

REVIEW ARTICLE

Risk Factors for the Occurrence of Asymptomatic Brain Lesions in Patients with β -Thalassemia: a Systematic Review and Meta-Analysis

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SUMMARY

Background: Several factors, including increased platelet aggregation, decreased platelet survival, decreased anti-thrombotic factors cause a hypercoagulable state in thalassemia patients. This is the first meta-analysis designed to summarize the association of age, splenectomy, gender, and serum ferritin and hemoglobin levels with the occurrence of asymptomatic brain lesions in thalassemia patients using MRI.

Methods: This systematic review and meta-analysis was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist. We searched four major databases and included eight articles for this review. The quality of the included studies was assessed based on the Newcastle-Ottawa Scale checklist. Meta-analysis was performed using STATA 13. Odds ratio (OR) and standardized mean difference (SMD) were considered as effect sizes for comparing the categorical and continuous variables, respectively.

Results: The pooled OR for splenectomy in patients with brain lesions compared to those without lesions was 2.25 (95% CI 1.22 - 4.17, $p = 0.01$). The pooled analysis for SMD of age between patients with/without brain lesions was statistically significant, 0.4 (95% CI 0.07 - 0.73, $p = 0.017$). The pooled OR for the occurrence of silent brain lesions was not statistically significant in males compared to females, 1.08 (95% CI 0.62 - 1.87, $p = 0.784$). The pooled SMD of Hb and serum ferritin in positive brain lesions compared to negatives were 0.01 (95% CI -0.28, 0.35, $p = 0.939$) and 0.03 (95% CI -0.28, 0.22, $p = 0.817$), respectively, which were not statistically significant.

Conclusions: Older age and splenectomy are risk factors for developing asymptomatic brain lesions in β -thalassemia patients. Physicians should consider a careful assessment of high-risk patients for starting prophylactic treatment.

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Supplementary Data

Table S1. Search strategy in databases.

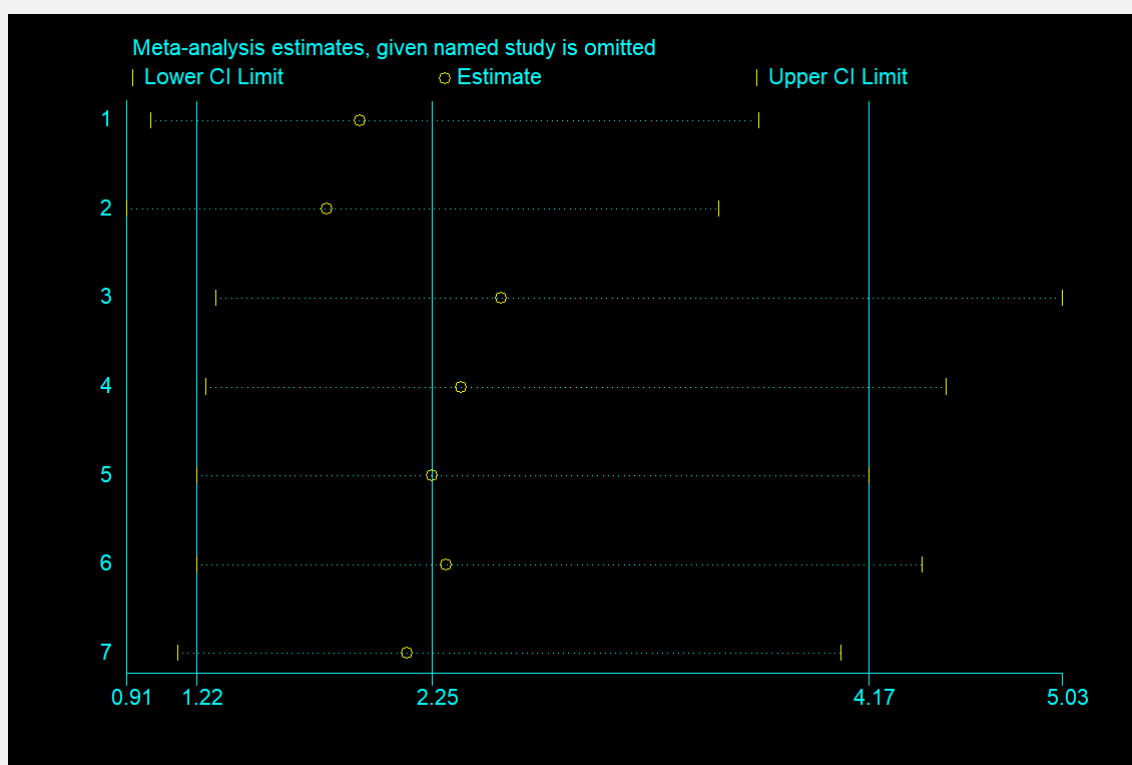
Databases	Search strategy in databases
PubMed	(Thalassemia [MeSH Terms]) OR (β -thalassemia [MeSH Terms]) OR ("Thalassemia*" [Title/Abstract]) OR (" β -thalassemia intermedia" [Title/Abstract]) OR (" β -TI" [Title/Abstract]) OR (" β -thalassemia*" [Title/Abstract]) OR (" β -thalassemia major" [Title/Abstract]) OR (" β -TM" [Title/Abstract]) OR ("Transfusion dependent thalassemia" [Title/Abstract]) OR ("Non Transfusion dependent thalassemia" [Title/Abstract]) OR (" β -thalassemia/Hb E" [Title/Abstract]) OR ("Thalassemia Major" [Title/Abstract]) OR ("Thalassemia Intermedia" [Title/Abstract]) OR ("Thalassemia Minor" [Title/Abstract]) OR (" β -Thalassemia Minor" [Title/Abstract]) AND (Cerebral infarction [MeSH Terms]) OR (Neuroimaging [MeSH Terms]) OR (Stroke [MeSH Terms]) OR (Brain Infarction [MeSH Terms]) OR (Brain Ischemia [MeSH Terms]) OR ("Asymptomatic brain lesion*" [Title/Abstract]) OR ("Brain lesion*" [Title/Abstract]) OR ("White matter lesion*" [Title/Abstract]) OR ("Diffusion-weighted imaging" [Title/Abstract]) OR ("DWI" [Title/Abstract]) OR ("Silent Cerebral Infarct" [Title/Abstract]) OR ("Cerebral infarction" [Title/Abstract]) OR ("Neuroimaging Abnormality*" [Title/Abstract]) OR ("Brain imaging" [Title/Abstract]) OR ("Neuroimaging" [Title/Abstract]) OR ("Brain MRI" [Title/Abstract]) OR (Stroke [Title/Abstract]) OR (Brain [Title/Abstract]) OR ("Brain Infarction*" [Title/Abstract]) OR ("Brain abnormality*" [Title/Abstract]) OR ("Cerebrovascular Disorder*" [Title/Abstract]) OR ("Brain Ischemia" [Title/Abstract]) OR ("Cerebrovascular accident*" [Title/Abstract]) OR ("CVA" [Title/Abstract])
Scopus	TITLE-ABS-KEY ("Thalassemia*" OR " β -thalassemia intermedia" OR " β -TI" OR " β -thalassemia*" OR " β -thalassemia major" OR " β -TM" OR "Transfusion dependent thalassemia" OR "Non-Transfusion dependent thalassemia" OR " β -thalassemia/Hb E" OR "Thalassemia Major" OR "Thalassemia Intermedia" OR "Thalassemia Minor" OR " β -Thalassemia Minor") AND TITLE-ABS-KEY ("Asymptomatic brain lesion" OR "Brain lesion*" OR "White matter lesion*" OR "Diffusion-weighted imaging" OR "DWI" OR "Silent Cerebral Infarct" OR "Cerebral infarction" OR "Neuroimaging Abnormality*" OR "Brain imaging" OR "Neuroimaging" OR "Brain MRI" OR "Stroke" OR "Brain" OR "Brain Infarction*" OR "Brain abnormality*" OR "Cerebrovascular Disorder*" OR "Brain Ischemia" OR "Cerebrovascular accident*" OR "CVA")
WOS	TS = ("Thalassemia*" OR " β -thalassemia intermedia" OR " β -TI" OR " β -thalassemia*" OR " β -thalassemia major" OR " β -TM" OR "Transfusion dependent thalassemia" OR "Non-Transfusion dependent thalassemia" OR " β -thalassemia/Hb E" OR "Thalassemia Major" OR "Thalassemia Intermedia" OR "Thalassemia Minor" OR " β -Thalassemia Minor") AND TS = ("Asymptomatic brain lesion" OR "Brain lesion*" OR "White matter lesion*" OR "Diffusion-weighted imaging" OR "DWI" OR "Silent Cerebral Infarct" OR "Cerebral infarction" OR "Neuroimaging Abnormality*" OR "Brain imaging" OR "Neuroimaging" OR "Brain MRI" OR "Stroke" OR "Brain" OR "Brain Infarction*" OR "Brain abnormality*" OR "Cerebrovascular Disorder*" OR "Brain Ischemia" OR "Cerebrovascular accident*" OR "CVA")

Table S2. Quality assessment of the studies included in the quantitative synthesis.

ID	Author (year)	Type of study	Selection	Comparability	Outcome	Total score
1	Karimi, 2012	cross-sectional	***	*	**	6
2	Karimi, 2015	cross-sectional	**	*	**	5
3	Ramamoorthy, 2019	cross-sectional	**	*	**	5
4	Metarugcheep, 2008	cross-sectional	**	*	**	5
5	TAHER, 2010	prospective study	***	*	**	6
6	Pazgal, 2016	cross-sectional	**	*	**	5
7	Leblebisatan, 2012	cross-sectional	**	*	**	5
8	Premawardhena, 2019	cohort	**	*	**	5

Table S3. Combined OR and sensitivity analysis with heterogeneity and Egger’s test for splenectomy in thalassemia patients.

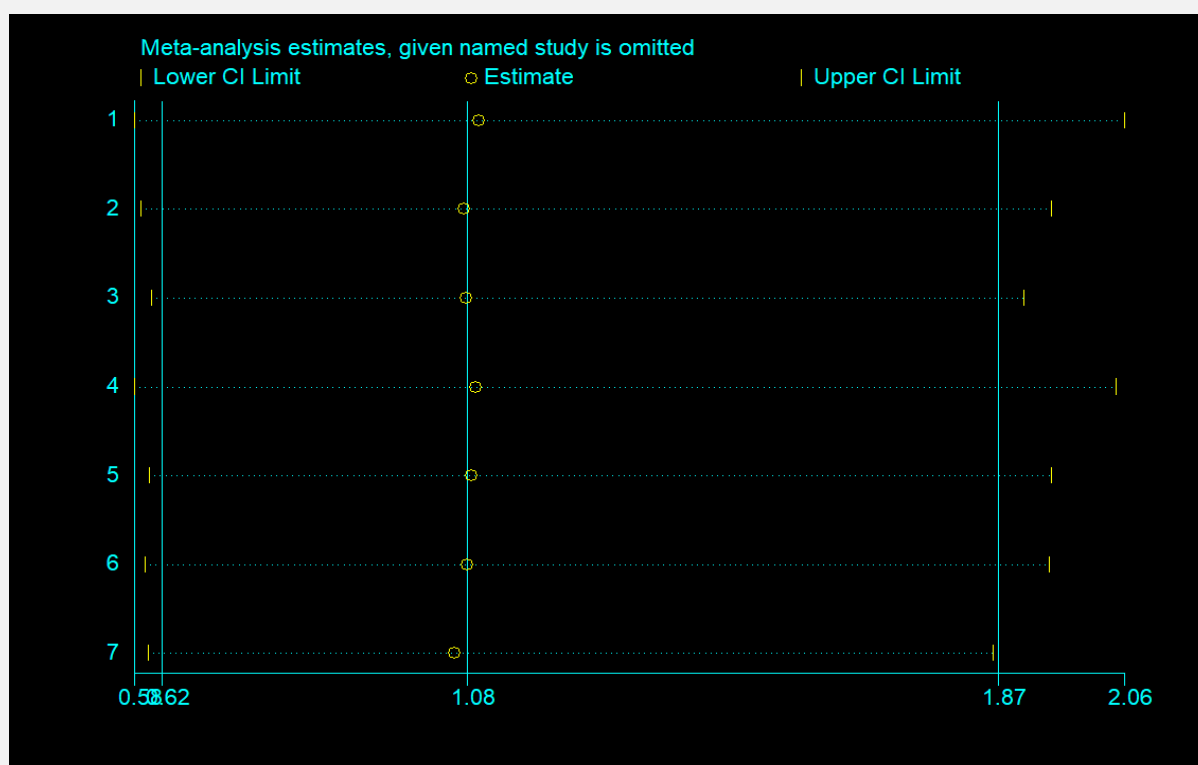
	Combined OR			Heterogeneity			Egger’s test			
	OR (95% CI)	Z for OR = 1	p-value	I^2 (%) ^a	chi squared	p-value	bias	95% CI for bias	p-value	
Overall index	<u>2.25</u> (1.22 - 4.17)	<u>2.59</u>	<u>0.010</u>	<u>14.2</u>	<u>6.99</u>	<u>0.321</u>	<u>1.25</u>	<u>(-2.22, 4.73)</u>	<u>0.398</u>	
Sensitivity analysis (index after delete study #)	1	1.93 (1.01 - 3.69)	2.01	0.044	0	4.57	0.470	0.69	(-3.07, 4.46)	0.637
	2	1.79 (0.91 - 3.51)	1.69	0.091	0	4.31	0.506	1.33	(-1.71, 4.38)	0.292
	3	2.56 (1.30 - 5.02)	2.73	0.006	19.1	6.18	0.289	1.20	(-2.73, 5.14)	0.443
	4	2.38 (1.260 - 4.51)	2.67	0.008	23.9	6.57	0.225	1.96	(-2.08, 6.01)	0.250
	5	no data available								
	6	2.25 (1.21 - 4.17)	2.56	0.010	27.6	6.91	0.227	1.56	(-2.73, 5.87)	0.369
	7	2.31 (1.21 - 4.40)	2.35	0.019	24.5	6.62	0.250	1.15	(-3.60, 5.90)	0.538
	8	2.14 (1.13 - 4.05)	2.84	0.004	6.4	5.34	0.375	-0.04	(-6.62, 6.53)	0.984



Sensitivity analysis on OR for splenectomy.

Table S4. Combined OR and sensitivity with heterogeneity and Egger's test for gender in thalassemia patients.

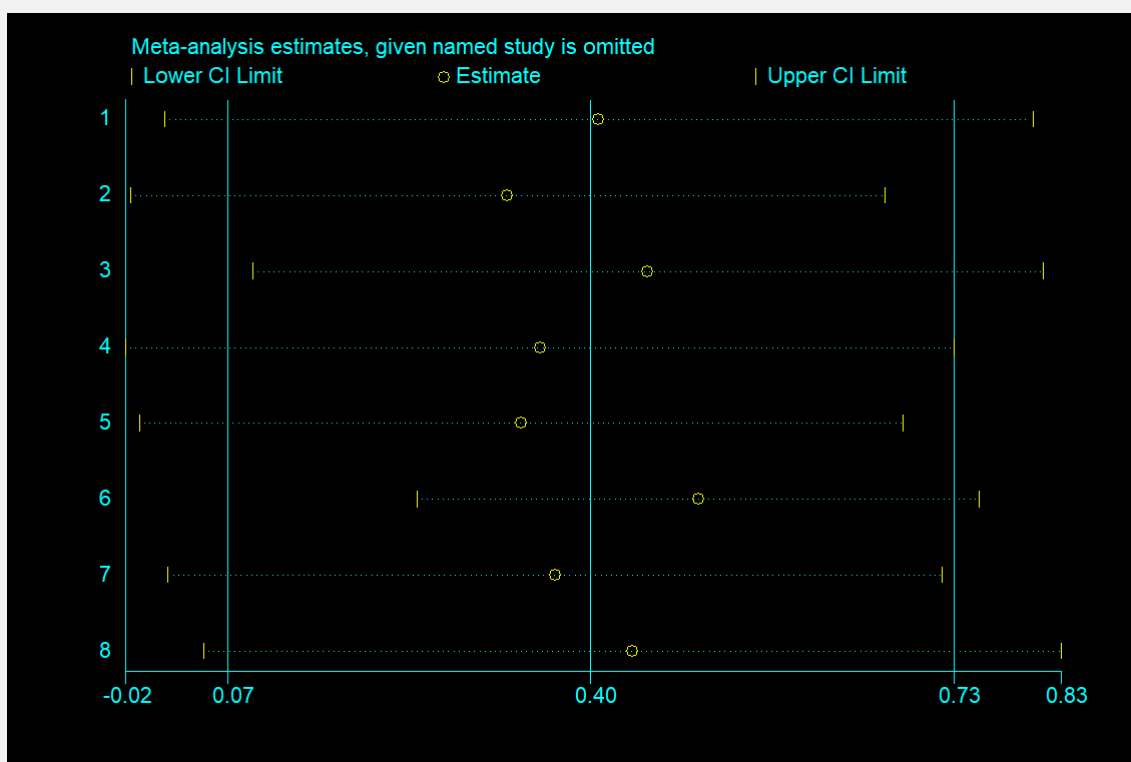
	Combined OR			Heterogeneity			Egger's test			
	OR (95% CI)	Z for OR = 1	p- value	I^2 (%) ^a	chi squared	p-value	bias	95% CI for bias	p-value	
Overall index	<u>1.08</u> (0.62 - 1.87)	<u>0.27</u>	<u>0.784</u>	<u>0</u>	<u>0.09</u>	<u>> 0.999</u>	<u>0.39</u>	<u>(-0.06, 0.71)</u>	<u>0.026</u>	
Sensitivity analysis (index after delete study #)	1	1.09 (0.58 - 2.05)	0.52	0.603	0	0.18	> 0.999	0.02	(-0.7, 0.72)	0.939
	2	1.07 (0.59 - 1.94)	0.47	0.639	0	0.21	> 0.999	0.09	(-0.62, 0.81)	0.751
	3	1.07 (0.60 - 1.90)	0.48	0.632	0	0.21	> 0.999	0.12	(-0.68, 0.93)	0.707
	4	1.09 (0.58 - 2.04)	0.51	0.610	0	0.18	> 0.999	0.03	(-0.66, 0.74)	0.896
	5	1.08 (0.60 -	0.50	0.616	0	0.19	> 0.999	0.13	(-0.57, 0.85)	0.639
	6	1.07 (0.59 - 1.94)	0.48	0.628	0	0.20	> 0.999	0.10	(-0.51 - 0.83)	0.714
	7	1.06 (0.60 - 1.86)	0.20	0.839	0	0.01	> 0.999	-0.23	(-0.99 - 0.52)	0.464
	8	no data available								



Sensitivity analysis on OR for gender in relationship with brain lesions.

Table S5. Combined standardized mean difference (SMD) and sensitivity with heterogeneity and Egger’s test for age in thalassemia patients.

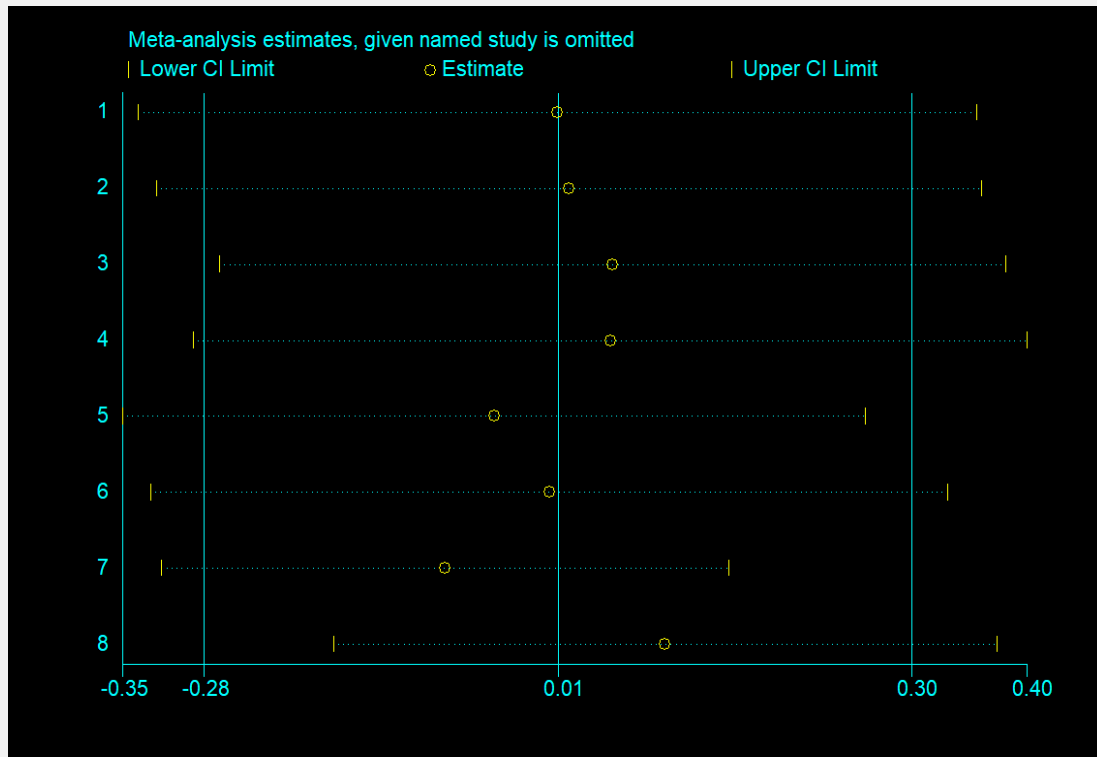
	Combined SMD			Heterogeneity			Egger’s test			
	SMD (95% CI)	Z for OR = 1	p-value	I^2 (%) ^a	chi squared	p-value	bias	95% CI for bias	p-value	
Overall index	0.40 (0.07 - 0.73)	2.39	0.017	46.9	13.19	0.068	0.39	(-5.53, 6.33)	0.875	
Sensitivity analysis (index after delete the study #)	1	0.40 (0.01 - 0.80)	2.04	0.042	54.5	13.17	0.040	0.36	(-6.77, 7.51)	0.899
	2	0.32 (-0.01 - 0.66)	1.87	0.062	43.6	10.64	0.100	0.20	(-5.94, 6.36)	0.934
	3	0.45 (0.09 - 0.81)	2.48	0.013	50.0	11.99	0.062	0.88	(-5.76, 7.53)	0.746
	4	0.35 (-0.02 - 0.73)	1.85	0.064	50.7	12.16	0.059	0.80	(-5.76, 7.48)	0.768
	5	0.33 (-0.00 - 0.68)	1.91	0.056	47.0	11.31	0.079	-0.24	(-6.83 - 6.35)	0.928
	6	0.49 (0.24 - 0.75)	3.83	< 0.001	7.0	6.45	0.374	1.77	(-2.78 - 6.34)	0.362
	7	0.36 (0.01 - 0.72)	2.06	0.039	52.2	12.54	0.051	-1.06	(-10.43 - 8.29)	0.781
	8	0.43 (0.05 - 0.82)	2.21	0.027	52.0	12.50	0.052	-0.40	(-8.13 - 7.32)	0.899



Sensitivity analysis on age in relationship with brain lesions.

Table S6. Combined standardized mean difference (SMD) and sensitivity with heterogeneity and Egger’s test for HB in thalassemia patients.

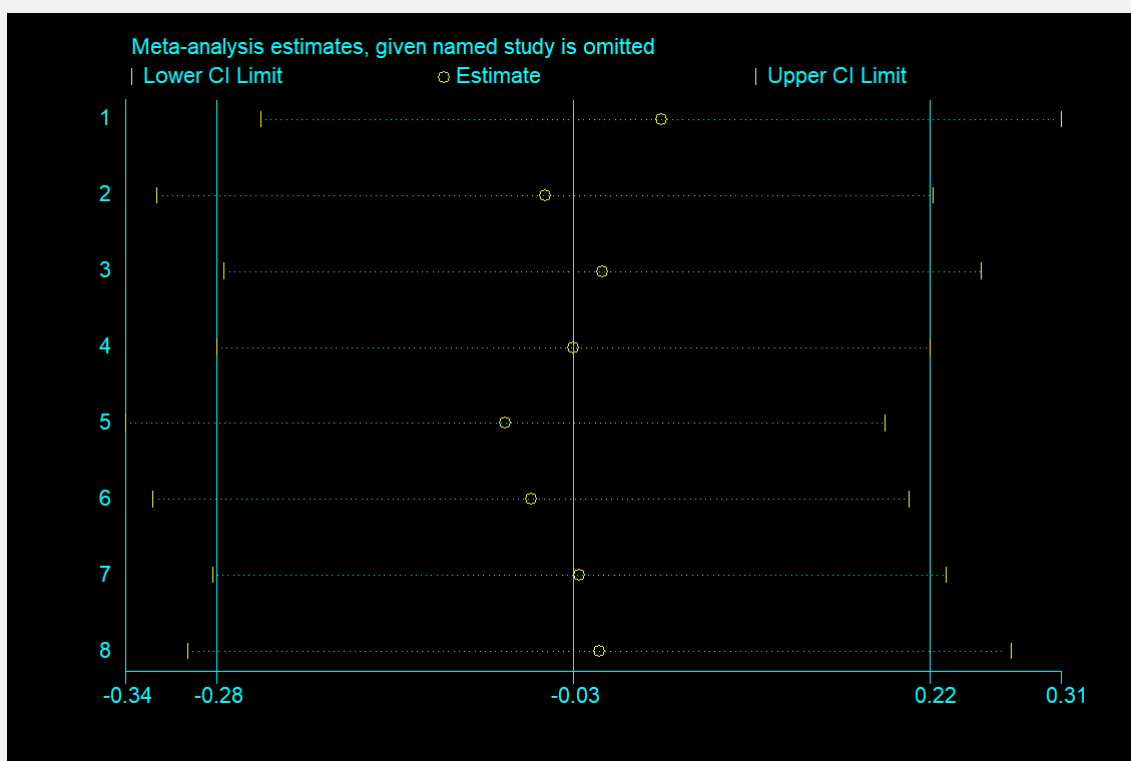
	Combined SMD			Heterogeneity			Egger’s test			
	SMD (95% CI)	Z for OR = 1	p-value	I^2 (%) ^a	chi squared	p-value	bias	95% CI for bias	p-value	
Overall index	0.01 (-0.28 - 0.35)	0.08	0.939	35.2	10.8	0.148	4.21	(0.87 - 7.54)	0.021	
Sensitivity analysis (index after delete the study #)	1	0.01 (-0.33 - 0.35)	0.06	0.950	43.3	10.59	0.102	4.79	(1.60 - 7.98)	0.012
	2	0.02 (-0.32 - 0.36)	0.12	0.907	44.2	10.75	0.096	4.21	(0.38 - 8.03)	0.037
	3	0.05 (-0.26 - 0.38)	0.34	0.733	41.5	10.26	0.114	4.88	(2.14 - 7.62)	0.006
	4	0.05 (-0.29 - 0.40)	0.31	0.757	43.2	10.57	0.103	4.26	(0.32 - 8.20)	0.039
	5	-0.04 (-0.34 - 0.26)	0.26	0.792	34.6	9.18	0.164	3.94	(0.21 - 7.66)	0.042
	6	0.00 (-0.32 - 0.33)	0.02	0.980	43.2	10.57	0.103	4.32	(0.35 - 8.29)	0.038
	7	-0.081 (-0.31 - 0.15)	0.68	0.495	0	5.64	0.465	3.25	(-2.33 - 8.84)	0.195
	8	0.10 (-0.17 - 0.37)	0.72	0.474	10.4	6.70	0.350	3.411	(-0.39 - 7.22)	0.070



Sensitivity analysis on Hb in relationship with brain lesions.

Table S7. Combined standardized mean difference (SMD) and sensitivity with heterogeneity and Egger’s test for ferritin in thalassemia patients.

	Combined SMD			Heterogeneity			Egger’s test			
	SMD (95% CI)	Z for OR = 1	p-value	I^2 (%) ^a	chi squared	p-value	bias	95% CI for bias	p-value	
Overall index	<u>-0.03</u> (-0.28, 0.22)	<u>0.23</u>	<u>0.817</u>	<u>0</u>	<u>2.39</u>	<u>0.880</u>	<u>0.90</u>	<u>(-2.02, 3.82)</u>	<u>0.464</u>	
Sensitivity analysis (index after delete the study #)	1	0.03 (-0.24, 0.31)	0.22	0.823	0	1.50	0.913	0.38	(-2.72, 3.49)	0.749
	2	-0.04 (-0.32, 0.22)	0.35	0.723	0	2.26	0.812	0.91	(-2.49, 4.33)	0.496
	3	-0.00 (-0.27, 0.25)	0.23	0.817	0	2.39	0.880	0.90	(-2.02 - 3.82)	0.464
	4	data not available								
	5	-0.07 (-0.34, 0.18)	0.57	0.570	0	1.34	0.931	0.53	(-2.23, 3.31)	0.620
	6	-0.05 (-0.32, 0.20)	0.44	0.662	0	1.95	0.855	0.63	(-2.77, 4.04)	0.632
	7	-0.02 (-0.28, 0.23)	0.19	0.848	0	2.37	0.796	2.24	(-2.14, 6.63)	0.229
	8	-0.01 (-0.30, 0.27)	0.08	0.940	0	2.33	0.802	0.97	(-3.35, 5.30)	0.565



Sensitivity analysis on ferritin in relationship with brain lesions.