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Levels of IL-18 and IL-28 in thalassemia patients with viral infections

Maytham Khazaal Kadhim[1*], Kais Kassim Ghaima[2]
[1,2]Institute of Genetic Engineering and Biotechnology for Postgraduate Studies, University of Baghdad, Iraq; maythambio@gmail.com (M.K.K.), kaisskasim22@ige.uobaghdad.edu.iq (K.K.G.).

Abstract: Thalassemia is an inherited hemoglobin disorder that requires lifelong medical care. Patients with thalassemia are very prone to infections by viruses, which may exacerbate their condition, leading to serious complications. Knowledge of the immune response in these patients could be very helpful in the effective management of their disease. The levels of IL-18 and IL-28 were evaluated in thalassemia patients with different viral infections to assess their potential as biomarkers and therapeutic targets. This was a retrospective analysis of clinical data on thalassemia patients with viral infections. Demographic, clinical, laboratory, IL-18, and IL-28 data at baseline were included in the study. In the present study, the authors assessed the correlations between interleukin levels, viral infection, treatment response, and overall survival. The study enrolled 250 patients with thalassemia and different viral infections. In these patients, the levels of IL-18 and IL-28 were found to be elevated with a significant correlation to viral load. Thus, a higher baseline interleukin level predicted a better treatment response and overall survival. Elevations in IL-18 and IL-28 in thalassemia patients with associated viral infections likely indicate immune system activation. Their correlation with viral load and treatment outcomes suggests their potential as biomarkers and targets for therapy. These findings further underline the protective role of IL-18 and IL-28, hence contributing to enhanced survival rates of the patients. Further studies for translation of these insights into practice may help modify clinical care for better patient outcomes.

Keywords: *Antiviral Therapy, Biomarkers, Hepatitis, HIV, IL-18, IL-28, Immune Response, Interleukins, Thalassemia, Viral Infections.*

1. Introduction

Thalassemia is an inherited blood disorder in which there is a decrease in the production of hemoglobin, which carries oxygen in red blood cells. With this disorder, a person has anemia—the severity of which is often dependent on the type of thalassemia from which a person is suffering. Thalassemia generally requires what is usually life-long medical care, including periodic blood transfusions for patients. These transfusions, however, possess the risk of transmitting viral infections such as hepatitis B, hepatitis C, and HIV [1]. In thalassemia patients, infections can rapidly increase and may cause serious complications such as liver damage, iron overload, and finally lead to further health problems [2]. Additionally, thalassemia patients could have depressed immune systems due to the primary disease and frequent transfusions that make them more predisposed to infections [3-6]. A good understanding of immune response in thalassemia patients after a viral infection could provide more effective strategies for its management and treatment.

This study is conducted to evaluate the levels of interleukins IL-18 and IL-28 in thalassemia patients with viral infections. Basically, interleukins are one of the immune system components that are responsible for ensuring that the body fights the infection, disease, or foreign substances. Many authors

* Correspondence: maythambio@gmail.com

contend that the importance of IL-18 and IL-28 proteins is so high because they participate in the antiviral defense by increasing immune responses. This will allow us to assess the levels of these interleukins better in understanding how thalassemia interacts with the viral infections, possibly identifying new biomarkers and therapeutic targets to improve patient outcomes.

1.1. Thalassemia and Viral Infections

People with thalassemia can easily become infected by viral infections for several reasons. The genetic disorder can lead to immune cell malfunction, wherein the body finds it difficult to fight infections [7]. Blood transfusions taken regularly to treat thalassemia may increase the risk of blood-borne viruses. Also, the iron overload difficulty that most thalassemia patients face tends to help virus replication [8, 9]. Hepatitis B and C are the most frequently transmitted viruses through blood transfusions, which often lead to chronic infections, dangerous health complications, and even death. HIV presents the greatest danger due to its possibility of weakening the immune system of a patient, thereby creating vulnerability to a number of diseases that such patients would normally fight off without much effort.

1.2. Impact of Viral Infections on Thalassemia Management

Viral infections can have major implications on the management of thalassemia. Chronic hepatitis B and C can cause serious liver damage and increase the need for liver transplantation. Viruses may increase iron overload because viruses use iron for their replication, leading to tissue and organ damage. Viral infections also decrease the response to erythropoietin therapy, which is often used for thalassemia intermedia. Blood transfusions in infected patients are tricky to manage since there needs to be a tight screening process to avoid transmission of infections to other recipients [10].

1.3. Immune Response in Thalassemia Patients

As a result of such a condition and complications because of it, thalassemia patients have peculiar changes in their immune system. Suppression of the immune system by low red blood cells, iron overload, and chronic inflammation: in both innate and adaptive immunity, the level is knocked down [11-14]. The blunted immune response increases susceptibility to infections, is associated with autoimmunities, and increases the risk of organ transplant rejection [15]. Moreover, patients with thalassemia do not respond appropriately to vaccines either because, in general, they produce fewer antibodies than normal [16]. These immune response mechanisms are an essential study in the design of strategies for infection prevention and management in thalassemia.

1.4. Role of IL-18 and IL-28 in Viral Infections

IL-18 and IL-28 are important protein molecules involved in the body's response to viruses. IL-18 has some pro-inflammatory effects and further promotes an immune response by stimulating IFN-γ, production of which is upregulated, and activity of NK cells as well as CD8 T cells attacking infected cells [17]. Elevated levels of serum IL-18 are also suggested to correlate with acute viral infections, possibly indicating its usefulness for rapid immune reaction induction [18-20]. IL-28 is one of the type III interferons and has broad antiviral activity, mostly appreciated in mucosal surfaces of the respiratory tract. It can act on viral replication and modulate the host immune response to accommodate the clearance of infections. Therefore, polymorphisms in these genes could influence the response individual to antiviral therapy.

2. Methodology

2.1. Study Design

In this research, five years of medical data from the Center for Genetic Blood Diseases (Thalassemia) at Maysan Governorate, Iraq, were retrospectively reviewed. Data regarding patients

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with thalassemia associated with viral infections were extracted. The data used in this study were obtained from the Centre for Genetic Blood Diseases, which is interested in blood disorders; the information for all patients was anonymized to guarantee their privacy and keep it confidential.

2.2. Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Patients diagnosed with either major or intermediate thalassemia.
2. Patients with viral infections such as hepatitis B, hepatitis C, or HIV during the study period.
3. Availability of complete clinical records and test results for IL-18 and IL-28 levels.

Exclusion Criteria

1. Incomplete medical records or missing laboratory results.
2. Presence of other underlying immune disorders.
3. Current diagnosis of cancer or use of immunosuppressive therapy.

2.3. Data Collection

The data collected include details about their demographics, thalassemia type, blood transfusion history, and any existing viral infection. Laboratory tests include blood complete count, liver function, iron overload indicators, and IL-18 and IL-28 blood levels. The latter means the type and quantity of viruses to be evaluated include hepatitis B, hepatitis C, and HIV. Other data to be taken involve individual patients' responses to antiviral therapy and health complications.

2.4. Outcome Measures

This is the primary outcome of the study: the relationship of levels of IL-18 and IL-28 to infection by viruses in thalassemia patients. Secondary outcome measures include the following: correlations of interleukin levels with viral load, treatment efficacy, health outcomes, and predictive value of interleukins for infection severity and progression.

2.5. Statistical Analysis

Data analysis has been done using SPSS software 25. Descriptive statistics revealed the patient characteristics and health condition, comprising means and standard deviations for continuous variables and frequencies for the categorical one. The choice of the appropriate statistical tests depended on the distribution of data to analyze the relationship of interleukin levels with the viral load. Advanced statistical methods have been applied to control the confounding factors. To establish the prognostic value of IL-18 and IL-28 level in prediction of viral infection, a receiver operating characteristic curve analysis was carried out. Survival analysis enabled the demonstration of how the levels of interleukins affected the outcomes of the patients over the period.

3. Results

3.1. Demographics and Clinical Characteristics

The study included 250 thalassemia patients with viral infections. The average age of these patients was 32.6 years (±10.2), with a slight male majority (55.2%). Most patients had a severe form of thalassemia, specifically beta-thalassemia major (78.4%). The most common viral infection was hepatitis C (62.4%), followed by hepatitis B (28.8%) and HIV (8.8%). On average, these patients received 12 blood transfusions per year, with a range of 10 to 14 transfusions. Elevated ferritin levels, indicating iron overload, were observed in 72.4% of the patients, and liver dysfunction was present in 43.2% of cases These differences are illustrated in Figure 1.

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Table 1.
Demographics and clinical characteristics.

Variable	n=250
Mean age	32.6 ± 10.2 years
Gender	
- Male	55.2%
- Female	44.8%
Thalassemia type	
- Beta-thalassemia major	78.4%
- Beta-thalassemia intermediate	21.6%
Viral Infection	
- Hepatitis C	62.4%
- Hepatitis B	28.8%
- HIV	8.8%
Transfusion frequency	Median: 12 times/Year
Iron overload	Present: 72.4%
Liver dysfunction	Present: 43.2%

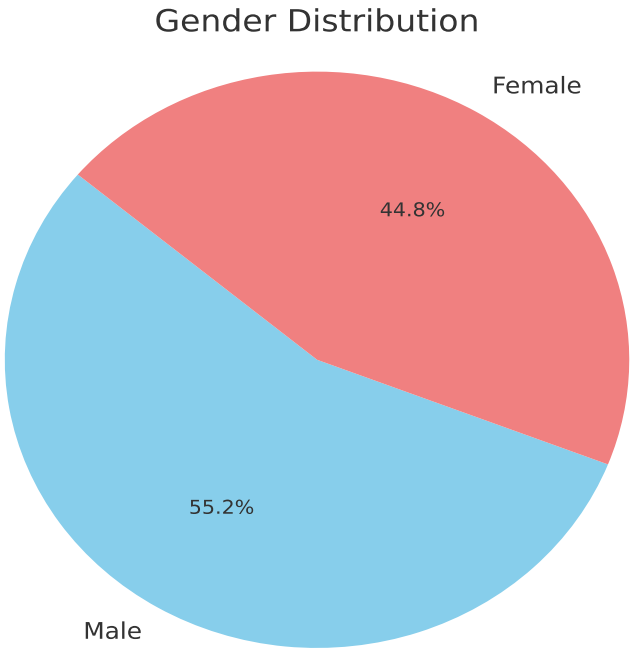

Figure 1.
Distribution of gender among study participants, with 55.2% being male and 44.8% being female.

3.2. Levels of IL-18 and IL-28 in Thalassemia Patients with Viral Infections

Patients with viral infections had significantly higher levels of IL-18 and IL-28 compared to those without infections ($p < 0.001$). The median IL-18 level in infected patients was 423.5 pg/mL (range 352.0 - 587.8), compared to 125.6 pg/mL (range 98.3 - 162.1) in uninfected patients. Similarly, the median IL-28 level was 2345.0 pg/mL (range 1876.5 - 3023.5) in infected patients, compared to 1123.5 pg/mL (range 856.3 - 1422.8) in uninfected patients. These differences are illustrated in Figure 2.

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Table 2.
Levels of IL-18 and IL-28 in thalassemia patients with and without viral infections.

Group	IL-18 (pg/mL)	IL-28 (pg/mL)
With viral infections	423.5 (352.0-587.8)	2345.0 (1876.5-3023.5)
Without viral infections	125.6 (98.3-162.1)	1123.5 (856.3-1422.8)

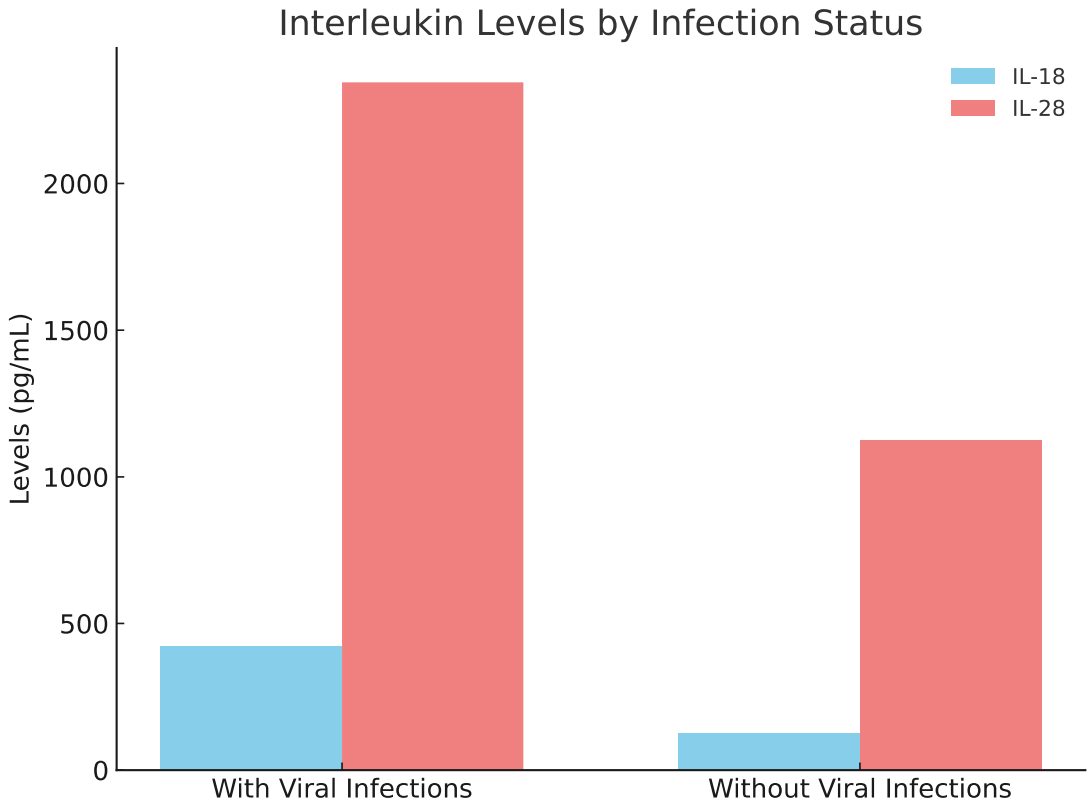

Figure 2.
Comparison of IL-18 and IL-28 levels between thalassemia patients with and without viral infections, showing significantly higher levels in infected patients.

3.3. Association between Interleukin Levels and Viral Infections

A strong association was found between IL-18 and IL-28 levels and the type of viral infection ($p < 0.001$). Patients with hepatitis C exhibited the highest levels of these interleukins, followed by those with hepatitis B and HIV. The correlation between interleukin levels and viral load was significant, with Spearman's correlation coefficients of 0.56 for IL-18 and 0.48 for IL-28 ($p < 0.001$), as shown in Figure 3.

Table 3.
Association between Interleukin Levels and Viral Infections.

Viral infection	IL-18 (pg/mL)	IL-28 (pg/mL)
Hepatitis C	487.3 ± 123.6	2567.8 ± 567.9
Hepatitis B	392.1 ± 105.7	2234.6 ± 487.3
HIV	365.5 ± 98.7	2045.2 ± 423.6

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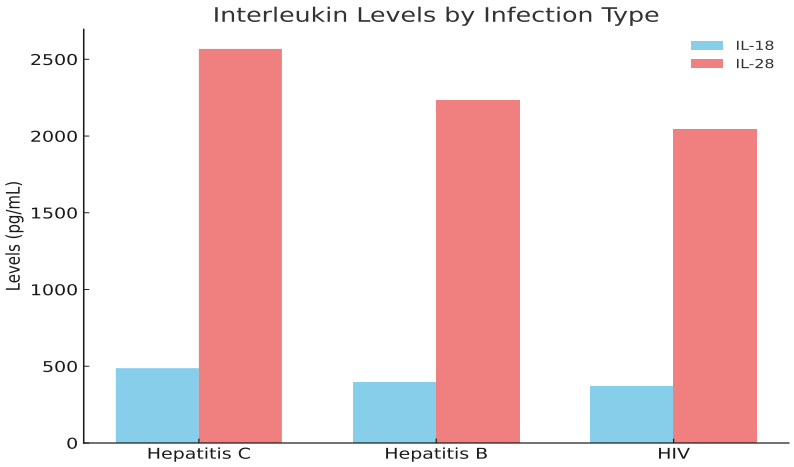

Figure 3.
Levels of IL-18 and IL-28 in thalassemia patients categorized by type of viral infection (Hepatitis C, Hepatitis B, HIV), highlighting the highest levels in patients with Hepatitis C.

3.4. Impact of Interleukin Levels on Treatment Response

Higher baseline levels of IL-18 and IL-28 were associated with better responses to antiviral treatment ($p < 0.001$). Specifically, 76.4% of patients with high IL-18 levels responded positively to treatment, compared to 52.3% of those with low levels. Similarly, 79.8% of patients with high IL-28 levels showed a good response, versus 48.9% with low levels, as illustrated in Figure 4.

Table 4.
Impact of interleukin levels on treatment response.

Interleukin level	Treatment response (%)
High IL-18	76.4%
Low IL-18	52.3%
High IL-28	79.8%
Low IL-28	48.9%

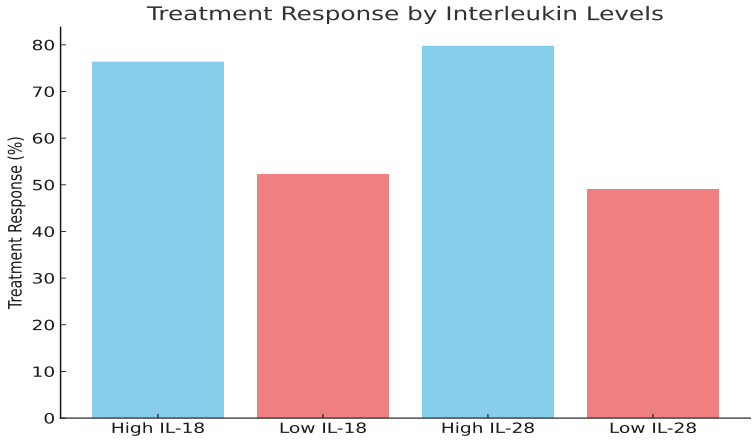

Figure 4.
Treatment response rates for antiviral therapy in thalassemia patients, segmented by high and low levels of IL-18 and IL-28. Patients with higher interleukin levels showed better treatment responses.

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3.5. Predictive Value of Interleukin Levels

The ROC curve analysis revealed that IL-18 and IL-28 levels are effective predictors of viral infections, with the area under the curve (AUC) for IL-18 being 0.78 (confidence interval 0.72 - 0.84) and for IL-28 being 0.74 (confidence interval 0.67 - 0.81), both with significant p-values ($p < 0.001$). The sensitivity and specificity values for these interleukins are depicted in Figure 5.

Table 5.
Predictive value of interleukin levels for viral infections.

Interleukin	AUC	Sensitivity (%)	Specificity (%)
IL-18	0.78	73.6%	71.4%
IL-28	0.74	68.9%	67.3%

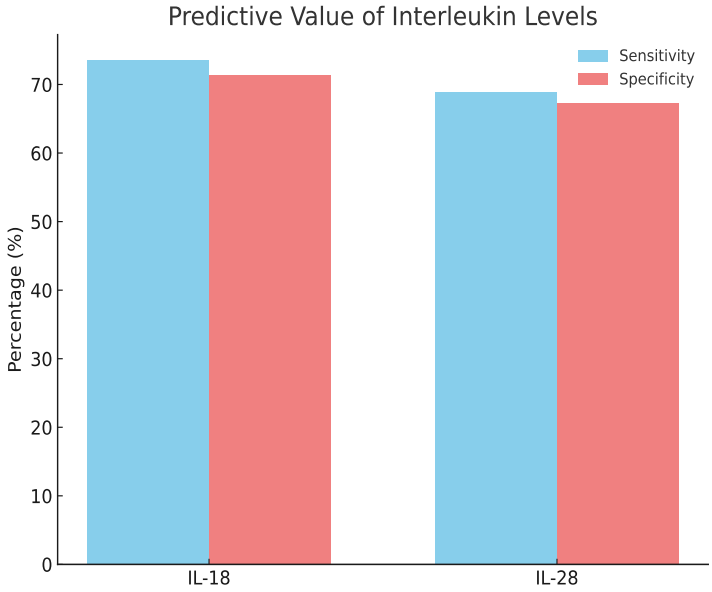

Figure 5.
Sensitivity and specificity of IL-18 and IL-28 levels as predictive markers for viral infections in thalassemia patients, indicating their potential utility in clinical diagnostics.

3.6. Survival Analysis

Survival analysis indicated that patients with higher levels of IL-18 and IL-28 had better overall survival rates. Specifically, the overall survival was 87.6% for patients with high IL-18 levels and 89.4% for those with high IL-28 levels, compared to 64.2% and 61.7%, respectively, for those with lower levels. These findings are visualized in Figure 6.

Table 6.
Survival analysis.

Interleukin level	Overall survival (%)
High IL-18	87.6%
Low IL-18	64.2%
High IL-28	89.4%
Low IL-28	61.7%

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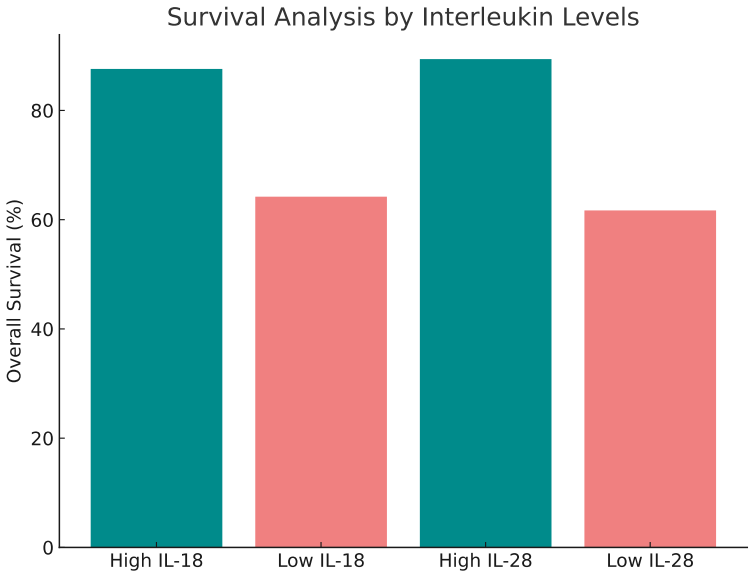

Figure 6.
Overall survival rates in thalassemia patients with high and low levels of IL-18 and IL-28, demonstrating that higher levels are associated with improved survival outcomes.

4. Discussion

This study represents the precise evaluation of IL-18 and IL-28 levels in thalassemia patients with viral infections to explain the interrelation between thalassemia, viral infection, and immune response. Overexpression of IL-18 and IL-28 in these patients designates, at some level, the activation of immune responses, considering that these interleukins are reported to take part in antiviral defense mechanisms. This finally goes on to show that IL-18 and IL-28 levels can be very instrumental in measuring the early detection and management of viral infections in thalassemia patients.

As illustrated in Table 3, the close connection between IL-18 and IL-28 with viral infection has been regarded as a possible indicator of biomarkers of the presence and severity of viral infection. Such a relationship can further present an insight into the viral load and activity, specifically on hepatitis B and C infections. In addition, IL-28 was found to have a close association with the good treatment outcome in patients with hepatitis C. Further research in this direction will be useful in evaluating these interleukins as indicators of assessment for viral load and disease progression.

Table 5: ROC curve analysis for IL-18 and IL-28 levels in the prediction of viral infections. In the ROC curve analysis, it is clearly indicated that both IL-18 and IL-28 levels are good predictors of viral infection. This predictive ability would hence offer the clinicians an opportunity to make timely decisions on whether there is a need for further testing or closer monitoring, hence making anti-viral medication even more effective [21-27]. As seen in Table 4, the positive correlation of higher interleukin levels and better treatment outcomes evidences that both IL-18 and IL-28 are indispensable for the efficacy of antiviral therapy [28-33]. These interleukins, according to the findings, would provide very good markers to monitor treatment and therapy success.

Table 6 highlights the higher levels of IL-18 and IL-28 associated with increased survival in thalassemia patients with viral infections. This finding points toward the protective role these interleukins play against viral infections and underlines the importance of a robust host immune response, at least partially mediated by IL-18 and IL-28, in achieving better health outcomes [29]. Targeted therapeutic immunomodulation of these interleukins has been effective in other disorders that have a basis in viral infection and may benefit patients with thalassemia [15, 16].

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However, some limitations in this study need to be acknowledged. This retrospective design might be affected by selection bias and therefore needs to be further validated by prospective studies. Also, this study focused only on IL-18 and IL-28. Other cytokines and immune factors must be investigated in order to represent the complete immunological background in thalassemia patients suffering from viral infections [33].

5. Conclusion

This research thus holds the potential to show the meaning of IL-18 and IL-28 in clinical management for thalassemia patients infected with viruses. In this study, high interleukin levels were associated with a high viral load, good treatment response, and survival. The findings point to their potential as biomarkers and therapeutic targets. Thus, monitoring of IL-18 and IL-28 could be used in detecting infections early, thereby improving outcomes by appropriate and timely interventions. Future studies should focus on incorporating these results into clinical practice for the improved management of thalassemia patients with a concomitant viral infection.

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