

## Supplemental Material

**SUPPLEMENTARY TABLE S1.** Medline (via Ovid) search strategy for beta-thalassemia population.

Search number	Search string
1.	exp beta-Thalassemia/ or beta-thalassemia.tw. or thalassemia.tw. or thalassaemia.tw. or (cooley* or cooleys) and (anemia or anaemia)).tw.
2.	exp Iron-Binding Proteins/ or serum ferritin.mp.
3.	1 and 2
4.	(animals not humans).sh.
5.	(case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti.
6.	case reports/ or case report\$.jw.
7.	(Ephemera or Introductory Journal Article or News or Newspaper Article or Editorial or Comment or Overall or Letter or Congress).pt. or In Vitro Techniques/ or (commentary or editorial or comment or letter or congress or mice or rat or mouse or animal or murine).ti.
8	review.pt. not (systematic or meta\$).mp.
9.	3 not (4 or 5 or 6 or 7 or 8)
10.	(pediatric\$ or paediatric\$ or preterm\$ or newborn\$ or child\$ or infant\$ or infancy or neonat\$ or preschool\$ or young\$ or early years or adolescen\$ or teenage\$ or preteen\$ or youth or girl\$ or boy\$ or student\$ or juvenile\$ or minor or minors or baby or babies).ti.
11.	(pediatric\$ or paediatric\$ or preterm\$ or newborn\$ or child\$ or infant\$ or infancy or neonat\$ or preschool\$ or young\$ or early years or adolescen\$ or teenage\$ or preteen\$ or youth or girl\$ or boy\$ or student\$ or juvenile\$ or minor or minors or baby or babies).ti. and (exp adult/ or adult\$.ti.)
12.	10 not 11
13.	9 not 12
14.	limit 13 to english language

15.	limit 13 to yr="2009 -Current"
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**SUPPLEMENTARY TABLE S2.** Embase (via Ovid) search strategy for beta-thalassemia population.

Search number	Search string
1.	exp beta thalassemia/ or beta-thalassemia.tw. or beta thalassemia.tw. or thalassemia.tw. or thalassaemia.tw. or ((cooley* or cooleys) and (anemia or anaemia)).tw.
2.	exp ferritin blood level/ or serum ferritin.mp.
3.	1 and 2
4.	limit 3 to (article or article in press)
5.	(animal not human).sh.
6.	(case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti.
7.	case study/ or case report\$.jx. or case report\$.jw.
8.	(editorial or note or letter).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti.
9.	review.pt. not (systematic or meta\$).mp.
10.	4 not (5 or 6 or 7 or 8 or 9)
11.	(pediatric\$ or paediatric\$ or preterm\$ or newborn\$ or child\$ or infant\$ or infancy or neonat\$ or preschool\$ or young\$ or early years or adolescen\$ or teenage\$ or preteen\$ or youth or girl\$ or boy\$ or student\$ or juvenile\$ or minor or minors or baby or babies).ti.
12.	(pediatric\$ or paediatric\$ or preterm\$ or newborn\$ or child\$ or infant\$ or infancy or neonat\$ or preschool\$ or young\$ or early years or adolescen\$ or teenage\$ or preteen\$ or youth or girl\$ or boy\$ or student\$ or juvenile\$ or minor or minors or baby or babies).ti. and (exp adult/ or adult\$.ti.)
13.	11 not 12
14.	10 not 13
15.	limit 14 to english language
16.	Limit 11 to yr="2009 -Current"

**SUPPLEMENTARY TABLE S3.** Screening/eligibility criteria for  $\beta$ -thalassemia.

Domain	Inclusion criteria	Exclusion criteria
Population	Adults ( $\geq 18$ years) with $\beta$ -thalassemia	Publications reporting on children or healthy volunteers
Prognostic/ predictive factors	Studies must have assessed and reported SF levels using quantitative methods. <sup>a</sup>	NA
Outcomes	<b>Clinical outcomes</b> <ul style="list-style-type: none"> <li>• Incidence of complications related to iron overload, including cardiac failure, hypogonadism, hypothyroidism, carcinoma, diabetes, liver failure</li> <li>• Progression to high-risk disease</li> <li>• Overall survival</li> <li>• Treatment duration</li> <li>• Subsequent therapies, or combinations of different types of ICTs, or maintenance on personalized regimen</li> <li>• Total mortality</li> <li>• Liver fibrosis, stiffness, or siderosis</li> <li>• Skeletal outcomes such as bone disease, density, osteoporosis, skeletal changes, or fracture</li> <li>• Cardiac siderosis</li> <li>• Pulmonary hypertension</li> <li>• Fertility</li> </ul> <b>Humanistic outcomes:</b> <ul style="list-style-type: none"> <li>• Utility studies</li> </ul>	Publications that only report data on pharmacokinetics/pharmacodynamics

Domain	Inclusion criteria	Exclusion criteria
	<ul style="list-style-type: none"> <li>Health-related quality of life (e.g., EQ-5D, SF-36, and EORTC QLQ-C30)</li> </ul> <p><b>Economic outcomes:</b></p> <ul style="list-style-type: none"> <li>Healthcare resource utilization <ul style="list-style-type: none"> <li>Specialist visits</li> <li>Unscheduled physician visits</li> <li>Emergency room visits</li> <li>Transfusion clinic visits</li> <li>Hospitalization</li> </ul> </li> <li>Costs <ul style="list-style-type: none"> <li>Direct costs</li> <li>Total treatment costs</li> <li>Costs of healthcare and social care</li> <li>Indirect costs</li> <li>Productivity</li> <li>Absenteeism and presenteeism</li> </ul> </li> </ul>	
Study designs	<ul style="list-style-type: none"> <li>Observational cohort studies (prospective or retrospective)</li> <li>RCTs</li> </ul>	<p>Publications of studies with the following designs:</p> <ul style="list-style-type: none"> <li>Animal studies</li> <li><i>In vitro/ex vivo</i> studies</li> <li>Gene expression/protein expression studies</li> <li>Narrative publications</li> <li>Non-systematic reviews</li> <li>Case studies</li> <li>Case reports</li> </ul>

Domain	Inclusion criteria	Exclusion criteria
		<ul style="list-style-type: none"> <li>• Editorials</li> <li>• Systematic reviews and meta-analysis (Will be included for reference checking only. Full papers will be excluded using a separate exclusion code.)</li> </ul>
Duplicate	If duplicates are identified, the copy of the record with the lower refID number will be included	<p>Publications that are duplicates of other publications in the search yield</p> <p>The copy of the record with higher refID number will be excluded.</p>
Study limits	<p>Only English language articles/conference abstracts will be included</p> <ul style="list-style-type: none"> <li>• Studies published from 2009 to present<sup>b</sup></li> <li>• Conference proceedings from 2018 to present will be searched</li> </ul>	<p>Journal articles and conference abstracts without English full text</p> <p>Studies published outside the timeframe of interest</p>
Geography	None	

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0; EQ-5D, European Quality of Life Five Dimension; ICT, iron chelation therapy; RCT, randomized controlled trial; SF-36, 36-item Short Form Survey; SF, serum ferritin.

<sup>a</sup>Studies assessing efficacy of an intervention without investigating the relationship of SF and the outcomes were excluded. Studies assessing the relationship between SF level and any of the outcomes of interest listed in the table above were of interest. Studies with quantitative outcomes refer to those based on univariate or multivariate models or adjusted analysis with some kind of quantification results, as opposed to studies making unsupported statements about association in the discussion (which were excluded).

<sup>b</sup>This limit ensured the most recent and relevant data.

**SUPPLEMENTARY TABLE S4.** Serum ferritin and survival in  $\beta$ -thalassemia studies.

Study author, year country study design	Population (n)	Univariate or multivariable and type of statistical analysis performed	Model variables	When SF evaluated	Continuous or categorical, and categories	Outcome	Effect
Hahalis, 2009 [1] Greece Prospective case-control	Overall 36	Univariate Cox proportional hazards	None	Baseline	Categorical Per 1000 ng/mL SF	Mortality	HR (95% CI), 1.72 (1.3, 2.29) $P <$ 0.0001
	Overall 36	Multivariable Cox proportional hazards	Variables included sex, age at the start of deferoxamine treatment, SF concentrations before chelation therapy, median SF concentrations, proportion of ferritin measurements exceeding certain threshold values, and degree of reduction in the SF concentrations approximately 1 and 2 years after initiation of therapy	Baseline	Categorical Per 1000 ng/mL SF	Mortality	HR (95% CI), 1.95 91.22, 3.12) $P =$ 0.005

Abbreviations: CI, confidence interval; HR, hazard ratio; SF, serum ferritin.

**SUPPLEMENTARY TABLE S5.** Serum ferritin and liver fibrosis in  $\beta$ -thalassemia studies.

Study author, year country study design	Population (n)	Univariate or multivariable and type of statistical analysis performed	Model variables	When serum SF	Continuous or categorical, and categories	Outcome	Effect
	Overall 42	Univariate Linear regression	None	Throughout study period	Continuous	Liver fibrosis	Model coefficient: $R^2$ : 0.836 $P < 0.001$
Musallam, 2012[2] Italy Retrospective cohort	Subgroup: Non- chelated group: 28	Univariate Linear regression	None	Throughout study period	Continuous	Liver fibrosis	Model coefficient: $R^2$ : 0.806 $P < 0.001$
	Subgroup: Chelated group: 14	Univariate Linear regression	None	Throughout study period	Continuous	Liver fibrosis	Model coefficient: $R^2$ : 0.758 $P < 0.001$

Abbreviation: SF, serum ferritin.



**SUPPLEMENTARY TABLE S6.** Serum ferritin and skeletal outcomes in  $\beta$ -thalassemia studies.

Study author, year, country, study design	Population (n)	Univariate or multivariable and type of statistical analysis performed	Model variables	When serum ferritin evaluated	Continuous or categorical, and categories	Outcome	Effect
		Univariate T test or chi square	Sex, age, hemoglobin, RBC, platelet, NRBC and ferritin level Gender, age, hemoglobin, RBC, platelet, NRBC and ferritin level Gender, age, hemoglobin, RBC, platelet, NRBC and ferritin level	Baseline	Continuous	Skeletal complications : trabeculation	$P = 0.028$
Foroughi, 2015[3] Iran Cross-sectional	Subgroup: $\beta$ -thalassemia intermedia patients 47	Univariate T test or chi square	Sex, age, hemoglobin, RBC, platelet, NRBC and ferritin level Gender, age, hemoglobin, RBC, platelet, NRBC and ferritin level	Baseline	Continuous	Skeletal complications : rib widening	$P = 0.015$
		Univariate T test or chi square	Sex, age, hemoglobin, RBC, platelet, NRBC and ferritin level	Baseline	Continuous	Skeletal complications : facial bone deformity	$P = 0.009$

Ebrahimpour, 2012[4] Iran Prospective cross-sectional	Subgroup: Patients $\geq 20$ years old with osteomalacia/osteoporosis NR	Univariate T test	None	Baseline	Continuous	BMD	Model coefficient: -0.561, $P < 0.05$
	Subgroup: Patients $\geq 20$ years old with normal BMD NR	Univariate T test	None	Baseline	Continuous	BMD	Model coefficient: 0.239
	Subgroup: Patients $\geq 20$ years old with osteomalacia/osteoporosis NR	Univariate T test	None	Baseline	Continuous	BMD	Model coefficient: -0.55, $P < 0.05$
	Subgroup: Patients $\geq 20$ years old with normal BMD NR	Univariate T test	None	Baseline	Continuous	BMD	Model coefficient: 0.466, $P < 0.05$
	Subgroup: Patients with osteomalacia/osteoporosis 30	Univariate T test	None	Baseline	Continuous	BMD	Model coefficient: -0.52, $P < 0.05$
	Subgroup: Patients with normal BMD 50	Univariate T test	None	Baseline	Continuous	BMD	Model coefficient: 0.12

Abbreviations: BMD, bone mineral density; NR, not reported; NRBC, nucleated red blood cell; RBC, red blood cell.

**SUPPLEMENTARY TABLE S7.** Serum ferritin and cardiac or pulmonary outcomes in  $\beta$ -thalassemia studies.

Study author, year country study design	Population (n)	Univariate or multivariable and type of statistical analysis performed	Model variables	When SF evaluated	Continuous or categorical, and categories	Outcome	Effect
Chen, 2015[5] Taiwan Retrospective Case-control	Subgroup: All $\beta$ -thalassemia in study: 37	Univariate Pearson or Spearman correlation coefficients	NR	Baseline	Continuous	Cardiac failure: longitudinal strain	Model coefficient : $r = 0.42$ $P = 0.012$
	Subgroup: All $\beta$ -thalassemia in study: 37	Univariate Pearson or Spearman correlation coefficients	NR	Baseline	Continuous	Cardiac failure: radial strain	Model coefficient : $r = 0.41$ $P = 0.0163$
	Subgroup: All $\beta$ -thalassemia in study: 37	Univariate Pearson or Spearman correlation coefficients	NR	Baseline	Continuous	Cardiac failure: circumferential strain	Model coefficient : $r = 0.17$ $P = 0.438$
	Subgroup: All $\beta$ -thalassemia in study: 37	Multivariable Cox proportional hazards	Age, sex, renal function, SF level, and echocardiographic covariates including LV	Baseline	Continuous	Cardiac events or death	$P = 0.06$

Vlahos, 2012 [6] Greece Prospective cohort	Overall: 27	Univariate Logistic regression	mass index and ejection fraction  None	The average value from 10 consecutive values taken during a period of $12 \pm 13$ months prior to the echocardiographi c assessment The average value from 10 consecutive values taken during a period of $12 \pm 13$ months prior to the echocardiographi c assessment	Continuous	Pulmonary hypertension	Model coefficient : $R = 0.44$ $P = 0.019$
	Overall: 27	Multivariable Logistic regression	Age, ferritin level and age at chelation onset		Continuous	Pulmonary hypertension	Model coefficient : $R = 0.48$ $P = 0.0328$

Abbreviations: LV, left ventricular; NR, not reported; SF, serum ferritin.

**SUPPLEMENTARY TABLE S8.** Serum ferritin and endocrine complications in  $\beta$ -thalassemia studies.

Study author, year country study design	Population (n)	Univariate or multivariable and type of statistical analysis performed	Model variables	When serum ferritin evaluated	Continuous or categorical, and categories	Outcome	Effect
Chirico, 2013 [7] Italy Prospective cohort with randomized phase	Overall 72	Multivariable Cox proportional hazards	NR	Baseline	Continuous	Incidence of thyroid dysfunction	HR (95% CI), 1.2 (1.10, 1.26) $P < 0.0001$
	Overall 72	Univariate Pearson or Spearman correlation coefficients	NR	Baseline	Continuous	Incidence of thyroid dysfunction	HR (95% CI), 1.36 (1.22, 1.59) $P < 0.0001$
	Overall 72	Univariate Log rank test	NR	Baseline	Categorical SF >1800 $\mu\text{g/L}$ vs. SF <1800 $\mu\text{g/L}$	Time to thyropathy	HR (95% CI), 0.3 (0.1, 0.7)
Ang, 2014[8] UK Retrospective cohort	Overall 92	Univariate Logistic regression	Age, worst liver T2* and average SF	Average over 10 years	Categorical Average 10-year SF of >1500 $\mu\text{g/L}$	Hypogonadism	OR (95% CI), 1.9 (0.8, 4.7) $P = 0.18$
	Overall 92	Univariate Logistic regression	Age, worst liver T2* and average SF	Average over 10 years	Categorical Average 10-year SF of >1500 $\mu\text{g/L}$	Hypoparathyroidism	OR (95% CI), 0.4 (0.1, 1.3) $P = 0.13$

Study author, year country study design	Population (n)	Univariate or multivariable and type of statistical analysis performed	Model variables	When serum ferritin evaluated	Continuous or categorical, and categories	Outcome	Effect
Chirico, 2015[9] Italy Prospective cohort	Overall 92	Multivariable Logistic regression	Age, worst liver T2* and average SF	Average over 10 years	Categorical Average 10-year SF of >2000 µg/L	Hypogonadism	OR (95% CI), 2.9 (1.0, 8.3) <i>P</i> = 0.047
	Overall 92	Univariate Logistic regression	Age, worst liver T2* and average SF	Average over 10 years	Categorical Average 10-year SF of >1500 µg/L	Diabetes mellitus	OR (95% CI), 3.4 (1.2, 9.6) <i>P</i> = 0.02
	Overall 92	Univariate Logistic regression	Age, worst liver T2* and average SF	Average over 10 years	Categorical Average 10-year SF of >1250 µg/L	Diabetes mellitus	OR (95% CI), 4.9 (1.3, 18.3) <i>P</i> = 0.016
	Overall 92	Multivariable Logistic regression	Age, worst liver T2* and average SF	Average over 10 years	Categorical Average 10-year SF of >1250 µg/L	Diabetes mellitus	OR (95% CI), 14.8 (2.4, 90.0) <i>P</i> = 0.003
	Overall 72	Multivariable Logistic regression	Age, sex	Baseline	Continuous	Endocrine complications	Model coefficient: $\beta$ : 0.26 <i>P</i> = 0.002
	Overall 72	Multivariable Logistic regression	Age, sex, and other covariates that are causally linked to	Baseline	Continuous	Endocrine complications	Model coefficient: $\beta$ : 0.22

Study author, year country study design	Populati on (n)	Univariate or multivariable and type of statistical analysis performed	Model variables	When serum ferritin evaluated	Continuous or categorical, and categories	Outcome	Effect
			endocrine diseases in thalassemic patients				$P = 0.01$
	Overall 72	Univariate Kaplan–Meier curves	None	Baseline	Categorical SF >1800 µg/L vs. SF <1800 µg/L	Hypothyroidism	HR (95% CI), 0.3 (0.1, 0.7) $P = 0.005$
	Overall 72	Univariate Kaplan–Meier curves	None	Baseline	Categorical SF >893 µg/L vs. SF <893 µg/L	Hypogonadism	HR (95% CI), 0.2 (0.1, 0.6) $P = 0.001$
	Overall 72	Univariate Kaplan–Meier curves	None	Baseline	Categorical SF >2300 µg/L vs. SF <2300 µg/L	Endocrine complications	HR (95% CI), 0.3 (0.1, 0.8) $P = 0.02$
	Overall 72	Univariate Cox proportional hazards	None	Baseline	Continuous	Endocrine complications	HR (95% CI), 1.3 (1.18, 1.50) $P < 0.0001$
	Overall 72	Multivariable Cox proportional hazards	Age, markers of iron overload (SF, liver, and cardiac*T2 values), hemoglobin	Baseline	Continuous	Endocrine complications	HR (95% CI), 1.23 (1.13, 1.28) $P < 0.0001$

Study author, year country study design	Populati on (n)	Univariate or multivariable and type of statistical analysis performed	Model variables	When serum ferritin evaluated	Continuous or categorical, and categories	Outcome	Effect
			levels, splenectomy, and HCV infection				
Poggi, 2016[10] Italy Retrospective cohort	Overall 165	Univariate Chi-squared and Fisher exact tests	None	Over the study period of 5 years	Categorical SF level >1300 ng/mL over 5 years	Endocrine complications	Model coefficient: AUC: 0.810 <i>P</i> = 0.025
	Overall 165	Univariate Chi-squared and Fisher exact tests	None	Over the study period of 5 years	Categorical SF level <200 ng/mL at baseline	Endocrine complications	Model coefficient: AUC: 0.746 <i>P</i> = 0.147

Abbreviations: AUC, area under the curve; CI, confidence interval; HCV, hepatitis C virus; HR, hazard ratio; NR, not reported; OR, odds ratio; SF, serum ferritin; UK, United Kingdom.



**SUPPLEMENTARY TABLE S9.** QUIPS quality assessment of  $\beta$ -thalassemia studies.

Author and year of publication	Summary study participation	Study attrition summary	PF measurement summary	Outcome measurement summary	Study confounding summary	Statistical analysis and presentation summary
	The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.	Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.	<i>PF</i> is adequately measured in study participants to sufficiently limit potential bias.	<i>Outcome of interest</i> is adequately measured in study participants to sufficiently limit potential bias.	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between <i>PF</i> and <i>outcome</i> .	The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.
Chirico, 2013	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk
Foroughi, 2015	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk
Ang, 2013	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk
Chen, 2015	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk
Chirico, 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

<b>Author and year of publication</b>	<b>Summary study participation</b>	<b>Study attrition summary</b>	<b>PF measurement summary</b>	<b>Outcome measurement summary</b>	<b>Study confounding summary</b>	<b>Statistical analysis and presentation summary</b>
Ebrahimpour, 2012	Low risk	Low risk	Low risk	Low risk	Moderate risk	High risk
Hahalis, 2009	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Musallam, 2012	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk
Poggi, 2016	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk
Vlahos, 2012	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk

Abbreviations: PF, prognostic factor; QUIPS, Quality in Prognostic Studies; SF, serum ferritin.

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