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Impact of COVID-19 Pandemic on Pre-Transfusion Hemoglobin Level and Frequency of Transfusion in Transfusion-Dependent Thalassemia Patients in Indonesia

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Abstract: Transfusion-dependent thalassemia is the most severe form of thalassemia; patients require regular blood transfusions to maintain their hemoglobin level. The COVID-19 pandemic has disrupted the routine measures for controlling chronic diseases like thalassemia. This study aims to measure the difference in pre-transfusion hemoglobin levels and the frequency of transfusions before and during pandemic. This retrospective cross-sectional study utilized medical record data of 101 transfusion-dependent thalassemia (TDT) patients treated in Cipto Mangunkusumo Hospital (CMH) from 2019–2021. The dependent variables of this study were pre-transfusion hemoglobin level and transfusion attendance. The pre-pandemic phase was defined as 30 March 2019 to 29 March 2020, whereas the during-pandemic phase was from 30 March 2020 to 29 March 2021. Up to 59.4% of subjects had suboptimal Hb levels of <9.0 g/dL, even before the pandemic, and this increased to 71.3% during the pandemic. The mean pre-transfusion hemoglobin level before the pandemic was 8.71 g/dL, and this decreased to 8.46 g/dL (p value < 0.001). Transfusion attendance before and during the pandemic showed no significant difference (p-value = 0.990). Our study shows poorer control of pre-transfusion Hb levels during the pandemic. This puts patients at higher risk of developing many long-term complications.

Keywords: thalassemia; transfusion-dependent thalassemia; COVID-19; pre-transfusion hemoglobin level; transfusion

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1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic was declared a global public health emergency on 30 January 2020 by the World Health Organization (WHO). Worldwide efforts to stop the transmission of the disease were applied, and the WHO declared COVID-19 a global pandemic on 11 March 2020 [1]. Since the start of pandemic, the Indonesian government has applied nationwide limitations on the use of public transport as well as access to public areas and facilities as an effort to limit local transmission of the disease [2].

Thalassemia is one of the most prevalent hematological genetic diseases in Indonesia. The number of thalassemia patients in Indonesia was around 10,500 in 2019 [3]. Transfusion-dependent beta-thalassemia (TDT) is a severe form of the disease. Most TDT patients suffer severe anemia and require regular blood transfusions. Repeated blood transfusions put TDT patients at risk of developing adverse effects related to blood transfusions and iron-overload complications. In addition, there are multiple complications that can arise from

iron-chelator therapy (ICT) itself [4]. On average, TDT patients spend up to 4–5 days per month in the hospital receiving blood transfusions.

Since the start of COVID-19, with the reinforcement from the government to limit mobility and access to public spaces, the number of blood donations has also significantly decreased. Thus, TDT patients are forced to find blood donors on their own; this makes the process of regular blood transfusion very difficult. This challenge has also been experienced by other countries, such as Pakistan [5]. This makes it difficult for TDT patients to receive blood transfusions. As a result, TDT patients do not have optimal hemoglobin levels, putting them at higher risk of developing severe anemia, extramedullary hematopoiesis, and subsequent complications. This is just one of the challenges TDT patients have had to endure during the pandemic. This study aims to measure the difference in pre-transfusion hemoglobin levels and frequency of transfusion before and during the pandemic.

2. Materials and Methods

This is a single-center retrospective cross-sectional study, with the utilization of medical records to obtain the data. The research was conducted at Cipto Mangunkusumo Hospital (CMH), Jakarta, Indonesia, from April 2022 to June 2022. Transfusion-dependent thalassemia patients that were regularly treated in CMH from 2019–2021 that were older than 2 years old were eligible for this study. Thalassemia patients that were not transfusion dependent, younger than 2 years old, or had incomplete medical records from 2019–2021 were excluded from analysis.

The dependent variables of this study were records of pre-transfusion hemoglobin levels and transfusion attendance of subjects. The pre-pandemic phase was recorded from 30 March 2019 to 29 March 2020, while the pandemic phase was from 30 March 2020 to 29 March 2021. Study population baseline data such as age, gender, and occupation were also recorded. The minimal sample size required for this study was 96 subjects, with an estimated 10% dropout included. The sampling method used in this study was consecutive sampling.

Descriptive analysis was used to define study participants' baseline characteristics. The paired T-test was used to analyze the transfusion attendance frequency pre- and post-pandemic. Pre-transfusion Hb values were analyzed using the Wilcoxon test (Figure 1).

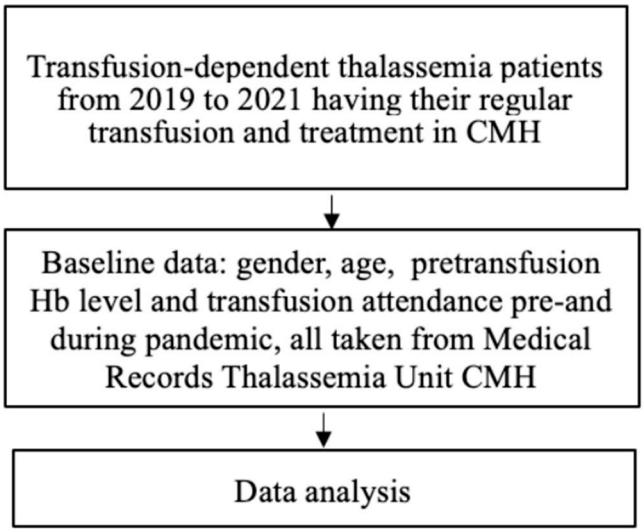

Figure 1. Research procedure.

3. Results

3.1. Population Characteristics

A total of 101 subjects fulfilled the inclusion criteria and were eligible for analysis. The percentage of males and females in our study was similar (50.5% and 49.5%, respectively).

The percentage of adult patients and pediatric patients was also similar (53.5% vs. 46.5%). Most of our subjects were either students or unemployed (73.3%); 13.8% were employees of private/public companies, 8.9% were entrepreneurs, 2.0% were housewives, and 2.0% were freelancers. It is worth noting that only 26 out of 54 adult patients (48.1%) had a job (Table 1).

Table 1. Study population characteristics.

Characteristic	*n* = 101	%
Gender		
Male	51	50.5
Female	50	49.5
Age group (years old)		
2–18	47	46.5
>18	54	53.5
Occupation		
Student/Unemployed	74	73.3
Employee	14	13.8
Entrepreneur	9	8.9
Housewife	2	2.0
Freelancer	2	2.0
Diagnosis		
β-Thalassemia	84	83.2
β-HbE Thalassemia	17	16.8
Transfusion interval		
Every 2 weeks	50	49.5
Every 3 weeks	34	33.7
Every 4 weeks	17	16.8

The majority of our subjects were beta(β)—thalassemia major patients (83.2%), while 16.8% were beta-HbE thalassemia patients. Almost half of the subjects came every 2 weeks for transfusion (49.5%), 33.7% of subjects came every 3 weeks, and 16.8% came every 4 weeks (Table 1).

3.2. Changes in Pre-Transfusion Hb Levels before and during COVID-19 Pandemic

We recorded pre-transfusion Hb levels of 101 patients pre-pandemic and during the pandemic. The number of patients who had an optimal Hb level of above 9.0 g/dL was only 41 (40.6%) before the pandemic, and it decreased to 29 (28.7%) during the pandemic. The number of patients who had an average pre-transfusion Hb level of below 9.0 g/dL was high even before the pandemic (59.4%), and it increased to 71.3% during the pandemic. In addition, up to 69 patients (68.3%) were found to have decreased Hb levels during the pandemic, while 29 (28.7%) patients had increased average Hb levels during the pandemic (Table 2). Up to 5 patients (5%) experienced an increased in average Hb level from being classified as suboptimal prior to pandemic, progressing to optimal during the pandemic. When analyzed further, there was a significant reduction of pre-transfusion hemoglobin levels from before the pandemic as compared to during the pandemic ($p \leq 0.001$) (Table 3).

Table 2. Pre-transfusion Hb level of TDT patients before and during pandemic.

Hb Level	Optimal (%)	Suboptimal (%)
Pre-pandemic	41 (40.6)	60 (59.4)
During pandemic	29 (28.7)	72 (71.3)
Average Hb level change	*n* = 101	%
Decreased average Hb level	69	68.3
No change in average Hb level	3	3.0
Increased average Hb level	29	28.7

Table 3. Analysis of change of pre-transfusion hemoglobin level before and during pandemic.

Hb Level	Mean (Min–Max) (g/dL)	*p*-Value
Pre-pandemic	8.70 (5.94–11.08)	<0.001
Post-pandemic	8.45 (3.48–10.18)	

3.3. Transfusion Frequency during COVID-19 Pandemic

Out of the 101 eligible for analysis, three were ruled out because of incomplete data. Thus, we counted the transfusion attendance of 98 TDT patients pre-pandemic (30 March 2019–29 March 2020) and during the pandemic (30 March 2020–29 March 2021). The number of patients who had decreased transfusion attendance frequency during the pandemic was 47 (48%), while 37 patients (37.8%) had increased transfusion attendance frequency during the pandemic (Table 4). When analyzed further using paired *t*-tests, the difference between the frequency of blood transfusions pre- and post-pandemic was not significant (p value = 0.990) (Table 5).

Table 4. Change of transfusion attendance during pandemic.

Transfusion Attendance	*n* = 98	%
Increasing during pandemic	37	37.8
Decreasing during pandemic	47	48.0
No change	14	14.2

Table 5. Analysis of change of transfusion attendance before and during pandemic.

	Mean	Standard Deviation	*p*-Value
Frequency pre-pandemic	18.61	4.720	0.990
Frequency during pandemic	18.60	8.287	

4. Discussion

4.1. Population Characteristics

Out of the 101 subjects eligible for analysis, the number of male and female participants was similar. The ratio of pediatric to adult patients was 0.87. The average and median age of our subjects was 18 years old. Most of our subjects were still students or unemployed (73.3%), and only 48.1% of our adult subjects had a job. This is similar to previous studies in Indonesia and Lebanon. Employment status of thalassemia patients remains one of the determinants of health-related quality of life, because regular hospital visits and the presence of other comorbidities or complications might limit employment [6,7]. A study in Malaysia reported that 77% had experienced difficulties in their job and 57% experienced major discrimination because of thalassemia [8]. In addition, the COVID-19 pandemic significantly increases the unemployment rate, as many businesses experienced bankruptcy. Economic growth slowed down, as the unemployment rate reached up to 7.07% in 2021, which resulted in 9.77 million Indonesians being unemployed [9].

Up to 83.2% of our subjects were β-thalassemia homozygote patients, while 16.8% were beta-HbE thalassemia patients. Both types of thalassemia are commonly found in Southeast Asia [10]. Around 49.5% of our subjects had a transfusion interval of every 2 weeks, followed by 3 weeks (33.7%), and 4 weeks (16.8%). The Thalassemia International Federation (TIF) recommends a transfusion interval of 2–5 weeks [4]. Several factors affect the transfusion interval, such as average pre-transfusion Hb level, the presence of comorbidities/complications, and patients' preference and schedule. A shorter transfusion interval is needed if a patient has lower hemoglobin levels or comorbidities. With age, transfusion-dependent thalassemia patients are more likely to have shorter transfusion intervals because of their increased risk of iron overload.

4.2. Impact of COVID-19 on Thalassemia Patients

Ever since the COVID-19 pandemic started, Indonesia, along with other countries, has struggled to maintain the number of blood donors. A systematic review mentioned that the average decrease in blood donations was 38–67%. Blood scarcity during the COVID-19 pandemic was impacted by two major factors: first, the implementation of social distancing measures led to a significant reduction of donors, and second, there was an increased demand for blood transfusion. Blood donor scarcity is worse in low-middle income countries such as Indonesia [11]. Increased demand for blood transfusions during the pandemic was also due to COVID-19, among other diseases. Up to 13.4% of COVID-19 cases required blood transfusion compared to non-COVID patients [12]. The decreased blood donor rates were mostly due to fear of visiting areas with high risk of COVID-19 transmission, such as hospitals, considering that most donors are driven by altruism.

One of the solutions to combat the lack of blood donors for patients with thalassemia is to find blood donors independently. This method has been used for TDT patients in Indonesia, especially since the COVID-19 pandemic started. TDT patients are advised to find donors that weigh at least 60 kg, because the blood obtained will be processed and filtered further to create leuco-reduced packed red blood cells. Often, TDT patients will search for voluntary non-remunerated donors on social media platforms. Occasionally, parents are asked to donate, which might lead to suboptimal post-transfusion Hb levels. Nevertheless, many TDT patients struggle to find blood donors and are unable to receive regular blood transfusions. It takes up to 4 weeks to obtain a voluntary blood donor; this process is time-consuming and exhausting, as a TDT patient needs to ensure that the blood donor arrives on time to the transfusion unit and is eligible to give blood, and then must wait for the blood to be processed. The blood given is transported to CMH hospital or other hospitals that do not have an independent transfusion unit. This means that for TDT patients that need regular bi-weekly transfusions, they need to find a blood donor one to two weeks before their next transfusion. The blood donor shortage during COVID-19 in Indonesia was alarming; some TDT patients were reported to have been staying overnight at blood donation centers to find voluntary blood donors.

Another challenge for blood donation during the COVID-19 pandemic was the strict protocol for donators. For example, the Ministry of Health in Indonesia specified that those who diagnosed with COVID-19 can only donate blood 14 days after they are completely recovered. In addition, those who received the COVID-19 vaccination can only donate blood 7 days after vaccination [13]. Even though these protocols are intended to ensure the quality of the blood donated, some patients mentioned that they lost their blood donors for these reasons.

This implies that there is a risk of under-transfusion for thalassemia patients, which can result in low pre-transfusion hemoglobin levels and shorter transfusion intervals, as patients need to receive blood transfusion faster in order to maintain their hemoglobin level at optimal levels.

4.3. Hemoglobin Level

According to TIF, the recommended pre-transfusion Hb level is 9.5–10.5 g/dL. Hb should be maintained at this level to promote normal growth and development, allow patients to have normal physical activities, suppress bone marrow activity, and decrease iron overload complications.

This study showed that up to 68.3% of respondents had decreased mean pre-transfusion Hb levels compared to before the pandemic. The Hb level even before the pandemic was only 8.70 g/dL, and it significantly decreased to 8.45 g/dL during the pandemic (p value < 0.001). The suboptimal pre-transfusion Hb level before the pandemic in this study was probably due to low post-transfusion Hb levels, as reported in a study in Indonesia in 2021 [7]. Another similar study also reported a decrease of 0.27 g/dL in mean pre-transfusion Hb values before and during the pandemic [14].

Only 40.6% of patients achieved a pre-transfusion Hb of above 9.0 g/dL pre-pandemic, and this decreased to 28.7% during the pandemic. Low pre-transfusion Hb levels are affected by inadequate previous blood transfusions. In CMH itself, the post-transfusion Hb level is not measured due to financial constraints [7]. In addition, pediatric patients are more reluctant when being asked to provide another blood sample post-transfusion.

Another possible cause of under-transfusion in Indonesia is refusal to finish the transfusion regimen. The national health insurance scheme can only cover up to two blood bags (equal to approximately 500–600 mL of blood) per day in CMH, and this should be on a different day than the thalassemia outpatient clinic visit. Patients who need more than two blood bags to reach their target Hb level need to visit the hospital for at least 3 consecutive days. For patients with more hectic work/school schedules, this is quite demanding, and not all institutions allow that many days of absence. As a consequence, clinicians often find patients skipping their last day of transfusion, leading to under-transfusion. Ideally, post-transfusion hemoglobin should be 14–15 g/dL in order to maintain a pre-transfusion Hb level of 9–10.5 g/dL [15]. In reality, only about 20% of adult TDT patients in Indonesia are able to achieve the targeted post-transfusion Hb level [7].

Low pre-transfusion Hb level is associated with complications such as hepatic iron overload, extramedullary hematopoiesis, thrombosis, hypogonadism, pulmonary hypertension, and osteoporosis. Apart from these complications, a study also found that patients with pre-transfusion Hb levels of <9 g/dL have significantly lower health-related quality of life [16]. As a consequence, a higher volume of blood transfusion is needed in order to achieve the target Hb level. In reality, many patients still struggle to receive adequate blood transfusion volume due to the shortage of blood donations during the COVID-19 pandemic. This creates a vicious cycle of having low pre-transfusion Hb levels, requiring a higher volume of blood for transfusion, which cannot be addressed due to a shortage of blood donations (Figure 2).

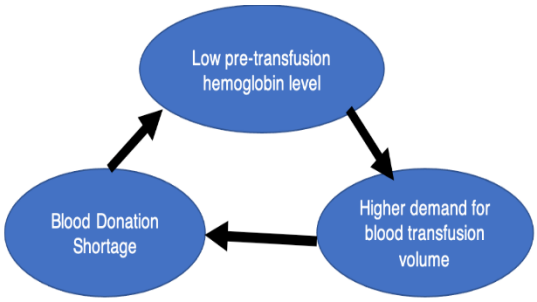

Figure 2. Cycle of having low pre-transfusion hemoglobin levels, requiring a higher volume of blood transfusion, while faced with worldwide blood donation shortage due to COVID-19 pandemic.

It is of utmost importance to achieve and maintain an optimal pre-transfusion Hb level above 9.5 g/dL in order to prevent fatal complications, break the vicious cycle, and ultimately increase patients' quality of life.

4.4. Transfusion Frequency during COVID-19 Pandemic

During the first few months of the COVID-19 pandemic in Indonesia, a nationwide government restriction that included lockdown prevented patients from travelling by public transportation or accessing public areas. Hospitals also applied a strict protocol regarding outpatient clinics, in which only emergent cases were taken, while non-emergent cases were addressed virtually by video calls or online consultation. Moreover, the application of social distancing limited transfusion unit capacity. Additionally, the number of healthcare staff was also limited. These factors limited the daily capacity of transfusion units. A study done in Pakistan revealed a strong negative correlation of COVID-19 cases and patients missing their transfusion sessions [5]. Many patients with chronic diseases such as diabetes and cancer were also negatively affected by COVID-19 [17,18].

Contrary to what we previously thought, our study revealed that the transfusion attendance of 98 of TDT patients in CMH did not decrease significantly (p-value = 0.990) during the pandemic. The difference in mean value of frequency of transfusion before and during the pandemic was only 0.01. A study done in 2021 had similar results: there was no significant difference in the frequency of transfusions before and during the pandemic [14]. This is consistent with our previous result; the significantly lowered pre-transfusion Hb level and previously inadequate blood transfusions prior to the COVID-19 pandemic mean that TDT patients needed shorter transfusion intervals in order to achieve optimal pre-transfusion hemoglobin levels, which ultimately increased the frequency of blood transfusions annually. By decreasing the overall blood requirements during transfusion, TDT patients did not need to find more blood donors, as it was difficult to find independent blood donors, and they did not need to stay in the hospital for a long period, in order to comply to government restrictions of mass lockdown and social distancing.

4.5. Clinical Implications

The results of this study are important in several ways. First, the COVID-19 pandemic caused blood donation shortages in many countries, including Indonesia. The shortage of blood products made it difficult for TDT patients to receive regular, adequate blood transfusion, resulting in significantly low pre-transfusion Hb levels. Patients with chronically low pre-transfusion Hb levels are at risk of developing fatal complications and having low quality of life.

Successful measures have been taken by other countries to increase the rate of blood donations. Turkey has created blood donation programs specifically for patients with Thalassemia; donations are mainly provided by the relatives of patients [19]. Local blood drives and remuneration increased blood supply in Oman in 1990 [20]. Another way to attract voluntary donors is to create public awareness campaigns. Myanmar applied this strategy, and blood donation rates increased significantly [21].

In order to create a safe space for donors to donate blood under the conditions of COVID-19, blood banks need to actively collaborate with companies, mosques, or churches to hold blood donation events. Potential donors should be informed that blood donation will take place in areas with good ventilation and with the implementation of social distancing in order to convince them that it is safe to donate blood. Moreover, contact numbers of these donors should be saved so that blood banks can regularly invite them for subsequent blood donation events.

4.6. Limitations and Suggestions

Our study did not measure the serum ferritin level or MRI T2*/ms value as parameters of iron overload complications because ferritin level and MRI were not routinely measured in TDT patients in CMH during the COVID-19 pandemic due to the overload of patients. Due to the combination of the chronic low level of pre-transfusion Hb level, higher demand for more blood volume, and low compliance of iron chelation therapy, TDT patients are at high risk of developing iron overload complications; thus, it is best to measure serum ferritin regularly in order to regularly screen for iron concentration and effectivity of iron chelator.

5. Conclusions

The COVID-19 pandemic abruptly disrupted care for thalassemia patients, putting them at risk of developing many long-term complications related to chronic severe anemia and iron overload, which can ultimately lower their quality of life.

1. The percentage of patients who had suboptimal hemoglobin levels before the pandemic was 59.4%, and it increased to 71.2% during the pandemic.
2. The mean frequency of blood transfusions before the pandemic was 18.61, and it became 18.60 during the pandemic; the difference was not significant (p value = 0.990).

3. The mean pre-transfusion hemoglobin level before the pandemic was 8.71 g/dL, and it decreased to 8.46 g/dL. The difference was statistically significant (p value < 0.001).

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