ORIGINAL ARTICLE

Assessment of Antibody Response to SARS-CoV-2 Vaccination in Thai Thalassemic Patients: A Prospective Study

Pornpim Tuntibundit, MD[1], Ronnarit Boonyarat, MD[2], Thidarat Pimlor, BS[2], Chinadol Wanitpongpun, MD[1], Theerin Lanamtieng, MD[1], Pisa Phiphitaporn, MD[1], Nattiya Teawtrakul, MD, PhD[1]

[1] Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

[2] Blood transfusion center, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

Background: The COVID-19 pandemic has led to significant morbidity and mortality worldwide, especially among high-risk groups like thalassemic patients. Vaccination is pivotal in preventing severe disease, yet limited data exists regarding the immune response post-SARS-CoV-2 vaccination in this population.

Objective: To evaluate the rate of antibody response after two doses of the SARS-CoV-2 vaccine and to identify factors influencing immunogenicity in patients with thalassemia.

Materials and Methods: A prospective study was conducted among adult thalassemic patients at Srinagarind Hospital in Thailand. Clinical risk factors, including iron overload, thalassemic genotype, use of iron chelators, and history of splenectomy, were collected and analyzed. Serum samples obtained 14 to 42 days post-second vaccine dose were tested for anti-spike IgG (IgGsp) antibodies.

Results: Out of the 70 patients studied, 65 (92.9%) exhibited a positive IgGsp antibody response. No significant clinical risk factors affecting the immune response were identified. However, there was a tendency for a history of splenectomy, the beta thalassemia group, and high serum ferritin levels (greater than 2,500 ng/mL) to correlate with a decreased antibody response (Odds ratio [OR] = 0.3, p=0.22; OR=0.5, p=0.62; and OR=0.6, p=0.62, respectively).

Conclusion: The administration of two doses of the SARS-CoV-2 vaccine resulted in a 92.9% antibody response rate in thalassemic patients. Although no significant factors were found to diminish the antibody response, a history of splenectomy, beta thalassemia genotype, and high serum ferritin levels may potentially be associated with lower IgG response levels, warranting further investigation.

Keywords: SARS-CoV2 vaccine; Antibody response; Clinical risk factors; Thalassemia disease

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Thalassemia is acknowledged as the most prevalent genetic disorder worldwide, with a notably higher incidence in populations residing in the Mediterranean region, Africa, and Southeast Asia, including Thailand[1]. The disease is characterized by a pathological mechanism involving an imbalance in the globin chain, caused by impaired synthesis of the globin chain. This results in ineffective erythropoiesis, a crucial contributor to the development of chronic anemia.

In patients with thalassemia, infections significantly contribute to increased morbidity and mortality[2,3]. This increased vulnerability to infections in these patients is due to various mechanisms, including compromised chemotaxis and phagocytosis in macrophages and neutrophils, changes in T-lymphocyte subsets, reduced numbers and functionality of natural killer cells, increased levels and activity of B lymphocytes, hindered immunoglobulin secretion, and weakened complement system function[4-8]. Additionally, in beta thalassemia, the elevated expression of heme oxygenase 1 leads to decreased production of IFN γ, affecting immune cell counts and inducing T cell apoptosis[9].

The coronavirus disease 2019 (COVID-19) pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), presents with a spectrum of clinical severities, ranging from mild to critical. Patients with co-morbidities, including thalassemia, tend to experience higher mortality rates compared to the

Correspondence to:

Teawtrakul N.

Department of Internal Medicine, Faculty of Medicine, Khon Kaen University, Mitraphab Road, Maung, Khon Kaen 40000, Thailand.

Phone: +66-43-363664, Fax: +66-43-204430

Email: nattiya@kku.ac.th

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general population[10]. Prior research has indicated that individuals with thalassemia are at increased risk of severe complications from COVID-19[11,12]. Recent findings reveal that although the prevalence of COVID-19 among those with hemoglobinopathies is similar to the general population, the mortality rate from SARS-CoV-2 in this demographic is five times higher than in age-matched controls[13]. A 2023 study updates that patients with transfusion-dependent thalassemia (TDT) generally experience mild or asymptomatic COVID-19 and develop an IgG antibody response comparable to that of controls. However, this serological response diminishes over three to six months, underscoring the importance of vaccination for sustained protection in thalassemic patients[14].

Although numerous studies have explored the safety and efficacy of anti-SARS-CoV-2 vaccines in patients with hematological malignancies, there is a relative paucity of data on their impact on non-neoplastic blood disorders, particularly thalassemia. Recent research indicates that the SARS-CoV-2 vaccine is safe for patients with TDT; however, its efficacy in this specific patient population has not been thoroughly addressed[15]. Past research on vaccinations in thalassemia patients has indicated a diminished immune response to several vaccines, including those for tetanus[16], hepatitis B[17], and pneumococcal infection[18]. Clinical risk factors identified as contributing to a low immune response include iron overload[16] and splenectomy[18].

In the present study study, we aim to investigate the rate of antibody response and the level of anti-spike IgG antibodies following a full two-dose vaccination in thalassemic patients. Additionally, we aim to identify clinical risk factors associated with vaccine immunogenicity.

Materials and Methods

Participants

A prospective study was conducted on adult patients with thalassemia at the Hematology Clinic of Srinagarind Hospital, Khon Kaen, Thailand, from January 2022 to August 2022. Inclusion criteria included individuals aged 18 years or older diagnosed with thalassemia of any genotype, who had completed the full course of SARS-CoV-2 vaccination and were within the 14 to 42 days interval following their second vaccine dose. Exclusion criteria consisted of individuals with a documented history of prior COVID-19 infection.

Operational definition and instrument

Anti-Spike IgG antibodies

We used the Elecsys Anti-SARS-CoV-2 S assay, designed for the qualitative and semi-quantitative identification of antibodies to SARS-CoV-2 in human serum and plasma. This assay was conducted using the Cobas e411 analyzers (Roche Diagnostics International Ltd). This electrochemiluminescence immunoassay employs a double-antigen sandwich assay format, utilizing a recombinant protein representing the receptor-binding domain (RBD) of the spike antigen. The assay specifically targets antibodies to the SARS-CoV-2 spike protein RBD. The manufacturer has established cut-off values: <0.8 U/ml, which indicates negativity, and ≥0.8 U/ml, which indicates positivity for anti-SARS-CoV-2 S.

Procedure

All participants underwent a comprehensive assessment of their medical history and clinical risk factors associated with thalassemia. This assessment included parameters such as age, gender, co-existing medical conditions, transfusion frequency, splenectomy history, thalassemia genotype, hemoglobin and ferritin levels, details of iron chelation therapy, and information about the administered SARS-CoV-2 vaccine. Blood samples were collected from consenting thalassemia patients during their follow-up visits to the hematology clinic, and the residual blood remaining after the cross-matching procedure was used for analysis.

Ethical approval, referencing the Helsinki Declaration, was granted by the ethics committee of the Faculty of Medicine, Khon Kaen University, with the reference number HE641657.

Statistical analysis

The baseline clinical characteristics were presented as medians with an interquartile range (IQR) for continuous variables. Categorical variables were expressed as numbers and percentages. Crude odds ratios were calculated using univariate logistic regression to determine associations, and the strength of these associations was indicated by reporting odds ratios along with their respective 95% confidence intervals. Statistical significance was considered at a p-value less than 0.05. Data analysis was performed using STATA version 10.0 (StataCorp, College Station, Texas).

Results

Seventy patients diagnosed with thalassemia were enrolled in the study. They had received two doses of the SARS-CoV-2 Vaccine between January 2022 and August 2022. The demographic and clinical characteristics of these patients are summarized in Table 1.

The median age of the participants is 29 years, with an interquartile range (IQR) of 24 to 44 years. Among the enrolled patients, all 42 individuals were female, and approximately half of them had the beta-thalassemia/HbE genotype. The median pre-transfusion hemoglobin level measured at 7.7 g/dL (IQR; 7, 8.2). The median serum ferritin concentration was 1,263 ng/dL. Thirteen patients

Table 1. Baseline data of the participants

Variables	All participants (n=70)	Immune responder (n=65)	Non-immune responder (n=5)
Age (years), med (IQR)	29 (24, 44)	29 (23, 44)	32 (31, 39)
Gender; n (%)			
Male	28 (40)	25 (38.5)	3 (60)
Female	42 (60)	40 (61.5)	2 (40)
Splenectomy; n (%)			
Yes	13 (18.6)	11 (16.9)	2 (40)
No	57 (81.4)	54 (83.1)	3 (60)
Types of thalassemia; n (%)			
Beta-thalassemia/Hb E	49 (70)	45 (69.2)	4 (80)
Alpha-thalassemia	21 (30)	20 (30.8)	1 (20)
Red blood cell transfusion interval; n (%)			
3 weeks	3 (4.3)	3 (4.6)	0 (0)
4 weeks	44 (62.9)	43 (66.2)	1 (20)
5 weeks	13 (18.6)	11 (16.9)	2 (40)
6 weeks	5 (7.1)	3 (4.6)	2 (40)
8 weeks	5 (7.1)	5 (7.7)	0 (0)
Types of vaccines; n (%)			
Two doses of inactivated virus vaccine (1)	32 (45.7)	28 (43.1)	4 (80)
Inactivated virus vaccine and ChAdOx1 n CoV-19 vaccine (2)	16 (22.9)	16 (24.6)	0 (0)
Two doses of ChAdOx1 n CoV19 vaccine (3)	8 (11.4)	8 (12.3)	0 (0)
Two doses of mRNA vaccine (4+5)	8 (11.4)	8 (12.3)	0 (0)
Inactivated virus vaccine and mRNA vaccine	3 (4.3) 6,8	2 (3.1)	1 (20)
ChAdOx1 n CoV-19 vaccine and mRNA vaccine (7)	2 (2.9)	2 (3.1)	0 (0)
mRNA vaccine and ChAdOx1 n CoV-19 vaccine (9)	1 (1.4)	1 (1.5)	0 (0)
Serological response; n (%)	65 (92.9)	65 (100)	0 (0)
Hemoglobin (g/dL); med, IQR	7.7 (7.0, 8.2)	7.7 (7.0, 8.2)	7.0 (6.6, 7.4)
Ferritin (ng/mL); med, IQR	1,262 (783, 3,186)	1,235 (792, 3,186)	1,369 (371, 3,117)
Antibody titer (U/mL); med, IQR	183 (18.6, 250)	199 (29, 250)	0.4 (0.4, 0.4)

IQR=Interquartile range

(18.6%) had previously undergone splenectomy.

Most patients received red blood cell transfusions at 4-week intervals (44 patients, 62.9%), followed by 3-week intervals (13 patients, 18.6%). Blood tests to assess the immune response to the SARS-CoV-2 vaccine were performed before the next transfusion, and none of the patients were tested within 2 weeks of receiving a blood transfusion.

The majority of patients received two doses of the inactivated virus vaccine (32 patients, 45.7%), followed by a combination of the inactivated virus vaccine for the first dose and the ChAdOx1 nCoV-19 vaccine for the second dose (16 patients, 22.9%), as indicated in Table 1. After receiving two doses of SARS-CoV-2 vaccines, a serological response (IgG Antibody titer ≥0.8 U/mL) was observed in 65 out of 70 vaccinated patients (92.9%), as shown in Table 1. The median antibody titer was 183 U/mL with an IQR of 18.6 to 250 U/mL.

Table 2 presents the immune responses observed in thalassemia patients following various vaccination schedules. It appears that most combinations of vaccines are effective in triggering an immune response. Notably, schedules combining inactivated virus vaccines with either another inactivated virus vaccine or a different type of vaccine tend to show a slightly lower immune response. However, the small number of patients in these categories makes it difficult to draw definitive conclusions about these differences.

Factors associated with immune response

The univariate analysis of clinical risk factors influencing the immune response in individuals with thalassemia subsequent to SARS-CoV-2 vaccination is presented in Table 3. No clinical risk factors exhibited statistically significant associations with the immune response. However, three factors, including; 1) history of

Table 2. The immune response in individuals with thalassemia by vaccination types

Vaccination types	Antibody titer (U/mL); med, IQR	Serological response; n (%)
Two doses of inactivated virus vaccine (n=32)	56.7 (6.5, 250)	28 (87.5)
Inactivated virus vaccine and ChAdOx1 n CoV-19 vaccine, (n=16)	250 (221.3, 250)	16 (100)
Two doses of ChAdOx1 n CoV19 vaccine, (n=8)	187 (106.2, 250)	8 (100)
Two doses of mRNA vaccine, (n=8)	109.8 (12.2, 227.9)	8 (100)
Inactivated virus vaccine and mRNA vaccine, (n=3)	250 (0.4, 250)	2 (66.6)
ChAdOx1 n CoV-19 vaccine and mRNA vaccine, (n =2)	8.4, 250	2 (100)
mRNA vaccine and ChAdOx1 n CoV-19 vaccine, (n=1)	21.3	1 (100)

Table 3. Factors associated with the immune response in individuals with thalassemia following two doses of SARS-CoV-2 vaccination

Variables	OR	95% CI	p-value
Age (every increase 1 year of age)	0.9	0.9 to 1.0	0.52
Female sex	2.4	0.4 to 15.4	0.35
Splenectomy	0.3	0.05 to 2.0	0.22
Hb level (every increase level 1 g/dl)	1.5	0.5 to 4.3	0.37
Serum ferritin >2,500 ng/mL	0.6	0.2 to 4.0	0.62
Beta thalassemia group	0.5	0.06 to 5.3	0.62

OR=odds ratio; 95% CI=95% confidence interval

splenectomy (odds ratio [OR] = 0.3, 95% CI 0.05 to 2.0, p=0.22), 2) beta-thalassemia genotype (OR=0.5, 95% CI 0.06 to 5.3, p=0.62), and 3) elevated serum ferritin levels exceeding 2,500 ng/mL (OR=0.6, 95% CI 0.1 to 4.0, p=0.62) tended to be associated with a lower level of IgG response following SARS-CoV-2 vaccination.

Figure 1 depicts the correlation between the level of SARS-CoV-2 anti-spike IgG and the history of splenectomy. The immune response shows no statistically significant difference between the splenectomy and non-splenectomy groups (p=0.22). However, a trend suggests a negative correlation between the immune response and a history of splenectomy.

Figure 2 presents a box graph depicting the level of SARS-CoV-2 anti-spike IgG by genotypes. Patients with beta-thalassemia exhibited a slightly lower immune response compared to those with alpha-thalassemia, although the difference was not statistically significant.

Figure 3 displays a box graph of the level of SARS-CoV-2 anti-spike IgG based on serum ferritin levels. Patients with severe iron overload (serum ferritin exceeding 2,500 ng/mL) are more likely to have a lower immune response than the other group.

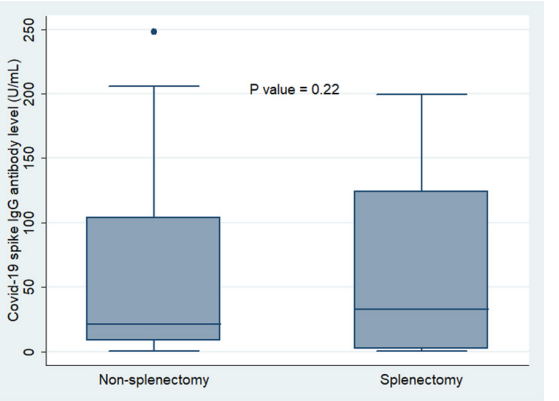

Figure 1. The level of SARS-CoV-2 anti-spike IgG and the history of splenectomy.

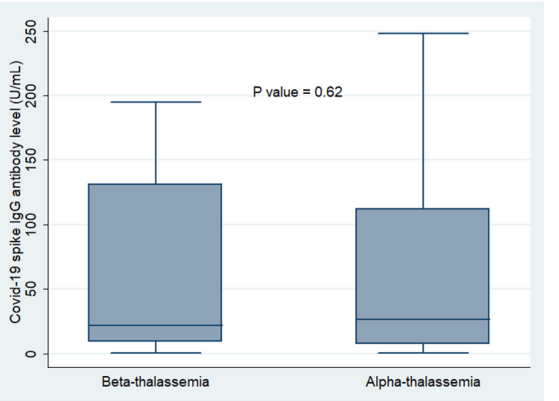

Figure 2. The level of SARS-CoV-2 anti-spike IgG by genotypes.

Discussion

COVID-19 infection manifests with a wide spectrum of clinical severity, ranging from mild to severe forms. Morbidity and mortality rates are particularly high among patients with multiple comorbidities. Previous studies have consistently shown an elevated mortality risk among COVID-19-infected individuals with thalassemia. It is well-established that COVID-19 vaccines can reduce the mortality associated with COVID-19 infection.

In the present study, the authors found that the majority of patients with thalassemia produced an immune response (92.9%) following the administration of two doses of the SARS-CoV-2 vaccine, a rate comparable to that of healthy individuals. These results align with those from a previous study on immune responses in patients with hemoglobinopathies, which reported a similar response rate

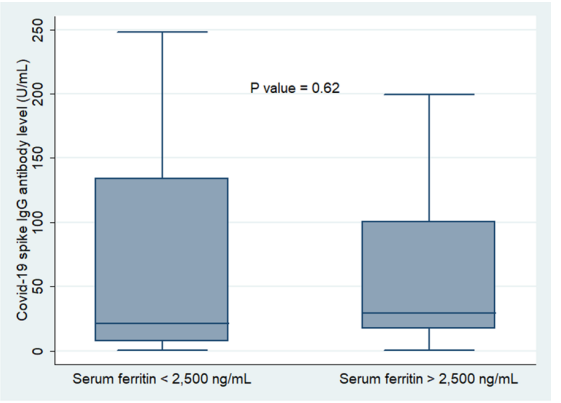

Figure 3. The correlation between the level of SARS-CoV-2 anti-spike IgG and serum ferritin levels.

ranging from 84.5% to 98.5%[19,20]. However, it is important to note that the immune response in this cohort is higher than that observed in a study by Karimi et al. involving Iranian patients with thalassemia, where only 55.6% of the patients exhibited an immune response[21].

It's important to recognize that the differences in reported rates of immune response across studies may be due to a variety of factors. A key factor is the variation in methods used for measuring antibody responses. Our research focused on assessing SARS-CoV-2 anti-spike IgG antibodies, whereas the studies mentioned earlier evaluated neutralizing antibodies (NAbs)[19,21]. Additionally, the types of vaccines administered also played a role in these discrepancies. In our study, we included both homologous and heterologous SARS-CoV-2 vaccines, reflecting the diverse vaccination approaches in Thailand. This differs from the specific focus of Karimi et al.[21], who reported antibody responses solely after the administration of inactivated virus vaccines. Conversely, the studies by Radhwi et al.[19], and Zucano et al.[20] observed antibody responses following mRNA and ChAdOx1 nCoV-19 vaccines.

Existing literature has demonstrated a diminished immune response to vaccinations in patients suffering from thalassemia. In their study, Abdolreza et al. observed that a significant proportion (66.2%) of patients with thalassemia exhibited a reduced response to the pneumococcal vaccine. This hyporesponsiveness was particularly notable in patients who had undergone splenectomy, highlighting splenectomy as a contributing factor to this reduced vaccine efficacy[18]. Similarly, Abdolreza et al. reported that the mean levels of anti-tetanus antibodies in patients with thalassemia were notably lower when compared to those in healthy individuals[16]. The present study also noted a trend of reduced immune response to the COVID-19 vaccine in patients who had undergone splenectomy surgery. However, due to the limited size of the sample group, this observation did not reach statistical significance.

Iron overload is a recognized risk factor for infection in patients with thalassemia[22]. Our study indicates a correlation between high serum ferritin levels and a diminished immune response to SARS-CoV-2 vaccination, a trend that mirrors findings from Karimi et al., who observed that serum ferritin levels exceeding 2,500 ng/mL may impair immune responsiveness[21]. However, these observations did not reach statistical significance, highlighting the need for further research in this patient group.

As iron accumulation progresses, the ability of serum transferrin—the principal protein for iron transport—to bind iron may be surpassed. This excess, non-transferrin-bound iron in the plasma fosters the production of free hydroxyl radicals, which are known to cause oxygen-related damage. Such damage can be more severe during infections[23]. Additionally, high ferritin levels correlate with a reduction in the number of cluster of differentiation 4 (CD4) T lymphocytes, crucial to cellular immunity. This depletion may lead to immune deficiencies in cases of significant iron overload[24].

An intriguing aspect of our investigation is the observed tendency for patients with the beta-thalassemia genotype to exhibit a lower immune response compared to those with alpha-thalassemia. This observation may be connected to an increase in heme oxygenase 1 expression, which could result in decreased production of IFN-γ. This, in turn, might affect immune cell counts and induce T cell apoptosis, thereby impacting the overall immune response[9].

The present study had several limitations. Firstly, the small sample size necessitates a larger cohort to enhance the generalizability of our findings. Secondly, our study did not assess the vaccine's efficacy in preventing SARS-CoV-2 infection or clinically significant COVID-19. Additionally, we eagerly await results from booster doses (third and fourth) for a more comprehensive understanding. Lastly, our evaluation solely focused on the serological response of anti-spike IgG antibodies, omitting an analysis of neutralizing IgG antibodies against the nucleocapsid and receptor-binding domain. Clear and definitive associations between these antibodies and protection against the virus have yet to be unequivocally established.

Conclusion

The administration of two doses of the SARS-CoV-2 vaccine led to a substantial 92.9% rate of antibody response among thalassemic patients. Although no significant factors were identified that notably decreased the antibody response, the history of splenectomy, presence of the beta thalassemia genotype, and elevated serum ferritin levels displayed potential associations with lower IgG response levels. These associations warrant further investigation in

this patient population.

What is already known on this topic?

Patients with thalassemia represent a vulnerable group that is at an increased risk of contracting high-risk COVID-19 infections with a high mortality rate. However, the assessment of the immune response and factors associated with the immune response to COVID-19 vaccination in Thai patients with thalassemia remains limited.

What this study adds?

This study revealed a high rate of antibody response following two doses of the SARS-CoV-2 vaccine among thalassemic patients. The history of splenectomy, the presence of the beta thalassemia genotype, and elevated serum ferritin levels exhibited potential associations with reduced IgG response levels in this patient population.

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Conflicts of interest

The authors declare no conflict of interest.

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