIPS) tool to assess risk of bias

Table 1. SLR inclusion criteria

Domain	Inclusion criteria
Population	Adult (≥ 18 years) patients with MDS
Prognostic/predictive outcomes	Studies must have assessed and reported SF levels using quantitative methods; studies must also have reported key context including transfusion burden and ICT dose, if being treated with ICT
Outcomes	Clinical outcomes: • Incidence of complications related to iron overload, including cardiac failure, hypogonadism, hypothyroidism, carcinoma, diabetes, liver failure • Time to development of AML • Progression to high-risk disease • PFS • EFS • RFS • OS • Treatment duration • Subsequent therapies, or combinations of different types of ICTs, or maintenance on personalized regime • Total mortality • Liver stiffness or siderosis Humanistic outcomes: • Utility studies • HRQoL (e.g. EQ-5D, SF-36, and EORTC QLQ-C30) Economic outcomes: Healthcare resource utilization • Specialist visits • Unscheduled physician visits • Emergency room visits • Transfusion clinic visits • Hospitalization Costs • Direct costs • Total treatment costs • Costs of healthcare and social care • Indirect costs • Productivity • Absenteeism and presenteeism
Study designs	• Observational cohort studies (prospective or retrospective) • RCTs
Duplicate	If duplicates are identified, the copy of the record with the lower refID number will be included
Study limits	Only English-language articles/conference abstracts will be included • Studies published from 2009 to April 23, 2020 • Conference proceedings from 2018 to April 23, 2020, for ASH, EHA, and ISPOR will be searched
Geography	• None

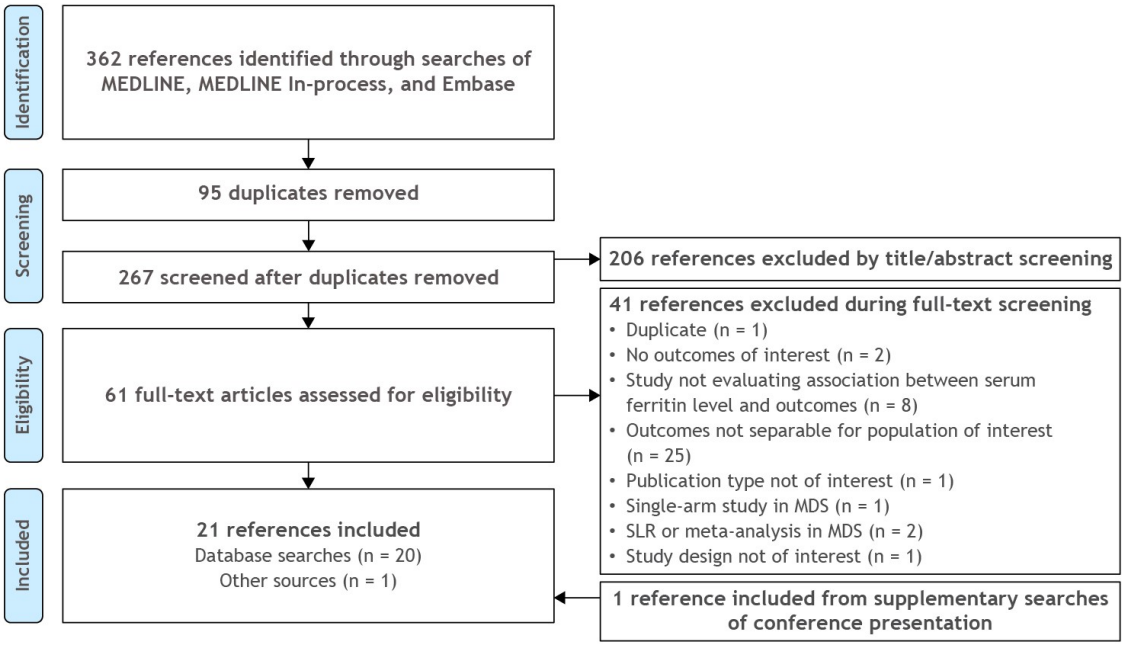
AML, acute myeloid leukemia; ASH, American Society of Hematology; EFS, event-free survival; EHA, European Hematology Association; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQol questionnaire, 5 dimensions; HRQoL, health-related quality of life; ICT, iron chelation therapy; ISPOR, International Society for Pharmacoeconomic and Outcomes Research; MDS, myelodysplastic syndromes; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; RFS, relapse-free survival; SF, serum ferritin; SF-36, 36-item Short Form Health Survey; SLR, systematic literature review.

RESULTS

Study results and quality assessment

- Of 362 references identified through database searches, 20 were selected for inclusion
  - 1 additional reference was identified, resulting in a total of 21 studies eligible for inclusion in the SLR (**Figure 1**)[5–25]
- Risk-of-bias assessment of the included full-text studies, using the QUIPS tool, determined that the studies were generally of good quality with low risk of bias
- Although baseline characteristics and presentation of model variables were reported inconsistently, studies did consistently report on other elements (study attrition, prognostic factor, outcome measurement, and statistical discussion)

Figure 1. PRISMA diagram of study attrition

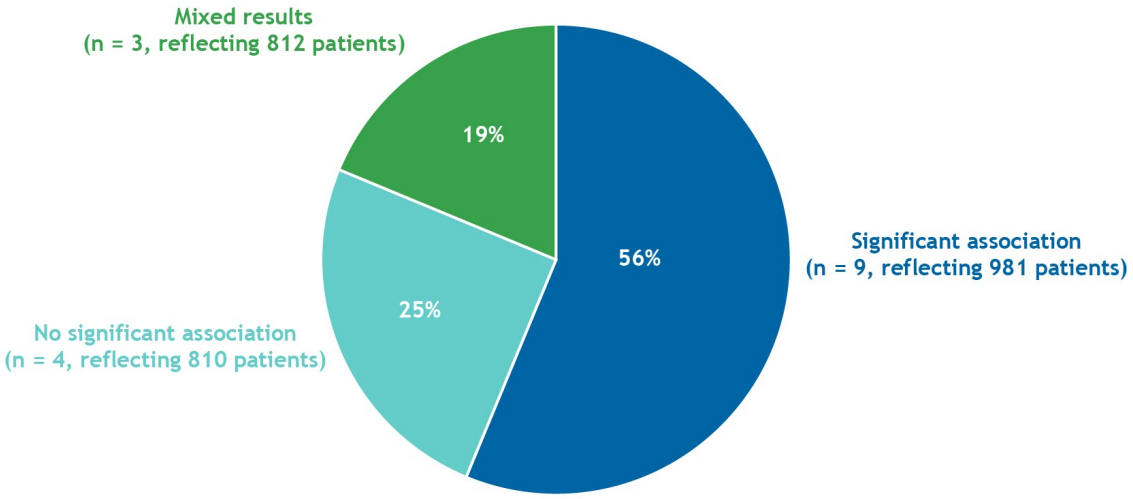


MDS, myelodysplastic syndromes; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Survival and mortality

- Most studies identified by the SLR (n = 16) explored the association between SF levels and survival or mortality outcomes; the outcomes evaluated included overall survival (OS), worsened survival, non-relapse mortality, and transplantation-related mortality[6–8,11–14,16–20,22–25]
- Studies most often reported significant associations between higher SF levels and reduced survival, but studies also found no significant association (**Figure 2**)
- Studies demonstrated the prognostic value of SF in OS, with higher SF levels often indicating worse survival outcomes

Figure 2. Number of studies reporting association between higher SF levels and worse survival



SF, serum ferritin.

Disease progression and relapse

- Across the 8 studies identified by the SLR that reported on disease progression or relapse-related outcomes, there were mixed results with respect to whether SF was a significant predictor of the outcomes of interest[7,11,13,16,18,20,23,24] (**Tables 2–4**)

Event-free survival (EFS)

- Studies suggested that higher SF levels indicated worse EFS; however, the number of studies reporting on this association was limited
- 1 study examined patient subgroups by risk category: SF level was associated with EFS in Low- or Int-1-risk patients, but not in Int-2- or High-risk patients[3]

Table 2. EFS survival reported in included studies

Study author, year Country Study design	Population (n)	Univariate or multivariable and type of statistical analysis performed	When SF evaluated	Continuous or categorical, and categories	Outcome	Effect size
Kadlckova, 2017[11] Czech Republic Prospective cohort	Overall 73	Multivariable Cox proportional hazards	Diagnosis (baseline)	Continuous	EFS	**HR 1.14** ***P* = 0.001**
Oran, 2014[16] USA Retrospective cohort	Overall 256	Univariate Log-rank test	All outcomes were measured from the time of stem cell infusion	Categorical SF > 1,130 µg/L	EFS	**HR 1.6** ***P* = 0.01**
				Categorical SF missing vs ≤ 1,130 µg/L	EFS	**HR 1.5** ***P* = 0.05**
		Multivariate[a] Cox proportional hazards or Fine and Gray method		Categorical SF > 1,150 µg/L	EFS	**HR 1.8** ***P* = 0.002**
				Categorical SF missing vs ≤ 1,150 µg/L	EFS	HR 1.0 *P* = 0.9
Sperr, 2010[23] Austria Retrospective cohort	Overall 419	Multivariate[b] Cox proportional hazards	Baseline	Continuous	EFS	**HR 2.0** ***P* < 0.01**
	Subgroup: Low- or Int-1-risk patients 293			Continuous	EFS	**HR 2.9** ***P* < 0.01**
	Subgroup: Int-2- or High-risk patients 126			Continuous	EFS	HR 1.2 *P* = not significant

Bold text indicates significant results. [a]Age, histological subtype, T-MDS, MK, SF, BM blast count at HSCT and transplantation year. [b]Age, LDH levels, SF, FAB subgroup, number of cytopenias, and karyotype (according to the IPSS criteria).
BM, bone marrow; EFS, event-free survival; FAB, French-American-British; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; Int-1, intermediate 1; Int-2, intermediate 2; IPSS, International Prognostic Scoring System; LDH, lactate dehydrogenase; MK, monosomal karyotype; SF, serum ferritin; T-MDS, therapy-related myelodysplastic syndromes.

Relapse-free survival (RFS) and relapse incidence

- Lower SF level was numerically associated with better RFS in the studies reporting on the outcome, though the association was not always significant

Table 3. RFS and relapse incidence in included studies

Study author, year Country Study design	Population (n)	Univariate or multivariable and type of statistical analysis performed	When SF evaluated	Continuous or categorical, and categories	Outcome	Effect
Cremers, 2019[7] European multi-country Prospective cohort	Overall 222	Multivariable[a] Cox proportional hazards	Baseline	Continuous (units of 1,000 ng/mL)	Relapse incidence	**HR 1.3 (95% CI 1.01-1.6) *P* = 0.04**
				Continuous (units of 1,000 ng/mL)	RFS	HR 1.2 (95% CI 0.98-1.4) *P* = 0.08
Oran, 2014[16] USA Retrospective cohort	Overall 256	Univariate Log-rank test	All outcomes were measured from the time of stem cell infusion	Categorical SF > 1,130 µg/L	Relapse incidence	HR 1.0 *P* = 0.8
				Categorical SF missing vs ≤ 1,130 µg/L	Relapse incidence	HR 1.7 *P* = 0.06
Prem, 2020[20] Canada Retrospective cohort	Overall 125	Univariate Log-rank test	Pretransplant SF levels were assessed within 30 days prior to admission for HSCT	Categorical SF ≤ 1,000 vs > 1,000 ng/mL	RFS	**HR 1.931 (95% CI 1.239-30.10) *P* = 0.0037**
		Multivariate Cox proportional hazards		Categorical SF ≤ 1,000 vs > 1,000 ng/mL	RFS	**HR 1.799 (95% CI 1.147-2.823) *P* = 0.0106**

Bold text indicates significant results. [a]Variables: RBC transfusions, CRP levels, SF levels (continuous in units of 1,000 ng/mL) and comorbidities, WHO classification, age at HSCT, donor type, sex match, and intensity of conditioning regimen.
CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; RBC, red blood cell; RFS, relapse-free survival; SF, serum ferritin; WHO, World Health Organization.

Disease progression and leukemia-free survival (LFS)

- Increased SF level was associated with worse likelihood of LFS in the study reporting this outcome
- SF was not associated with either transformation to AML or time to transformation to AML in the 2 studies evaluating these outcomes[18,24]

Table 4. Disease progression and LFS in included studies

Study author, year Country Study design	Population (n)	Univariate or multivariable and type of statistical analysis performed	When SF evaluated	Continuous or categorical, and categories	Outcome	Effect
Park, 2011[18] France Retrospective cohort	Overall 318	Univariate Wilcoxon test	Diagnosis (baseline)	Categorical SF > 300 ng/mL	Transformation to AML	*P* = 0.94
				Categorical SF > 1,000 ng/mL	Transformation to AML	*P* = 0.47
Waszczuk-Gajda, 2016[24] Poland Retrospective cohort	Overall 190	Univariate Chi-square test	Diagnosis (baseline)	Categorical SF > 1,000 ng/mL	Transformation to AML	*P* > 0.05
				Categorical SF > 1,000 ng/mL	Time to transformation to AML	*P* = 0.35
Kikuchi, 2012[13] Japan Retrospective cohort	Overall 47	Univariate Logistic regression	Diagnosis (baseline)	Categorical SF ≥ 500 ng/mL	LFS	**HR 21.16 (95% CI 2.062-217.1) *P* = 0.01**
				Categorical SF ≥ 300 ng/mL	LFS	HR 4.752 (95% CI 0.852-26.51) *P* = 0.076

Bold text indicates significant results.
AML, acute myeloid leukemia; CI, confidence interval; HR, hazard ratio; LFS, leukemia-free survival; SF, serum ferritin.

Other clinical outcomes

- A retrospective cohort study in Turkey suggested lower SF levels at MDS diagnosis were significantly associated with better treatment response (*P* = 0.004), but the study was not explicit about the types of treatment evaluated[5]
- A separate study reported that patients adherent to treatment with deferasirox had statistically significant lower SF levels compared with non-adherent patients (r = −0.288; *P* = 0.004)[9]
- Two studies noted a positive correlation between SF levels and number of RBC units received,[10,15] with increases in SF correlated with increases in RBC units, though only one reported it was significant (*P* = 0.04)[15]
- A study evaluating a potential tool to assess liver fibrosis in MDS reported that univariate analysis indicated no association between higher SF levels and higher liver stiffness measurements (*P* = 0.583)[21]

CONCLUSIONS

- This SLR was set up to review the correlation between SF levels and the impact/burden on specific outcomes
- The 21 studies identified suggested that, in MDS, higher levels of SF are frequently (but not conclusively) associated with poor clinical outcomes
- No studies were identified that reported on the association between SF levels and humanistic or economic outcomes
- In those studies that reported clinical outcomes, variability in patient stratification (e.g. risk categories) and the outcome measures reported complicated comparisons across the literature

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DISCLOSURES

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