COVID-19 in patients with transfusion dependent thalassemia in Indonesia: characteristics of the disease and patients, and comparison between epidemiological data for COVID-19 and thalassemia in Indonesia and South-East Asia

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Abstract

People living with transfusion dependent thalassemia have a high risk of getting infected by COVID-19. This can be caused both by internal factors, namely the formation of alloantibodies and autoimmune disorders, and external factors such as routine visits for blood transfusions. Chronic complications of thalassemia also render the patients more vulnerable to infectious diseases, including COVID-19. However, anecdotal data shows that thalassemia patients have less incidence of COVID-19 if compared to the general population. This study aims to find the correlation between COVID-19 in thalassemia-dependent transfusion patients in Indonesia and South-East Asia. This research used a cross-sectional design. The study was conducted at the Division of Haematology and Medical Oncology of the Cipto Mangunkusumo Hospital in Jakarta, from May 2020 to August 2021. Total sampling method was used involving all thalassemia major patients who had been infected with COVID-19 obtained directly from medical records and through the thalassemia patients' parents foundation. In 10,397 patients with thalassemia, 67 (0.64%) people were infected by COVID-19 and two (2.9%) died. Meanwhile, the incidence of COVID-19 in the general population of Indonesia was 0.87%, more than in the thalassemia population. This means that thalassemia might provide additional protection against COVID-19 due to several mechanisms. This phenomenon is also seen in other countries with a high prevalence of thalassemia, which show less COVID-19 cases despite the pandemic. On the contrary, countries with low rates of thalassemia carriers had experienced deadly surges of the pandemic. Indonesia and other countries with a high prevalence of thalassemia have lower COVID-19 incidence than countries with a low prevalence of thalassemia. Thalassemia might provide additional protection against COVID-19. Well designed studies are needed to provide better evidence on the protective effect of thalassemia against COVID-19.

Introduction

COVID-19 is a disease caused by coronavirus, and it causes various symptoms that generally attack the respiratory tract, ranging from mild to severe. This disease has become a global pandemic. Even though transfusion-dependent thalassemia patients are a high-risk group, there were no studies on thalassemia patients who were infected by COVID-19. Patients with thalassemia major generally have a higher risk for viral and bacterial infections. The occurrence of alloantibody and autoimmune disorders in thalassemia might impair the body’s immune system. Patients with transfusion-dependent thalassemia (TDT) routinely visit the hospital to receive blood transfusions every 2-5 weeks. During the COVID-19 pandemic, there was a blood donor shortage at blood banks, which deterred the patients from meeting the transfusion target. Since they found it difficult to get adequate blood volume in a single visit, the visits to transfusion services became more frequent, sometimes up to once a week. Routine blood transfusion is also a risk factor for COVID-19 infection, due to the increased exposure during the trip from the house to the hospital, the blood transfusion itself, and when travelling back from the hospital to the house.

Every day, in our clinic, there are approximately 300 adult TDT patients and 600 pediatric patients who receive regular transfusions. There is no nationwide data regarding this in Indonesia. Indonesia is located in the thalassemia belt, with a high prevalence of thalassemia beta hemoglobin E (HbE) and beta major. There are about 10,397 TDT patients managed in 56 centers. The prevalence of HbE thalassemia has been estimated to be around 1.5-3.6%.

In several countries, such as Italy, Cyprus and several South-East Asian countries, the number of cases of thalassemia patients affected by COVID-19 is lower than in the general population. In our clinic there were only three patients with transfusion-dependent thalassemia who were infected with SARS-CoV2 in 2020, despite the incremental increase in national daily cases. Based on the data above, there seems to be a discrepancy between the incidence of COVID-19 in patients with thalassemia if compared to the general population. Therefore, we want to study the characteristics of thalassemia patients, their correlation with thalassemia and COVID-19 epidemiological data, and undertake further studies on the possibilities that could cause the decreased incidence of COVID-19 in thalassemia patients.

Materials and methods

Diagnosis of COVID-19 was based on reverse transcriptase polymerase chain reaction involving all thalassemia major patients.
Results

There were 10,397 registered thalassemia patients with regular visits for blood transfusions in Indonesia. In our thalassemia center in Jakarta, we found 8 patients with COVID-19. Nationwide data were obtained from POPTI, a well-established organization which involves the parents of thalassemia patients. The members of the foundation mainly consist of parents, since people with thalassemia are often diagnosed at an early age. From March 2020 to August 2021, we obtained data from 38 provinces, and 67 (0.64%) thalassemia patients were confirmed with COVID-19. Two patients (2.9%) died. The highest number of thalassemia cases with COVID-19 was from Jakarta. The characteristics of thalassemia patients infected with COVID-19 in Indonesia and the relation between its variables can be seen in Table 1 and Table 2. Figure 1 shows that COVID-19 incidence in thalassemia patients was generally lower than in the general population. In provinces with a high prevalence of thalassemia, such as Aceh (0.012%), the incidence of COVID-19 was only 0.3%. This contrasts with other provinces with a low prevalence of thalassemia, such as East Borneo (0.004%), which has an incidence of COVID-19 six times higher than Aceh’s (1.8%). Detailed data on the incidence of COVID-19 in each province in Indonesia can be seen in Table 3.

Table 1. Characteristics of thalassemia patients infected by COVID-19 in Indonesia.

| General characteristics          | N=66 |
|---------------------------------|------|
| Gender, n (%)                   |      |
| Male                            | 29 (43.3) |
| Female                          | 37 (56.7) |
| Age, n (%)                      |      |
| 3.0–18.0                        | 30 (44.8) |
| 19.0–40.0                       | 26 (38.8) |
| 41.0–60.0                       | 10 (15.4) |
| Blood type, n (%)               |      |
| A (+)                           | 20 (29.9) |
| AB (+)                          | 10 (14.9) |
| B (+)                           | 14 (20.9) |
| O (+)                           | 23 (34.3) |
| Ethnicity, n (%)                |      |
| Batakneese                      | 1 (1.4) |
| Bengkulu                        | 1 (1.4) |
| Betawi                          | 14 (20.8) |
| Buginese                        | 1 (1.4) |
| Chinese                         | 2 (2.9) |
| Javanese                        | 24 (35.8) |
| Lampung                         | 1 (1.4) |
| Medan                           | 2 (2.9) |
| Malay                           | 2 (2.9) |
| Minang                          | 1 (1.4) |
| Sundanese                       | 18 (28.8) |
| Thalassemia type, n (%)         |      |
| Alfa 3 deletion                 | 2 (3.0) |
| Beta intermedia                 | 1 (1.5) |
| Beta HbETDT                     | 19 (28.4) |
| Beta major                      | 44 (65.7) |
| Beta minor                      | 1 (1.5) |
| COVID-19 clinical severity, n (%)|      |
| Asymptomatic                    | 31 (46.3) |
| Mild                            | 32 (47.8) |
| Moderate                        | 4 (6.0) |
| Severe                          | 0 (0.0) |
| Outcome, n (%)                  |      |
| Deceased                        | 2 (2.9) |
| Recovered                       | 65 (97.1) |
| Vaccination status prior to COVID-19 infection, n (%) |      |
| Already                         | 3 (4.2) |
| Not Done                        | 66 (91.7) |

Table 1 shows that most patients were aged 3-18 and 19-40 years old. We divided the subjects into these two age ranges, since children under 18 years old are managed by pediatricians, while those above 18 years old are managed by internists/adult hematologists. Our data showed that most patients were in this age range. This is due to a more active lifestyle and increased mobility. We only had several subjects older than 40, since a lot of patients could not survive beyond 40 due to complications of thalassemia.

Table 1 also showed that Betawi, Javanese, and Sundanese are the ethnicities most infected by COVID-19. They are the most common ethnicities in Indonesia, especially in Jakarta. Although there are hundreds of ethnicities in Indonesia, those

Discussion

In this nationwide study, we observed more than 10,000 people living with thalassemia, and conducted a survey to determine the impact of the COVID-19 pandemic. Due to COVID-19 travel and contact restrictions, data was collected using online methods. We successfully contacted thalassemia representatives in 34 provinces and found that, during the period spanning from March 2020 to August 2021, there were 67 thalassemia patients who were infected by COVID-19. Most of the cases originated from the capital Jakarta, which was also the epicentrum of the pandemic. Meanwhile, Indonesia is an archipelago with vast genetic diversity, especially in terms of hemoglobinopathies. Therefore, by obtaining detailed data from every province, we could get an overview of how thalassemia might be related to a reduced incidence of COVID-19.
three are the most prevalent, especially in the Java Island. In order to observe an association of ethnicity with COVID-19, more subjects from each ethnicity are needed.

We performed an analytical test between patient’s characteristics and COVID-19 status (survivor vs deceased), shown in Table 2. We can conclude that there is no relationship between the variables except for the clinical severity of COVID-19. The percentage of deceased subjects and moderate COVID-19 symptoms (33%) is quite high, and it makes the variable statistically significant. In the entire population of subjects, a total of two people died. The reported causes of death were active tuberculosis infection and chronic liver disease, rather than COVID-19 itself. Our data show that thalassemia patients displayed lower incidence of COVID-19 compared to the general population. For example, in the East Borneo province, the percentage of COVID-19 cases in thalassemia patients was less than 50% of the incidence in general population. Even in Jakarta, which was the most affected province with diverse ethnicities, the rate of COVID-19 in thalassemia was still below the general population. Moreover, the prevalence of thalassemia, including those undetected, silent carriers, seems to protect the hosts from COVID-19. In regions where there is a high prevalence of thalassemia, it is rational to hypothesize that the number of thalassemia minor or silent carriers is also higher. From Table 1, we can observe data regarding the proportion of COVID-19 in the general population compared to thalassemia patients. In most regions of Indonesia, the incidence of COVID-19 in thalassemia patients is generally lower than in the general population. However, we also found that there are some provinces with a higher COVID-19 incidence in thalassemia if compared with general population. This is caused by a low number of registered thalassemia patients if compared to other regions, thereby increasing the percentage of thalassemia patients affected by COVID-19 at the specific area due to a small denominator.

Nevertheless, thalassemia is not the only factor associated with the spread of COVID-19. In areas with high population density and high mobility, such as the capital, Jakarta, the incidence of COVID-19 is the highest in the country. However, our study showed that, even in “COVID hotspots”, people with thalassemia had a lower SARS-CoV-2 infection rate compared to general population. From the above-mentioned data, it seems probable that thalassemia might provide additional protection against SARS-COV2 infection.

In other words, theoretically, regions with a high prevalence of thalassemia should be less affected by COVID-19. Based on data collected from several countries in South-East Asia (ASEAN Countries), countries with a high prevalence of thalassemia carriers such as Vietnam, Cambodia, and Laos were less affected by COVID-19 rates if compared to countries with a low prevalence of thalassemia carriers such as Western countries, which can be seen in Table 4.

Table 4 depicts the number of COVID-19 cases and thalassemia prevalence in ASEAN countries. The thalassemia prevalence in the table is a rough estimate of the latest numbers. We were unable to observe the number of confirmed COVID-19 cases in other countries, since ours is the first publication reporting COVID-19 in thalassemia patients. However, from Table 4, it can be inferred that countries with a high prevalence of beta thalassemia have a reduced incidence of COVID-19. These findings are similar to those published by de Sanctis et al.,4 which showed that the proportion of beta-thalassemia patients being infected with COVID-19 was higher than other types of thalassemia, but the total thalassemia patients infected by COVID-19...
were less than the general population patients. Nevertheless, the study collected data from the UK, Iran, and Italy. Our study was the first in Asian thalassemia population.

A study conducted by Edouard Lansiaux et al.\(^5\) showed that a higher prevalence of beta thalassemia and a higher resistance against COVID-19 were found in the areas of Italy, Cyprus and Southeast Asia.\(^5,6\) This geographical pattern, known as the ‘thalassemia belt’, spans along countries from the Mediterranean Sea to the Asian continent. In Cyprus, according to data, there were 560 people with beta thalassemia major. From 560 patients, 33 (5.8%) people were affected by COVID-19. Among these, the mortality rate is 0%, while the average hospitalization day ranges from three to ten days. All patients recovered without being admitted to ICU or receiving ventilator support.\(^3\) In Italy, there are several studies about thalassemia and COVID-19. The incidence of COVID-19 in thalassemia patients was 0.00057%, with a mortality rate of 2%.\(^3\) These numbers were very low if compared to the general population in Italy, which was severely devastated by COVID-19. Another study by Papadopoulos et al.\(^6\) supported our findings, as shown in Table 4. During the spread of COVID-19, in areas with high hemoglobin E (HbE) thalassemia prevalence, such as Thailand, Cambodia, and Laos, the incidence of COVID-19 was lower.\(^6\) In Indonesia, there is an island named Sabu Island, which has the highest prevalence of beta HbE thalassemia. This phenomenon has been studied by Weatherall et al.,\(^7\) as expected, the incidence of COVID-19 in this region is lower (0.44%) if compared to national incidence (1.07%), and much lower than peak inci-

### Table 3. Recapitulation of thalassemia in each province and COVID-19 transfusion-dependent thalassemia patients.

| No | Province                  | Total population | Total TDT patients | Prevalence of TDT / population | Total COVID-19 cases in the general population | TDT patients with COVID-19 | TDT patients with COVID-19 (%) | Mortality in TDT patients with COVID-19 |
|----|---------------------------|------------------|--------------------|-------------------------------|-----------------------------------------------|-------------------------|-------------------------------|--------------------------------------|
| 1  | ACEH                      | 5,274,871        | 631                | 0.0120%                       | 20949                                         | 0                       | 0%                            | 0                                    |
| 2  | NORTH SUMATRA             | 14,799,361       | 162                | 0.0011%                       | 46053                                         | 3                       | 1,9%                          | 1                                    |
| 3  | WEST SUMATRA              | 5,534,472        | 22                 | 0.0004%                       | 61350                                         | 0                       | 0%                            | 0                                    |
| 4  | RIAU                      | 6,394,087        | 97                 | 0.0015%                       | 83628                                         | 0                       | 0%                            | 0                                    |
| 5  | Jambi                     | 3,548,228        | 54                 | 0.0015%                       | 16443                                         | 0                       | 0%                            | 0                                    |
| 6  | SOUTH SUMATRA             | 8,467,432        | 332                | 0.0039%                       | 37917                                         | 0                       | 0%                            | 0                                    |
| 7  | BENGKULU                  | 2,010,670        | 100                | 0.0050%                       | 14003                                         | 1                       | 1,0%                          | 0                                    |
| 8  | LAMPUING                  | 9,007,848        | 316                | 0.0035%                       | 29078                                         | 1                       | 0,3%                          | 0                                    |
| 9  | BANGKA BELLING ISLANDS    | 1,455,678        | 117                | 0.0080%                       | 26778                                         | 0                       | 0%                            | 0                                    |
| 10 | RIAU ISLANDS              | 2,064,564        | 97                 | 0.0047%                       | 36581                                         | 1                       | 1,0%                          | 0                                    |
| 11 | DKI JAKARTA               | 10,562,088       | 864                | 0.0082%                       | 746306                                        | 49                      | 5,6%                          | 1                                    |
| 12 | WEST JAVA                 | 48,274,162       | 4164               | 0.0086%                       | 530806                                        | 8                       | 0,19%                         | 0                                    |
| 13 | CENTRAL JAVA              | 36,516,035       | 1449               | 0.0040%                       | 329216                                        | 0                       | 0%                            | 0                                    |
| 14 | DI YOGYAKARTA             | 3,668,719        | 185                | 0.0045%                       | 92085                                         | 0                       | 0%                            | 0                                    |
| 15 | EAST JAVA                 | 40,665,696       | 695                | 0.0017%                       | 239168                                        | 2                       | 0,3%                          | 0                                    |
| 16 | BANTEN                   | 11,904,562       | 654                | 0.0055%                       | 92746                                         | 0                       | 0%                            | 0                                    |
| 17 | BALI                      | 4,317,404        | 23                 | 0.0005%                       | 61175                                         | 0                       | 0%                            | 0                                    |
| 18 | WEST NUSA TENGGARA        | 5,320,092        | 26                 | 0.0005%                       | 16331                                         | 0                       | 0%                            | 0                                    |
| 19 | EAST NUSA TENGGARA        | 5,325,586        | 0                  | 0%                            | 26363                                         | 0                       | 0%                            | 0                                    |
| 20 | WEST KALIMANTAN           | 5,414,390        | 234                | 0.0043%                       | 21149                                         | 1                       | 0,4%                          | 0                                    |
| 21 | CENTRAL BORNEO            | 2,669,969        | 38                 | 0.0014%                       | 30547                                         | 0                       | 0%                            | 0                                    |
| 22 | SOUTH BORNEO              | 4,073,584        | 157                | 0.0039%                       | 40029                                         | 0                       | 0%                            | 0                                    |
| 23 | EAST KALIMANTAN           | 3,766,039        | 137                | 0.0036%                       | 96564                                         | 1                       | 0,72%                         | 0                                    |
| 24 | NORTH KALIMANTAN          | 701,814          | 0                  | 0%                            | 16286                                         | 0                       | 0%                            | 0                                    |
| 25 | NORTH SULAWESI            | 2,621,923        | 0                  | 0%                            | 19718                                         | 0                       | 0%                            | 0                                    |
| 26 | CENTRAL SULAWESI          | 2,985,734        | 0                  | 0%                            | 16792                                         | 0                       | 0%                            | 0                                    |
| 27 | SOUTH SULAWESI            | 9,073,509        | 61                 | 0.0007%                       | 72240                                         | 0                       | 0%                            | 0                                    |
| 28 | SOUTHEAST SULAWESI        | 2,624,875        | 0                  | 0%                            | 13817                                         | 0                       | 0%                            | 0                                    |
| 29 | GORONTALO                 | 1,171,681        | 0                  | 0%                            | 6948                                          | 0                       | 0%                            | 0                                    |
| 30 | WEST SULAWESI             | 1,419,229        | 0                  | 0%                            | 7113                                          | 0                       | 0%                            | 0                                    |
| 31 | MALUKU                    | 1,848,923        | 0                  | 0%                            | 12127                                         | 0                       | 0%                            | 0                                    |
| 32 | NORTH MALUKU              | 1,282,937        | 0                  | 0%                            | 8204                                          | 0                       | 0%                            | 0                                    |
| 33 | WEST PAPUA                | 1,134,068        | 0                  | 0%                            | 15904                                         | 0                       | 0%                            | 0                                    |
| 34 | PAPUA                     | 4,303,707        | 0                  | 0%                            | 23826                                         | 0                       | 0%                            | 0                                    |

**Total**: 270,203,917, 10,397, 0.089%, 2,908,040, 67, 11.21% 2
dence in the capital (7.07%). In these two provinces in Indonesia, the percentage of COVID-19 patients is lower than in other regions. However, it should be also taken into account that population mobility also plays an important role in the spread of COVID-19. People in Sabu Island are significantly more isolated than those living in the capital, Jakarta. Therefore, although thalassemia itself might protect them from COVID-19, we should also consider their isolated location as the reason why the incidence of COVID-19 is lower in this population.

Mortality due to COVID-19 in thalassemia patients is 2 (2.9%). Meanwhile the mortality by COVID-19 in Indonesia as of July the 18th 2021 is 2.5%. The high death rates in thalassemia patients affected by COVID-19 might be affected by several factors, such as organ dysfunction due to chronic complication of thalassemia, inadequate iron chelation therapy, and unavailability of specialized COVID-19 referral hospital for such patients.

Theoretically, thalassemia patients should be more prone to have moderate to severe clinical severity. However, our data showed that the incidence is lower than in the general population. The lower incidence of COVID-19 in thalassemia is possibly due to a defect in the beta-globin chain, thereby inhibiting the pathogenetic mechanism of SARS-CoV-2 infection. Moreover, our data showed that most thalassemia patients (84.8%) had an asymptomatic or mild infection. An epidemiology study by Lansiaux et al. showed that beta-thalassemia might provide protection against COVID-19. A study conducted by Wenzhong et al. has shown that protein in COVID-19 like open reading frame ORF1ab, ORF3a, and ORF10 have a tendency to attack beta chain hemoglobin to form porphyrin. Porphyrin is needed for viruses to survive. Furthermore the lungs fail to exchange carbon dioxide and oxygen because of the dysfunction of hemoglobin. In thalassemia patients, the lack of, or even the absence of beta chain prevents the virus from entering host cells, rendering the host less susceptible.

Studies on immune competence in beta-thalassemia have revealed numerous quantitative and functional defects, involving T and B lymphocytes, immunoglobulin production, neutrophils and macrophages, chemotaxis, and phagocytosis, as well as the complement system. In non-thalassemic patients, in vitro cell experiments show that delayed release of cytokines and chemokines occurs in respiratory epithelial cells, dendritic cells (DCs), and macrophages at the early stage of SARS-CoV infection. Later, the cells secrete low levels of interferons (IFNs) and high levels of proinflammatory cytokines interleukin IL-1 β, IL-6, and tumor necrosis factor (TNF) and chemokine. Therefore in patients with thalassemia, the cytokine storm cascadle will be attenuated due to the incompetence on immunity that will affect the expression of cytokines.

Thalassemia patients have higher risk of exposure to SARS-CoV-2 due to the frequent hospital visits for regular blood transfusions. They are also burdened by chronic complications which attenuate their immune system, such as iron overload and splenectomy. Excessive transfusions can lead to the accumulation of iron, ferritin and hemosiderin in the blood. Iron overload can also occur due to ineffective erythropoiesis and increased intestinal iron absorption. This has been implicated as the main precipitating factor of immune deficiency in thalassemia. Iron directs the immune response toward a T-helper Th2 response pattern, which is unfavorable for fighting bacterial or viral infection. Cellular iron availability also modulates the differentiation and proliferation of Th1 and Th2 cell subsets, partly related to the different dependence of cells on transferrin-mediated iron uptake. Theoretically this attenuated immune response should render patients with thalassemia vulnerable to SARS-CoV-2 infection. However, the data in our study and other studies showed otherwise. Therefore, there might be an alternative mechanism explaining why people with thalassemia are somehow “more immune” to SARS-CoV-2. As a comparison, countries with a low prevalence of thalassemia carriers seem to be more affected by COVID-19. In Brazil, COVID-19 affected 8.9% of the population, with a mortality rate of 0.2%, and the prevalence of thalassemia carriers is 1.8%. Another example comes from one of the most affected countries by COVID-19, India, where the number of COVID-19 patients exceeded thirty million people. This country has a low prevalence of beta thalassemia carriers. From these two countries, it can be seen that the low number of thalassemia carriers can be associated with the high number of COVID-10.

The United Kingdom has experienced several waves of COVID-19 and explosions in the number of cases. This country has an extremely low number of thalassemia carriers. Moreover, despite nationwide vaccination strategies, the United States also suf-

### Table 4. Prevalence of COVID-19 and thalassemia in ASEAN countries.

| No | Country   | Total population | Number of COVID-19 cases | COVID-19 cases/1 million population (n) | Alpha thalassemia (%) | Beta thalassemia (%) | HbE thalassemia (%) | TDT patient mortality due to COVID-19 |
|----|-----------|------------------|--------------------------|---------------------------------------|-----------------------|---------------------|---------------------|-------------------------------------|
| 1  | Indonesia | 270,203,917      | 2,908,040                | 10,762                                | 0.5%                  | 3%                  | 1.25%               | 7                                   |
| 2  | Philippines | 104,900,000   | 1,605,762                | 15,308                                | 5.4%                  | 1.2%                | 1%                  | N/A                                |
| 3  | Vietnam   | 95,540,000      | 165,339                  | 1,731                                 | 0.05%                 | 1.6-25%             | 1.73%               | N/A                                |
| 4  | Thailand  | 69,400,000      | 652,185                  | 9,397                                 | 5.5-30%               | 1.9%                | 5-50%               | N/A                                |
| 5  | Myanmar  | 53,370,000      | 306,354                  | 5,740                                 | 10.5%                 | 4%                  | 1-26%               | N/A                                |
| 6  | Malaysia | 31,200,000      | 1,163,291                | 37,285                                | 1.8-7.5%              | 3.3%                | 5-46%               | N/A                                |
| 7  | Cambodia | 16,010,000      | 79,051                   | 4,938                                 | 10%                   | 3%                  | 31.63%              | N/A                                |
| 8  | Laos      | 7,364,903       | 7,015                    | 952                                  | 42%                   | 9%                  | 24.48%              | N/A                                |
| 9  | Singapore | 5,612,000       | 65,213                   | 11,620                                | 2.91%                 | 0.93%               | 0.64%               | N/A                                |
| 10 | Timor Leste | 1,339,862 | 10,982                   | 8,196                                | N/A                   | N/A                 | N/A                 | N/A                                |
| 11 | Brunei   | 428,607         | 338                      | 789                                  | 4.3%                  | 0.02%               | 0.01%               | N/A                                |

Notes: N/A (Not Available); HbE: hemoglobin E; TDT: transfusion-dependent thalassemia.

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fered from multiple waves of the pandemic. According to Weatherall et al., thalassemia patients in the United States are few. Therefore, the facts support the theory that a low number of thalassemia carriers leads to more cases of COVID-19.

Looking at the pattern described above, there is one country which showed an atypical presentation. The ground zero of COVID-19, People’s Republic of China (PRC), has a low prevalence of thalassemia carriers. However, despite being the first country affected by COVID-19, they could manage the pandemic well. This could be caused by a one-way government system, an extensive tracing system, a massive vaccination system and a high level of population awareness in preventing the transmission of COVID-19.

In Table 4, the prevalence of alpha thalassemia, beta thalassemia and HbE thalassemia in Malaysia was higher than in Indonesia. However, the total number of COVID-19 cases in the general population is higher in Malaysia. This might be due to several factors. First, Indonesia’s population is almost ten times that of Malaysia, with the population spread throughout the archipelago. There were some isolated islands where COVID-19 did not cause significant damage, especially in the islands furthest from the capital. Moreover, the prevalence of thalassemia in Indonesia might be underestimated, due to the unavailability of Hb electrophoresis and genetic testing throughout the country. It is estimated that the number of undiagnosed thalassemia patients in Indonesia may be higher. In addition, Malaysia had a high testing rate for COVID-19, being ranked 3rd in the ASEAN countries. On the other hand, Indonesia ranked 9th due to its huge population and large distribution of people among the islands.

Several previous studies had also investigated the association between blood type and susceptibility to COVID-19 infection. Zietz et al. found that people with blood group A had higher susceptibility to COVID-19 compared with blood group O. In general, people with O type blood group are less vulnerable than non-O blood group. It is hypothesized that polymorphism in ABO gene plays an important role in the natural immunity against SARS-COV-2. Our data shows high proportion of non-ABO subjects with COVID-19, far higher than the normal blood group distribution in the population. This might support the hypothesis that blood types play a role in susceptibility to COVID-19. From the data above, we can obtain valuable insight regarding the risk of contracting COVID-19 in people living with thalassemia. In general, countries with a high prevalence of thalassemia have a lower incidence of COVID-19 and a lower mortality rate. Other factors that should be considered are the government systems along with their respective healthcare policies.

Conclusions

Indonesia, along with other countries with a high prevalence of thalassemia, has lower COVID-19 incidence than western countries with low prevalence of thalassemia. Our data showed that in Indonesian population, thalassemia might provide additional protection against COVID-19. Since this phenomenon can be explained by theoretical possibilities, well-designed studies are needed to provide better evidence on the protective effect of thalassemia on COVID-19.

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