



Dynamics of Pro- and Anti-Inflammatory Cytokines (IL-6 and IL-10) in Thalassemia Patients: Evaluating the IL-6/IL-10 Ratio as a Candidate Biomarker for Detecting Latent *Toxoplasma gondii* Co-Infection

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Abstract: Thalassemia is a hereditary hemolytic anemia associated with profound chronic immune activation and heightened susceptibility to opportunistic infections, including latent *Toxoplasma gondii*. Although IL-6 and IL-10 are widely studied individually in thalassemia, their ratio as a composite immunological biomarker for detecting latent *Toxoplasma* co-infection has not been systematically explored. A cross-sectional comparative study enrolled 90 participants equally distributed across three groups: healthy controls (Normal, n = 30), thalassemia patients without co-infection (Thalassemia, n = 30), and thalassemia patients with confirmed *T. gondii* infection (Thala+Toxo, n = 30). Serum IL-6 and IL-10 were quantified by enzyme-linked immunosorbent assay (ELISA). Non-parametric group comparisons used the Kruskal–Wallis H test with Bonferroni-corrected Mann–Whitney U post-hoc tests (adjusted $\alpha = 0.017$), and Spearman rank correlation assessed cytokine co-regulation. Both cytokines were markedly elevated in the thalassemia groups compared with healthy controls ($p < 0.001$). The IL-6/IL-10 ratio was 0.895 in controls, 0.488 in the thalassemia-only group, and 0.556 in co-infected patients, representing a 14% directional shift associated with *Toxoplasma* co-infection. Pairwise cytokine differences between the two thalassemia subgroups did not reach significance individually (IL-6: $p = 0.167$; IL-10: $p = 1.000$), yet the ratio exhibited a consistent directional trend. No significant IL-6–IL-10 co-regulation was observed within any group. The IL-6/IL-10 ratio may serve as a supplementary immunological biomarker for latent *T. gondii* co-infection in thalassemia patients, complementing conventional serological screening. Validation in larger longitudinal cohorts with receiver operating characteristic (ROC) analysis is warranted.

Keywords: Thalassemia; interleukin-6; interleukin-10; cytokine ratio; *Toxoplasma gondii*

1. Introduction

Beta-thalassemia ranks among the most prevalent monogenic disorders globally, disproportionately affecting populations in the Mediterranean, Middle East, South Asia, and Southeast Asia [1]. Mutations in the beta-globin gene impair normal hemoglobin synthesis, leading to ineffective erythropoiesis, chronic hemolytic anemia, and progressive iron overload from repeated transfusions [2, 3]. Worldwide, approximately 56,000 severely affected neonates are born annually, placing a substantial burden on low- and middle-income

health systems [4]. Beyond its hematological manifestations, thalassemia profoundly disrupts both innate and adaptive immunity. Transfusion-related alloimmunization, iatrogenic splenectomy, and chronic iron overload collectively impair neutrophil and macrophage function, reduce complement activity, and alter T-cell subset distribution, collectively predisposing patients to opportunistic and blood-borne infections [5, 6]. Among these, *Toxoplasma gondii*, an obligate intracellular parasite estimated to infect approximately one-third of the global human population, is especially clinically relevant. While primary infection is typically self-limiting in immunocompetent individuals, reactivation of latent tissue cysts in immunocompromised hosts, including thalassemia patients, can cause severe neurological, ocular, and systemic disease [7, 8]. Seroepidemiological data from Iraq and broader Middle Eastern regions confirm a significantly elevated prevalence of anti-*Toxoplasma* IgG antibodies in thalassemia populations, suggesting that immunological defects in this group may facilitate parasite persistence in latent forms [9–11].

Interleukin-6 (IL-6) and interleukin-10 (IL-10) occupy central roles in the immunopathology of both thalassemia and toxoplasmosis. IL-6 is a pleiotropic pro-inflammatory mediator that drives acute-phase responses, suppresses erythropoiesis via hepcidin induction, and sustains chronic systemic inflammation [12]. Conversely, IL-10 is the principal anti-inflammatory immunoregulatory cytokine, restraining excessive immune activation and serving as a critical counter-regulatory signal in chronic parasitic infections [13]. Notably, *T. gondii* has evolved sophisticated immunoevasion strategies that exploit host IL-10 production through signal transducer and activator of transcription 3 (STAT3)/suppressor of cytokine signaling 3 (SOCS3) signaling, dampening protective Th1 responses and enabling parasite persistence [14, 15]. The concurrent dysregulation of both cytokines in thalassemia creates an immunological milieu that may not only promote latent infection but also obscure its detection using conventional serological markers alone [16, 17]. Although IL-6 and IL-10 have individually been characterized in thalassemia [18, 19], their ratio — reflecting the balance between pro- and anti-inflammatory signaling — has not been systematically investigated in the context of *T. gondii* co-infection. In other infectious disease contexts, cytokine ratios, including the IL-6/IL-10 ratio, have demonstrated superior discriminatory power compared with individual cytokine measurements, as they capture immunological imbalance that single biomarkers cannot adequately convey [20, 21]. This principle is particularly applicable in thalassemia, where both cytokines are concurrently elevated, and their relative dynamics may encode diagnostic information beyond absolute concentrations [22, 23].

This study therefore aimed to: (i) characterize IL-6 and IL-10 profiles across three well-defined groups, healthy controls, thalassemia patients without *T. gondii* infection, and thalassemia patients with confirmed co-infection; (ii) assess whether individual cytokine levels differ significantly between co-infected and non-co-infected thalassemia patients; and (iii) determine whether the IL-6/IL-10 ratio provides additional diagnostic utility as a candidate biomarker for latent toxoplasmosis in this vulnerable population [24].

2. Materials and Methods

2.1 Study Design and Participants

A cross-sectional comparative study was conducted from March 2023 to December 2023 at the Karbala Center for Hereditary Blood Diseases in Kerbala, Iraq. Ninety participants were enrolled and allocated equally across three groups ($n = 30$ each): (i) a healthy control group (Normal) comprising individuals with no chronic disease or immunosuppressive condition; (ii) a thalassemia-only group (Thalassemia) consisting of transfusion-dependent beta-thalassemia patients with negative *Toxoplasma* serology; and (iii) a thalassemia co-infection group (Thala+Toxo) comprising beta-thalassemia patients with serologically confirmed latent *T. gondii* infection. Diagnosis of beta-thalassemia was established by hemoglobin electrophoresis and complete blood count (CBC) profiling, consistent with institutional and international diagnostic criteria [25]. Confirmation of *Toxoplasma* co-infection was achieved through serological rapid testing and quantitative IgG/IgM index measurement; only patients with positive IgG and negative IgM (consistent with latent infection) were classified as co-infected. Individuals with acute inflammatory illnesses, autoimmune disease, malignancy, pregnancy, or current immunosuppressive therapy were excluded. Demographic profiles revealed important inter-group differences. Healthy controls had a mean age of 37.0 ± 12.8 years (range 21–61), whereas thalassemia patients (mean 17.7 ± 7.7 years; range 8–45) and co-infected patients (mean 18.9 ± 9.8

years; range 4–41) were substantially younger, reflecting the early onset and lifelong nature of the disease. Sex distribution in the healthy control group was balanced (15 males, 15 females), while male predominance was observed in both thalassemia groups (Thalassemia: 21 males, 9 females; Thala+Toxo: 17 males, 13 females). Written informed consent was obtained from all participants or their legal guardians before enrollment. All procedures were conducted in accordance with the Declaration of Helsinki.

2.2 Blood Sample Collection and Cytokine Quantification

Venous blood samples (5 mL) were collected under standardized aseptic conditions by trained phlebotomists. Samples were immediately centrifuged at $3,000 \times g$ for 10 minutes at 4°C ; serum was aliquoted and stored at -80°C until assay. Serum concentrations of interleukin-6 (IL-6) and interleukin-10 (IL-10) were quantified in duplicate using commercially available enzyme-linked immunosorbent assay (ELISA) kits (manufacturer and catalog numbers to be cited per actual kits used), following manufacturer protocols. All coefficients of variation (CV) for duplicate measurements were maintained at $\leq 10\%$. Results were expressed in picograms per milliliter (pg/mL). Laboratory personnel were blinded to group allocation during assay performance.

2.3 Statistical Analysis

Data were entered and independently verified before statistical processing. Descriptive statistics were computed for each continuous variable, including mean $\pm$ standard deviation (SD), median, and interquartile range (IQR). Distributional normality within each group was assessed using the Shapiro–Wilk test. Because cytokine distributions showed significant positive skewness ($p < 0.05$) in both disease groups, non-parametric methods were employed throughout. The Kruskal–Wallis H test was applied for omnibus comparison across the three groups, followed by pairwise Mann–Whitney U tests with Bonferroni correction to control for multiple comparisons (adjusted significance threshold: $\alpha = 0.05/3 = 0.017$). The IL-6/IL-10 ratio was calculated both for individual patients and for group means. Spearman's rank correlation coefficient (ρ) was computed within each group to assess the relationship between IL-6 and IL-10. All analyses were conducted using [SPSS version XX / R version XX], and statistical significance was defined at $p < 0.05$ unless otherwise stated.

3. Results and Discussion

3.1 Cytokine Concentrations Across Study Groups

Serum IL-6 and IL-10 concentrations differed substantially across the three study groups, as summarized in Table 1. In healthy controls, both cytokines remained within expected physiological baselines: IL-6, mean 2.48 ± 1.47 pg/mL (median 2.60 [IQR: 1.20–3.77]), and IL-10, mean 2.77 ± 1.46 pg/mL (median 2.60 [IQR: 1.70–4.10]). In the thalassemia-only group, IL-6 rose approximately 20-fold to a mean of 50.02 ± 25.94 pg/mL (median 40.82 [IQR: 38.20–46.69]), and IL-10 increased approximately 37-fold to a mean of 102.57 ± 145.98 pg/mL (median 53.15 [IQR: 38.39–74.80]). In co-infected patients, IL-6 reached 68.43 ± 39.89 pg/mL (median 47.42 [IQR: 38.76–87.87]), and IL-10 reached 123.13 ± 127.33 pg/mL (median 64.47 [IQR: 32.97–236.07]). The wide standard deviations observed within both disease groups reflect considerable inter-individual variability in cytokine responses—a recognized hallmark of chronic inflammatory states in thalassemia [18]. The magnitude of IL-10 elevation relative to IL-6 in both thalassemia subgroups is noteworthy: it reflects an expected counter-regulatory response in which IL-6-driven chronic inflammation is attenuated by compensatory IL-10 upregulation, thereby preventing excessive immunopathological tissue damage [13]. This concurrent elevation of both cytokines at vastly different ratios forms the biological rationale for examining their quotient rather than their individual absolute values.

Table 1. Descriptive statistics for serum IL-6 and IL-10 concentrations across the three study groups.

Group	IL-6 Mean $\pm$ SD (pg/mL)	IL-6 Median [IQR]	IL-10 Mean $\pm$ SD (pg/mL)	IL-10 Median [IQR]
Normal (n = 30)	2.48 $\pm$ 1.47	2.60 [1.20–3.77]	2.77 $\pm$ 1.46	2.60 [1.70–4.10]
Thalassemia (n = 30)	50.02 $\pm$ 25.94	40.82 [38.20–46.69]	102.57 $\pm$ 145.98	53.15 [38.39–74.80]
Thala+Toxo (n = 30)	68.43 $\pm$ 39.89	47.42 [38.76–87.87]	123.13 $\pm$ 127.33	64.47 [32.97–236.07]

IQR = interquartile range; pg/mL = picograms per milliliter; SD = standard deviation. Values reflect non-normally distributed data (Shapiro–Wilk $p < 0.05$ for all disease groups); median and IQR are the primary descriptive statistics. The mean $\pm$ SD is provided as a reference for the ratio calculation.

3.2 Kruskal–Wallis and Post-Hoc Pairwise Analysis

Kruskal–Wallis omnibus testing confirmed statistically significant overall differences across all three groups for both IL-6 ($H = 61.00$, $p < 0.001$) and IL-10 ($H = 59.41$, $p < 0.001$), as presented in Table 2. Bonferroni-corrected Mann–Whitney U post hoc comparisons (Table 3) revealed that both cytokines were significantly higher in each thalassemia subgroup compared with healthy controls ($p < 0.001$ for all 4 pairwise comparisons). However, no statistically significant difference was detected between the two thalassemia subgroups for either IL-6 (U-adjusted $p = 0.167$) or IL-10 (U-adjusted $p = 1.000$). The lack of cytokine significance between the Thalassemia and Thala+Toxo groups does not imply biological equivalence. Rather, it reflects the already-elevated cytokine baseline established by thalassemia, against which the additional immunological contribution of *T. gondii* is difficult to resolve with 30 samples per group. Detecting modest between-group differences when both the numerator and denominator of the standard deviation are large requires substantially larger cohorts [22]. This observation is consistent with previous reports that thalassemia itself generates an inflammatory milieu that partially mimics or obscures co-infection immune signatures [16].

Table 2. Kruskal–Wallis H test results for serum IL-6 and IL-10 across study groups.

Variable	Test Applied	Test Statistic	p-Value	Significance
IL-6	Kruskal–Wallis H	$H = 61.00$	< 0.001	***
IL-10	Kruskal–Wallis H	$H = 59.41$	< 0.001	***

*** $p < 0.001$.

Table 3. Post-hoc pairwise Mann–Whitney U test results with Bonferroni correction.

Variable	Normal vs. thalassemia (p-adj)	Normal vs. Thala+Toxo (p-adj)	Thalassemia vs. Thala+Toxo (p-adj)	Overall
IL-6	< 0.001	< 0.001	0.167 (ns)	***
IL-10	< 0.001	< 0.001	1.000 (ns)	***

Bonferroni-adjusted significance threshold: $\alpha = 0.017$ ($= 0.05/3$). *** $p < 0.001$; ns = not statistically significant.

3.3 IL-6/IL-10 Ratio as a Candidate Composite Biomarker

Although individual cytokine differences between thalassemia subgroups did not reach statistical significance, analysis of the IL-6/IL-10 ratio reveals a biologically meaningful directional shift across groups (Table 4). In healthy controls, the ratio was 0.895, reflecting near-equal basal pro- and anti-inflammatory tone. In thalassemia-only patients, the ratio dropped markedly to 0.488, indicating a relative predominance of IL-10, consistent with the compensatory anti-inflammatory response to chronic IL-6-driven inflammation. Notably, in the co-infected group, the ratio partially recovered to 0.556, a 14% increase over the thalassemia-only value. This 14% upward shift in the IL-6/IL-10 ratio in the Thala+Toxo group is mechanistically consistent with the known immunobiology of *T. gondii*. The parasite activates nuclear factor kappa B (NF- κ B) and mitogen-activated protein kinase (MAPK) signaling pathways that transcriptionally upregulate IL-6 expression, while simultaneously inducing host IL-10 production through STAT3/SOCS3-mediated immunoevasion [14, 15, 26]. The net result, a relatively greater increase in IL-6 compared to IL-10, is precisely what the ratio captures, even

when neither cytokine alone reaches significance at this sample size. In other parasitic co-infection contexts, the IL-6/IL-10 ratio has shown superior discriminatory capacity to either cytokine alone in distinguishing active from resolved infection or in identifying latent co-infected states [20,21,23]. From a translational perspective, the IL-6/IL-10 ratio holds promise as a low-cost, non-invasive adjunct screening tool in thalassemia patients who may not exhibit overt clinical symptoms of *Toxoplasma* reactivation. Patients with a ratio trending upward from their individual baseline — or with values exceeding a clinically validated threshold, could be prioritized for formal serological *Toxoplasma* screening before progression to overt disease. However, the formal clinical utility of the ratio requires derivation of sensitivity, specificity, and optimal cut-off values through ROC curve analysis in larger prospective cohorts before it can be recommended for routine clinical use.

Table 4. IL-6/IL-10 ratio and Spearman rank correlation within each study group.

Group	IL-6 Mean (pg/mL)	IL-10 Mean (pg/mL)	IL-6/IL-10 Ratio	Spearman ρ (p-value)
Normal (n = 30)	2.48	2.77	0.895	-0.300 (p = 0.107)
Thalassemia (n = 30)	50.02	102.57	0.488	-0.062 (p = 0.745)
Thala+Toxo (n = 30)	68.43	123.13	0.556 (↑14%)	0.055 (p = 0.771)

IL-6/IL-10 ratio calculated from group mean values. ρ = Spearman rank correlation coefficient; ns = not statistically significant. ↑14% denotes the percentage increase in the ratio from the thalassemia to the Thala+Toxo group.

3.4 Spearman Correlation Analysis Between IL-6 and IL-10

Spearman rank correlation analysis within each group revealed no statistically significant relationship between IL-6 and IL-10 concentrations. In healthy controls, a weak negative correlation was observed ($\rho = -0.300$, $p = 0.107$), suggesting a mild antagonistic homeostatic relationship between these cytokines under baseline conditions, consistent with normal immunoregulatory balance [22]. In the thalassemia-only group ($\rho = -0.062$, $p = 0.745$) and the co-infection group ($\rho = 0.055$, $p = 0.771$), correlations were near zero, confirming the absence of co-regulation. The decoupling of IL-6 and IL-10 in both disease groups has important implications. In acute inflammatory states, these cytokines tend to rise in concert, with IL-10 induced by IL-6 as a feedback regulatory mechanism [13]. The breakdown of this coupled relationship in thalassemia suggests that, under conditions of chronic inflammation, IL-6 and IL-10 are driven by at least partially independent upstream stimuli, including iron overload-related oxidative stress, transfusion-related immune activation, and pathogen-specific signaling cascades [17,22,23]. This independence further supports the utility of evaluating each cytokine separately and in combination via their ratio, rather than relying on either alone as a disease or infection marker.

3.5 Limitations and Future Directions

Several limitations must be acknowledged. First, the cross-sectional study design precludes causal inference and does not allow tracking of intra-individual cytokine trajectory over time. Second, each group contained only 30 participants, reducing statistical power to detect modest between-group differences in cytokines with high inter-individual variability. Specifically, the comparison between the two thalassemia subgroups was underpowered, and larger cohorts are needed to reach significance for moderate effect sizes. Third, the IL-6/IL-10 ratio was computed from group means in this exploratory analysis; individual-level ROC analysis is required to establish clinically actionable cut-off values. Fourth, important confounders that influence cytokine profiles in thalassemia, including the timing of last blood transfusion, iron chelation regimen, splenectomy status, and the presence of concurrent bacterial or viral co-infections, were not fully characterized or controlled for in this study [25]. Fifth, healthy controls were considerably older (mean 37.0 ± 12.8 years) than both thalassemia groups (mean 17.7–18.9 years), and male predominance was present in both thalassemia groups relative to the sex-balanced control group; as both age and sex are recognized determinants of baseline cytokine levels, these imbalances represent additional, only descriptively reported confounders that were not formally tested or statistically adjusted for in the present analysis. Sixth, no a priori

or post-hoc power calculation was performed; given the observed effect sizes and the high intra-group variability in IL-10 (SD $\approx$ 146 and 127 pg/mL in the two thalassemia groups), the non-significant pairwise comparisons between thalassemia subgroups (IL-6: $p = 0.167$; IL-10: $p = 1.000$) may reflect a Type II error rather than a true absence of difference, and this possibility should be explicitly considered when interpreting the ratio findings. Seventh, because the IL-6/IL-10 ratio reported here was derived from group-mean cytokine values rather than from per-participant ratios, it carries no inferential statistical weight in its current form; a methodologically rigorous evaluation would calculate the ratio for each participant individually and compare the two thalassemia subgroups using a non-parametric test (e.g., Mann–Whitney U), ideally complemented by receiver operating characteristic (ROC) curve analysis to estimate the sensitivity, specificity, and area under the curve (AUC) of the ratio as a discriminatory biomarker. Future prospective studies with larger, matched cohorts; longitudinal cytokine monitoring; formal ROC analysis; and multivariate adjustment for the aforementioned confounders are required to establish the clinical validity and utility of the IL-6/IL-10 ratio as a screening adjunct for latent *T. gondii* in thalassemia.

4. Conclusions

This study demonstrated that thalassemia produces a dramatic simultaneous elevation of both IL-6 (~20-fold) and IL-10 (~37-fold) relative to healthy controls, reflecting a sustained state of chronic inflammation counterbalanced by immunoregulatory compensation. While individual cytokine concentrations did not differ significantly between thalassemia patients with and without *T. gondii* co-infection at the current sample size, the IL-6/IL-10 ratio showed a consistent, biologically interpretable directional shift: 0.895 in healthy controls, 0.488 in thalassemia-only patients, and 0.556 (+14%) in co-infected patients. This ratio shift is mechanistically coherent with *T. gondii*'s known ability to simultaneously upregulate IL-6 via NF- κ B and induce host IL-10 through immunoevasion pathways, resulting in a net increase in relative IL-6 burden. The absence of significant IL-6–IL-10 co-regulation across groups further supports the interpretation of these cytokines as partially independent signals in chronic disease, where their ratio may carry more diagnostic information than either alone. We propose the IL-6/IL-10 ratio as a candidate composite biomarker to complement routine serological screening for latent toxoplasmosis in thalassemia patients. Validation in larger longitudinal cohort studies, incorporating ROC analysis, individual-level ratio monitoring, and rigorous control of transfusion- and chelation-related confounders, is necessary before clinical implementation. Integration of this simple immunological parameter into thalassemia management protocols could contribute to earlier identification of latent *T. gondii* reactivation risk, supporting more timely prophylactic and therapeutic decision-making in this immunocompromised population.

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