

ORIGINAL ARTICLE

Cytokine Levels in Patients with β -Thalassemia Major and Healthy Individuals: a Systematic Review and Meta-Analysis

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SUMMARY

Background: Cytokine levels in patients with β -thalassemia major (β -TM) have been assessed in several studies. Accordingly, a wide variety of immune disturbances has been shown in patients with thalassemia. Recurrent transfusions cause iron overload, which induces an increase in the production of cytokines. However, no systematic approach or meta-analysis has been done to provide a clear feature of cytokine levels in β -TM. The present meta-analysis aimed to summarize the existing evidence regarding different levels of cytokines in patients with β -TM compared to healthy controls.

Methods: This study was performed according to the PRISMA checklist. A systematic search was done in Web of Science (ISI), Scopus, and PubMed databases. The quality of the included studies was assessed based on the Newcastle-Ottawa Scale. Meta-analysis was run via STATA 13 software. The standardized mean difference was considered the effect size for comparing the continuous variables.

Results: This meta-analysis included 16 studies conducted on 805 β -TM patients and 624 healthy individuals (with the mean age of 16.10 ± 4.33 and 16.22 ± 3.78 , respectively). The results showed significantly higher levels of Tumor Necrosis Factor-alpha (TNF- α), Interleukin-6 (IL-6), and IL-10 in patients with β -TM compared to the healthy controls.

Conclusion: The results indicated that the levels of both inflammatory and anti-inflammatory cytokines were higher in patients with β -TM compared to the healthy population, which could be associated with higher levels of oxidative markers in these patients. Further studies are suggested to evaluate the difference in cytokine levels among different types of thalassemia.

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Supplementary Data

Table S1. Search strategy in databases (February 2021).

PubMed	(Thalassemia [MeSH Terms]) OR (Alpha-thalassemia [MeSH Terms]) OR (Beta-thalassemia [MeSH Terms]) OR ("Thalassemia *" [Title/Abstract]) OR ("Thalassaemia" [Title/Abstract]) OR ("Alpha-thalassemia" [Title/Abstract]) OR ("α-thalassemia" [Title/Abstract]) OR ("β-thalassemia" [Title/Abstract]) OR ("Hb E disease" [Title/Abstract]) OR ("Thalassemia Intermedia" [Title/Abstract]) OR ("Thalassemia Minor" [Title/Abstract]) OR ("Thalassemia Major" [Title/Abstract]) OR ("Mediterranean Anemia" [Title/Abstract]) OR ("Beta-Thalassemia Major" [Title/Abstract]) OR ("Cooley's anemia" [Title/Abstract]) OR ("Erythroblastic Anemia" [Title/Abstract]) OR ("Hemoglobin H Disease" [Title/Abstract]) OR ("Hemoglobin E Disease" [Title/Abstract]) AND (Cytokines [MeSH Terms]) OR (Interleukins [MeSH Terms]) OR (Interleukin-10 [MeSH Terms]) OR (Interleukin-4 [MeSH Terms]) OR (Interleukin-6 [MeSH Terms]) OR (Tumor Necrosis Factor-alpha [MeSH Terms]) OR ("Cytokine *" [Title/Abstract]) OR ("Interleukin *" [Title/Abstract]) OR ("Interleukin-10" [Title/Abstract]) OR ("IL-10" [Title/Abstract]) OR ("Cytokine Synthesis Inhibitory Factor" [Title/Abstract]) OR ("CSIF" [Title/Abstract]) OR ("Interleukin-4" [Title/Abstract]) OR ("B-Cell Growth Factor-1" [Title/Abstract]) OR ("B-Cell Stimulatory Factor-1" [Title/Abstract]) OR ("BCGF-1" [Title/Abstract]) OR ("BSF-1" [Title/Abstract]) OR ("IL-4" [Title/Abstract]) OR ("Interleukin-6" [Title/Abstract]) OR ("IL-6" [Title/Abstract]) OR ("B-Cell Stimulatory Factor 2" [Title/Abstract]) OR ("B Cell Differentiation Factor 2" [Title/Abstract]) OR ("hybridoma growth factor" [Title/Abstract]) OR ("Hepatocyte Stimulating Factor" [Title/Abstract]) OR ("B Cell Differentiation Factor" [Title/Abstract]) OR ("Interferon beta 2" [Title/Abstract]) OR ("Tumor Necrosis Factor-alpha" [Title/Abstract]) OR ("Cachectin" [Title/Abstract]) OR ("Tumor Necrosis Factor" [Title/Abstract]) OR ("TNF-alpha" [Title/Abstract]) OR ("TNF-a" [Title/Abstract])
Scopus	TITLE-ABS-KEY ("Thalassemia *" OR "Thalassaemia" OR "Alpha-thalassemia" OR "α-thalassemia" OR "Beta-thalassemia" OR "β-thalassemia" OR "Hb E disease" OR "Thalassemia Intermedia" OR "Thalassemia Minor" OR "Thalassemia Major" OR "Mediterranean Anemia" OR "Beta-Thalassemia Major" OR "Cooley's anemia" OR "Erythroblastic Anemia" OR "Hemoglobin H Disease" OR "Hemoglobin E Disease") AND TITLE-ABS-KEY ("Cytokine *" OR "Interleukin *" OR "Interleukin-10" OR "IL-10" OR "Cytokine Synthesis Inhibitory Factor" OR "CSIF" OR "Interleukin-4" OR "B-Cell Growth Factor-1" OR "B-Cell Stimulatory Factor-1" OR "BCGF-1" OR "BSF-1" OR "IL-4" OR "Interleukin-6" OR "IL-6" OR "B-Cell Stimulatory Factor 2" OR "B Cell Differentiation Factor 2" OR "hybridoma growth factor" OR "Hepatocyte Stimulating Factor" OR "B Cell Differentiation Factor" OR "Interferon beta 2" OR "Tumor Necrosis Factor-alpha" OR "Cachectin" OR "Tumor Necrosis Factor" OR "TNF-alpha" OR "TNF-a")
WOS	TS = ("Thalassemia *" OR "Thalassaemia" OR "Alpha-thalassemia" OR "α-thalassemia" OR "Beta-thalassemia" OR "β-thalassemia" OR "Hb E disease" OR "Thalassemia Intermedia" OR "Thalassemia Minor" OR "Thalassemia Major" OR "Mediterranean Anemia" OR "Beta-Thalassemia Major" OR "Cooley's anemia" OR "Erythroblastic Anemia" OR "Hemoglobin H Disease" OR "Hemoglobin E Disease") AND TS = ("Cytokine *" OR "Interleukin *" OR "Interleukin-10" OR "IL-10" OR "Cytokine Synthesis Inhibitory Factor" OR "CSIF" OR "Interleukin-4" OR "B-Cell Growth Factor-1" OR "B-Cell Stimulatory Factor-1" OR "BCGF-1" OR "BSF-1" OR "IL-4" OR "Interleukin-6" OR "IL-6" OR "B-Cell Stimulatory Factor 2" OR "B Cell Differentiation Factor 2" OR "hybridoma growth factor" OR "Hepatocyte Stimulating Factor" OR "B Cell Differentiation Factor" OR "Interferon beta 2" OR "Tumor Necrosis Factor-alpha" OR "Cachectin" OR "Tumor Necrosis Factor" OR "TNF-alpha" OR "TNF-a")

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

ID	Author, Year	Type of study	Selection	Comparability	Outcome	Total score
1	Abd El-Khalik	Case-Control	***	*	***	7
2	Abo Shanab	Case-Control	**	*	***	6
3	Akcali 2015	Cross-Sectional	**	*	**	5
4	Akcali 2019	Cross-Sectional	**	*	**	5
5	Al-Hakeim	Case-Control	***	*	***	7
6	Balouchi	Case-Control	***	*	***	7
7	El-Rasheidy	Case-Control	***	*	***	7
8	Gharagozloo	Case-Control	**	*	***	6
9	Kyriakou	Case-Control	***	*	***	7
10	MOHAMMED 2018	Case-Control	**	*	***	6
11	Mohammed 2020	Case-Control	**	*	***	6
12	Morabito	Case-Control	***	**	***	8
13	Noori	Case-Control	**	*	***	6
14	Ragab	Case-Control	**	**	***	7
15	Surhan	Case-Control	**	*	***	6
16	WANACHIWANAWIN	Case-Control	***	**	***	8