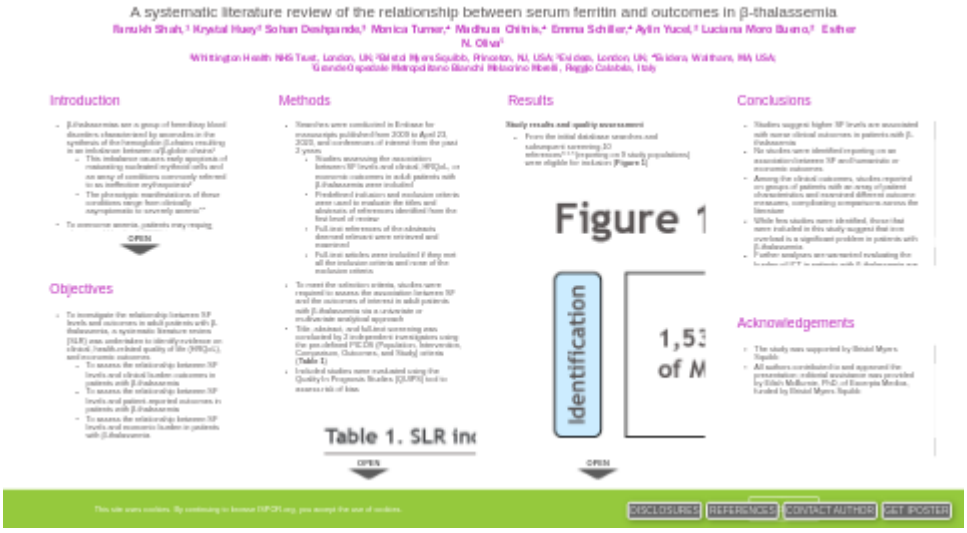
A systematic literature review of the relationship between serum ferritin and outcomes in β-thalassemia



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INTRODUCTION

- β-thalassemias are a group of hereditary blood disorders characterized by anomalies in the synthesis of the hemoglobin β-chains resulting in an imbalance between α/β-globin chains[1]
  - This imbalance causes early apoptosis of maturating nucleated erythroid cells and an array of conditions commonly referred to as ineffective erythropoiesis[2]
  - The phenotypic manifestations of these conditions range from clinically asymptomatic to severely anemic[3,4]
- To overcome anemia, patients may require chronic red blood cell (RBC) transfusions[4,5]
  - Chronic RBC transfusions may cause iron overload as the body is unable to eliminate iron, although in patients with β-thalassemia, this issue is compounded by the disease mechanism
    - Serum ferritin (SF) levels are an important marker to test for iron overload

OBJECTIVES

- To investigate the relationship between SF levels and outcomes in adult patients with β-thalassemia, a systematic literature review (SLR) was undertaken to identify evidence on clinical, health-related quality of life (HRQoL), and economic outcomes
  - To assess the relationship between SF levels and clinical burden outcomes in patients with β-thalassemia
  - To assess the relationship between SF levels and patient-reported outcomes in patients with β-thalassemia
  - To assess the relationship between SF levels and economic burden in patients with β-thalassemia

METHODS

- Searches were conducted in Embase for manuscripts published from 2009 to April 23, 2020, and conferences of interest from the past 2 years
  - Studies assessing the association between SF levels and clinical, HRQoL, or economic outcomes in adult patients with β-thalassemia were included
  - Predefined inclusion and exclusion criteria were used to evaluate the titles and abstracts of references identified from the first level of review
  - Full-text references of the abstracts deemed relevant were retrieved and examined
  - Full-text articles were included if they met all the inclusion criteria and none of the exclusion criteria
- To meet the selection criteria, studies were required to assess the association between SF and the outcomes of interest in adult patients with β-thalassemia via a univariate or multivariate analytical approach
- Title, abstract, and full-text screening was conducted by 2 independent investigators using the pre-defined PICOS (Population, Intervention, Comparison, Outcomes, and Study) criteria (**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 B-thalassemia
Prognostic/ predictive factors	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 • Progression to high-risk disease • OS, total mortality • Treatment duration • Subsequent therapies, or combinations of different types of ICTs, or maintenance on personalized regimen • Liver fibrosis, stiffness, or siderosis • Skeletal outcomes such as bone disease, density, osteoporosis, skeletal changes, or fracture • Cardiac siderosis • Pulmonary hypertension • Fertility **Humanistic outcomes:** • Utility studies • HRQoL (e.g. EQ-5D, SF-36, or 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 reference with the lower refID number will be included
Study limits	Only English-language references/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	Not present

ASH, American Society of Hematology; 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; OS, overall survival; RCT, randomized controlled trial; SF, serum ferritin; SF-36, 36-Item Short Form Health Survey; SLR, systematic literature review.

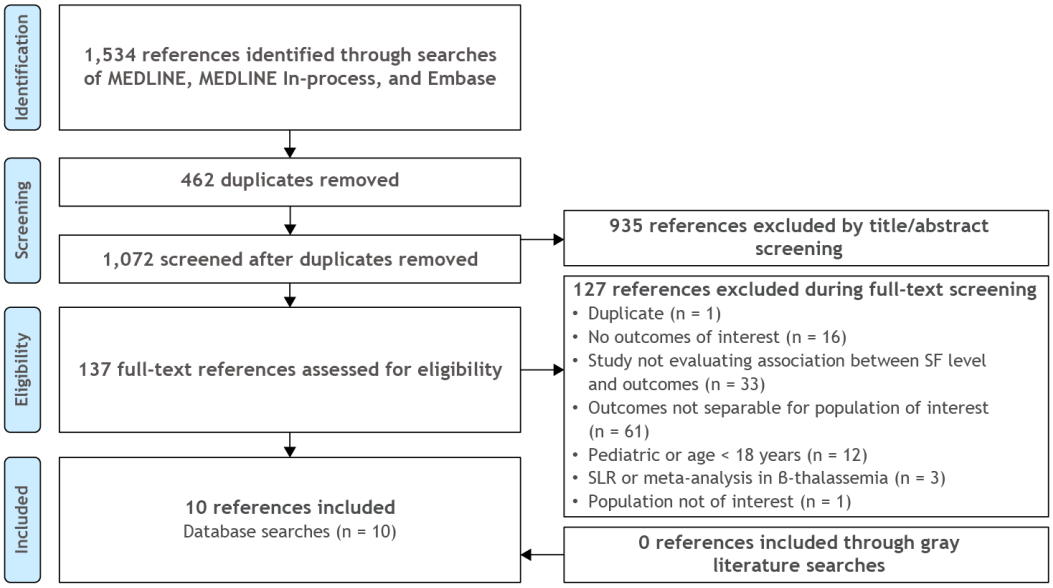
- A separate SLR and targeted literature review (TLR) were conducted to identify studies reporting on the clinical, humanistic, and economic burden associated with iron chelation therapy (ICT) in patients with β-thalassemia

RESULTS

Study results and quality assessment

- From the initial database searches and subsequent screening,10 references[6–15] (reporting on 9 study populations) were eligible for inclusion (**Figure 1**)

Figure 1. PRISMA diagram of study attrition



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SF, serum ferritin; SLR, systematic literature review.

- Studies reporting on the β-thalassemia population generally showed a low risk of bias when assessed with the QUIPS tool
  - However, in assessing confounding details, most studies were rated as providing a moderate risk of bias, typically, due to a lack of reporting on the variables for which analyses controlled
    - In such cases, it was less clear whether appropriate measures had been taken to account for potential confounding in the studies
  - One study also demonstrated a high risk of bias in its statistical analysis and presentation; reviewers determined that the manuscript was poorly written in its presentation of results, leading to potential for confusion and overall lack of clarity with respect to the association between SF levels and the clinical outcomes reported[10]

Clinical outcomes

Mortality

- Among the included studies, higher SF levels at baseline were reported to be a significant predictor for mortality in a Greek population with β-thalassemia intermedia[12] (**Table 2**)

Table 2. SF and mortality in included studies

Study author, year Country Study design	Population (n)	Univariate or multivariable and type of statistical analysis performed	Model variables	Continuous or categorical, and categories	Outcome	Effect size
Hahalis et al, 2009[12] Greece Prospective case-control	Overall 36	Univariate Cox proportional hazards	None	Categorical Per 1,000 ng/mL SF at baseline	Mortality	**HR 1.72 (95% CI 1.3-2.29) *P* < 0.0001**
		Multivariate Cox proportional hazards	Variables included sex, age at the start of deferoxamine treatment, SF concentrations before chelation therapy, median SF concentrations, proportion of SF measurements exceeding certain threshold values, and degree of reduction in the SF concentrations approximately 1 and 2 years after initiation of therapy	Categorical Per 1,000 ng/mL SF at baseline	Mortality	**HR 1.95 (95% CI 1.22-3.12) *P* = 0.005**

Cells in bold indicate significant results.
CI, confidence interval; HR, hazard ratio; SF, serum ferritin.

Hepatic complications

- One included study evaluated hepatic stiffness as a predictor of liver fibrosis within a population of Italian patients with β-thalassemia intermedia (hepatic stiffness measured via transient elastrography)[13] (**Table 3**)

Table 3. SF and hepatic complications in included studies

Study author, year Country Study design	Population (n)	Univariate or multivariable and type of statistical analysis performed	When serum evaluated	Continuous or categorical, and categories	Outcome	Effect size
Musallam et al, 2012[13] Italy Retrospective cohort	Overall 42	Univariate Linear regression	Throughout study period	Continuous	Liver fibrosis	**Model coefficient:** **R^2 = 0.836** **P < 0.001**
	Subgroup: Non-chelated group 28			Continuous	Liver fibrosis	**Model coefficient:** **R^2 = 0.806** **P < 0.001**
	Subgroup: Chelated group 14			Continuous	Liver fibrosis	**Model coefficient:** **R^2 = 0.758** **P < 0.001**

Cells in bold indicate significant results.
SF, serum ferritin.

Skeletal complications

- Two studies reported that increased SF levels at baseline were associated with skeletal complications[10,11] (**Table 4**)

Table 4. SF and skeletal complications in included studies

Study author, year Country Study design	Population (n)	Univariate or multivariable and type of statistical analysis performed	Continuous or categorical, and categories	Outcome	Effect
Foroughi et al, 2015[11] Iran Cross-sectional	Subgroup: B-thalassemia intermedia patients 47	Univariate[a] T test or chi-square test	Continuous	Skeletal complications: trabeculation	**P = 0.028**
			Continuous	Skeletal complications: rib widening	**P = 0.015**
			Continuous	Skeletal complications: facial bone deformity	**P = 0.009**
Ebrahimpour et al, 2012[10] Iran Prospective cross-sectional	Subgroup: patients ≥ 20 years old with osteomalacia/osteoporosis NR	Univariate T test	Continuous	BMD femoral	**Model coefficient: -0.561** **P < 0.05**
	Subgroup: patients ≥ 20 years old with normal BMD NR		Continuous	BMD femoral	Model coefficient: 0.239 P = not significant
	Subgroup: patients ≥ 20 years old with osteomalacia/osteoporosis NR		Continuous	BMD lumbar	**Model coefficient: -0.55** **P < 0.05**
	Subgroup: patients ≥ 20 years old with normal BMD NR		Continuous	BMD lumbar	**Model coefficient: 0.466** **P < 0.05**
	Subgroup: patients with osteomalacia/osteoporosis 30		Continuous	BMD femoral	**Model coefficient: -0.52** **P < 0.05**
	Subgroup: patients with normal BMD 50		Continuous	BMD femoral	**Model coefficient: 0.12** **P = not significant**

Cells in bold indicate significant results. SF values evaluated at baseline.
[a]Model controlled for sex, age, hemoglobin, RBC, platelet, HRBC, and SF level.
BMD, bone mineral density; NR, not reported; HRBC, nucleated red blood cell; RBC, red blood cell; SF, serum ferritin.

Cardiac and pulmonary complications

- Two studies analyzed cardiac and pulmonary complications and their association with SF levels, finding varied results[7,15] (**Table 5**)

Table 5. Cardiac and pulmonary complications 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
Chen et al, 2015[7] Taiwan Retrospective Case-control	Subgroup: All B-thalassemia in study 37	Univariate Pearson or Spearman correlation coefficients	Baseline	Continuous	Cardiac failure: longitudinal strain	**Model coefficient:** **r = 0.42** **P = 0.012**
				Continuous	Cardiac failure: radial strain	**Model coefficient:** **r = 0.41** **P = 0.0163**
				Continuous	Cardiac failure: circumferential strain	Model coefficient: r = 0.17 P = 0.438
		Multivariate[a] Cox proportional hazards		Continuous	Cardiac events or death	P = 0.06
Vlahos et al, 2012[15] Greece Prospective cohort	Overall 27	Univariate Logistic regression	The average value from 10 consecutive values taken during a period of 12 ± 13 months before the echocardiographic assessment	Continuous	Pulmonary hypertension	**Model coefficient:** **r = 0.44** **P = 0.019**
		Multivariate[b] Logistic regression		Continuous	Pulmonary hypertension	**Model coefficient:** **r = 0.48** **P = 0.0328**

Cells in bold indicate significant results.
[a]Model controlled for age, sex, renal function, SF level, and echocardiographic covariates including LV mass index and ejection fraction.
[b]Model controlled for age, ferritin level, and age at chelation onset.
LV, left ventricular; SF, serum ferritin.

Endocrine risk factors

- Higher SF levels were associated with a higher risk of endocrinopathy, including thyroid and parathyroid dysfunction, diabetes mellitus, hypogonadism, osteoporosis, and renal and gallbladder lithiasis[6,8,9,14]
  - **Diabetes**: risk of diabetes mellitus was significantly higher for those with an average 10-year SF level > 1,500 µg/L or > 1,250 µg/L compared to those with a lower average 10-year SF level[6]

- **Thyroid function**: risk of progression to thyroid dysfunction was significantly increased by increasing SF levels; patients with baseline SF values
  < 1,800 µg/L had a lower risk of developing thyroid dysfunction than those with baseline SF values
  > 1,800 µg/L[8,9]
- **Hypogonadism**: average 10-year SF
  > 2,000 µg/L was significantly associated with hypogonadism in a multivariate analysis; however, it was not significantly associated with an average 10-year SF level of > 2,000 µg/L when compared to a lower average 10-year SF level in a univariate analysis[6]

Humanistic or economic outcomes

- No studies reported on the relationship between SF levels and humanistic or economic outcomes

Burden of Iron Chelation Therapy

- The separate SLR conducted to identify studies reporting on the burden associated with ICT in patients with β-thalassemia did not identify any SLRs that met the inclusion criteria
- The TLR conducted to evaluate the burden of ICT suggested that patients continued to experience endocrinopathies despite treatment[16]
  - Patients also experienced a substantial financial burden resulting from receiving regular ICT, with little benefit to their HRQoL when compared with the general population[17-23]

CONCLUSIONS

- Studies suggest higher SF levels are associated with worse clinical outcomes in patients with β-thalassemia
- No studies were identified reporting on an association between SF and humanistic or economic outcomes
- Among the clinical outcomes, studies reported on groups of patients with an array of patient characteristics and examined different outcome measures, complicating comparisons across the literature
- While few studies were identified, those that were included in this study suggest that iron overload is a significant problem in patients with β-thalassemia
- Further analyses are warranted evaluating the burden of ICT in patients with β-thalassemia are warranted

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DISCLOSURES

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