EXPLORING THE PREVALENCE PATTERNS OF THALASSEMIA AND QUALITY OF LIFE AMONG PEDIATRIC AND ADOLESCENT PATIENTS IN SABAH

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EXPLORING THE PREVALENCE PATTERNS OF THALASSEMIA AND QUALITY OF LIFE AMONG PEDIATRIC AND ADOLESCENT PATIENTS IN SABAH

by

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α	Alpha
β	Beta

LIST OF ABBREVIATIONS

HWKKS	Hospital Wanita dan Kanak-kanak Sabah
HKB	Hospital Kota Belud
JKNS	Jabatan Kesihatan Negeri Sabah
QOL	Quality of life
HRQOL	Health related quality of life
TDT	Transfusion dependent
NTDT	Non-transfusion dependent
β-TM	Beta thalassemia major
TTC	Thalassemia Treatment Centre

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EKSPLORASI CORAK PREVALENS TALASEMIA DAN KUALITI HIDUP DALAM KALANGAN PESAKIT PEDIATRIK DAN REMAJA DI SABAH

ABSTRAK

Talasemia major adalah penyakit kronik yang memerlukan pesakit menjalani transfusi darah dan terapi *iron-chelation* sepanjang hayat. Sabah mempunyai jumlah talasemia yang tertinggi di Malaysia. Namun, gambaran sebenar beban talasemia di Sabah masih tidak jelas dan kajian mengenai kualiti hidup (QOL) pesakit talasemia juga terhad. Oleh itu, kajian ini dijalankan bertujuan memetakkan prevalens talasemia di Sabah, meneroka faktor penyumbang kepada kes yang tinggi di Sabah, dan menentukan tahap QOL pesakit pediatrik dan remaja talasemia di Sabah. Kajian ini dijalankan di Jabatan Kesihatan Negeri Sabah (JKNS) dan dua hospital di Sabah dari Julai 2018 hingga Mei 2020. Data pesakit talasemia yang dilaporkan sepanjang lima tahun diperolehi dari JKNS dan Micrososft Power Bi digunakan untuk memetakkan prevalens. Borang soalselidik diberi kepada 108 ibubapa β-talasemia major (β-TM) dan temubual separa berstruktur dengan 18 ibu yang mempunyai lebih dari satu anak β-TM dijalankan untuk meneroka faktor penyebab ibu mempunyai lebih dari satu anak β-TM. Analisis regresi logistik pelbagai dan analisis tematik telah dijalankan. Dalam kajian QOL, 115 pesakit β-TM, dari 8 hingga 18 tahun telah diberi soalselidik PedsQL^{TM} 4.0 untuk menilai QOL. Analisis regresi linear pelbagai dijalankan untuk mengenalpasti faktor kepada tahap QOL. Kajian ini mendapati talasemia adalah lazim di Pitas, Sabah. Keluarga dengan ramai anak lebih cenderung mempunyai lebih dari satu anak β-TM (OR: 2.1, 95% CI: 1.5, 2.9, P-value = 1.3 x 10-5). Lima tema utama sebab mempunyai lebih dari satu anak β-TM telah dikenalpasti: 1) niat untuk memiliki lebih banyak anak dan penerimaan terhadap keadaan anak; 2)

kurangnya pemahaman tentang bagaimana talasemia boleh diwarisi; 3) halangan dalam saringan prenatal; 4) halangan dalam pengguguran; dan 5) perancangan keluarga tidak berkesan. Manakala, skor QOL bagi pesakit talasemia adalah 76.2 (SD 14.5), dengan skor purata terendah adalah bahagian sekolah. Ibubapa yang bercerai dan penggunaan satu jenis iron-chelation (Adjusted β: −10.55, 95% CI: −19.38, −1.73, P-value=0.02; Adjusted β:10.02, 95% CI:4.05, 16.00, P-value=0.001) berkait dengan skor QOL pesakit. Kajian ini mencadangkan kerjasama pelbagai sektor dalam mengurangkan kelahiran talasemia dan memperkasakan peranan jururawat kesihatan masyarakat dalam memberi sokongan dalam perancang keluarga seawal mungkin kepada ibu yang ingin mengandung lagi. Selain itu, penting untuk menilai kualiti hidup pesakit talasemia secara berkala agar mereka dapat mencapai kesihatan dan kualiti hidup yang optima sepanjang tumbesaran. Jadual yang fleksibel untuk pemindahan darah dilihat penting untuk disediakan kepada pesakit talasemia. Kajian longitudinal berkaitan QOL dan kajian mengenalpasti cabaran yang dihadapi keluarga dan pesakit perlu pada masa depan.

EXPLORING THE PREVALENCE PATTERNS OF THALASSEMIA AND QUALITY OF LIFE AMONG PEDIATRIC AND ADOLESCENT PATIENTS IN SABAH

ABSTRACT

Thalassemia major is a chronic disease, requires life-long blood transfusion and iron chelation therapy. Sabah has the highest amount of thalassemia in Malaysia, however the true picture of the current burden of thalassemia is still not clear and studies on quality of life (QOL) of thalassemia patients are also limited in Sabah. This study aims to map the prevalence of thalassemia, to explore factors contributing to high prevalence of thalassemia and to determine the QOL among the pediatric and adolescent patients in Sabah. Study was conducted at Jabatan Kesihatan Negeri Sabah (JKNS) and two hospitals in Sabah from July 2018 to May 2020. Five years prevalence data was obtained from JKNS. Microsoft Power Bi was used for mapping the prevalence. Self-administered questionnaires to 108 β-thalassemia major (β-TM) parents and in-depth, semi-structured interviews with 18 mothers having multiple β-TM children were conducted to explore the factors of having multiple β-TM children. Multiple linear regression and thematic analysis were performed. In the QOL study, 115 β-TM patients aged 8 to 18 years were included. The Malay version of PedsQL 4.0 questionnaire was used. Multiple logistic regression was conducted to identify the factors associated with QOL scores. This study found; thalassemia is highly prevalent in Pitas, Sabah. Families with more children are more likely to have more β-TM children (OR: 2.1, 95% CI: 1.5, 2.9, P-value = 1.3 x 10-5). The thematic analysis identified five core themes for reasons of having multiple children with β-TM: 1) intention to have more children and acceptance towards child's condition; 2) lack of

understanding about thalassemia inheritance pattern; 3) barriers in prenatal screening; 4) barriers in abortion; and 5) ineffective family planning. The QOL score was 76.15 (SD 14.5) with lowest mean score in school functioning. Divorced parents and usage of single iron chelation therapy were significantly associated with lower QOL score (adjusted β:−10.55, 95% CI: −19.38, −1.73, P-value=0.02; adjusted β: 10.02, 95% CI:4.05, 16.00, P-value=0.001). The study recommends cross-sector coordination to reduce thalassemia births and empowerment of community health nurses in providing early support and education to carrier mothers about the risks and available options for better family planning. Furthermore, periodically assessment of thalassemia patients' QOL may be crucial to improve overall health outcomes throughout growth. Additionally, it may be imperative to provide flexible scheduling for blood transfusions. Longitudinal research on QOL and studies on challenges face by families and patients may be required in future.

CHAPTER 1

INTRODUCTION

1.1 Introduction

Chapter 1 of this thesis sets the context and background of thalassemia, emphasizing its genetic basis, clinical manifestations, and the public health challenges it poses. This introductory chapter sets the stage for the entire thesis, establishing the objectives and the importance of the research which providing a clear framework for the study.

1.2 Background of study

Thalassemia is an inherited disease. The two main types of thalassemia are α and β-thalassemia. α- thalassemia is caused by deletions or mutations in the α-globin gene complex, whereas β-thalassemia is caused by defects that occur within the β-globin gene (Bajwa and Basit, 2021; Farid, Bowman and Lecat, 2021). This autosomal recessive disorder results from an interruption in the globin chain synthesis which further impaired the haemoglobin production.

Thalassemia was once common in a region such as the Middle East, Indian Subcontinent, Southeast Asia, and South China. However, it is now prevalent globally due to an increase in the migration rates (Weatherall and Clegg, 2001; Li, 2016). According to WHO Bulletin (Modell & Darlison, 2008), approximately 20% of the world's population are carriers of α^{+}-thalassemia and 5.2% are carriers of significant variants including β-thalassemia and α^{0}-thalassemia. In Malaysia, about 3.1% of the population carry α^{+}-thalassemia, and 1.8% carry α^{0}-thalassemia, respectively (Fucharoen & Weatherall, 2016). For β-thalassemia, the carrier rate is about 4.5% among the Malays and Chinese in Malaysia (Fucharoen & Weatherall, 2016).

Thalassemia is a major public health issue in Malaysia, and Sabah continues to have the greatest number of thalassemia patients, with nearly half of those affected belonging to the indigenous ethnic group Kadazandusun (Clinical Practice Guidelines, 2009; Mohd Ibrahim, H. ed., 2019). Data from the Malaysian National Thalassemia Registry in 2018 showed a total of 7954 thalassemia patients in Malaysia and 73.1% of thalassemia cases in Sabah are transfusion dependent β-TM. While, reported total cumulative reported of death in Sabah are 303 patients (Mohd Ibrahim, H. ed., 2019). Over 86% of transfusion dependent β-TM patients in Sabah have Filipino β-deletion, with the mutation being most prevalent in the Kadazandusun group (Teh *et al*., 2014).

People with thalassemia require life-long blood transfusion due to anemia, as well as iron chelation therapy. The side effects of blood transfusion are associated with numerous complications, such as transmission of infection through blood and iron overload, which may interfere the endocrine, cardiovascular, and hepatic systems (Nienhuis and Nathan, 2012). Furthermore, patients with thalassemia may present with physical changes, such growth retardation, facial skull deformities, enlarged spleen and delayed sexual development (Nienhuis and Nathan, 2012; Hoffbrand and Moss, 2016). Over the past years, improvement in clinical management via multimodal treatment and early screening detection have led to better prognosis and increased survival rates of thalassemia patients (Olivieri and Brittenham, 2013; Bakhshi *et al.*, 2017).

On the contrary, patients must cope with ongoing routine of frequent visits to hospitals for blood transfusion and administration of iron chelation therapy at home throughout their lives. Patients also may require multiple hospital admissions due to complications associated with their treatments. While patients with thalassemia can live and reach older age, living with a chronic illness has a negative impact on their lives, often resulting in psychological, emotional, and social challenges for patients and their

families. Adverse effects may include school absenteeism, restricted family activities, family coping difficulties (Caro *et al.*, 2002), mental illness and financial problems (Deepika Shaligram, Girimaji and Chaturvedi, 2007; D. Shaligram, Girimaji and Chaturvedi, 2007; Ishfaq *et al.*, 2015). Therefore, the assessment of the health-related quality of life (QOL) of these patients is important for evaluating their overall health outcomes and identifying interventions to improve and maintain their QOL, particularly in children who rely on their caregivers for making decisions related to their care and treatment.

1.3 Problem statements

Although Sabah has the highest number of thalassemia cases in Malaysia (Mohd Ibrahim, H. ed., 2019), the geographical distribution of thalassemia in Sabah's population is not yet visualized to better understand the disease problems. Teh *et al*. (2014) found Filipino β-deletion was the most common gene defect causing transfusion-dependent β-TM among the indigenous population in Sabah, with highest prevalence among the Kadazandusun ethnic group, followed by Rungus, Murut, Sungai, Bruneian, and Bajau. The authors suggested that screening for Filipino β-deletion among thalassemia patients in Sabah should be prioritized as a cost-effective strategy. While their study provided molecular characterization of the most common thalassemia variant in Sabah, epidemiological studies to determine the incidence and prevalence pattern of thalassemia are still lacking.

In countries such as Pakistan, India and Iran, where consanguineous marriages are very common, high rates of thalassemia have been observed (Asadi-Pooya et al., 2004; Khan et al., 2012; Miri-Moghaddam et al., 2012). The cause of high prevalence of thalassemia in Sabah remains unknown. A study done by Ngim *et al.* (2013) in

Malaysia showed 28% of parents had more than one thalassemia children. To date, no epidemiological study has been conducted to understand this problem.

Currently, there have been limited thalassemia studies conducted in Sabah including the study of QOL among thalassemia patients. The available information on QOL of thalassemia patients is primarily from studies conducted in Peninsular Malaysia, particularly from Kuala Lumpur and Selangor areas (Ismail *et al*., 2006; Ismail *et al*., 2013; Sazlina *et al*., 2015). The findings from these studies may not be generalizable to the thalassemia patients in Sabah, as the population in Sabah has a different socioeconomic background than those in Peninsular Malaysia. As more children and adolescent patients with thalassemia are living longer due to improved treatment, this is an increasing burden on both patients and their families.

1.4 Study significances

Thus, accurate information on the distribution of thalassemia prevalence within each ethnic or district in Sabah would be useful in designing future targeted screening programs. Furthermore, understanding the underlying causes of the affected families having multiple children with thalassemia would help in developing strategies to reduce the number of new thalassemia births. For the QOL, assessing QOL among patients is important to identify aspect of their lives most affected by thalassemia and its treatments. This information will be helpful in planning an appropriate holistic care and treatment to improve patient's QOL

Additionally, studying the prevalence of thalassemia in Sabah and quality of life of thalassemia patients can provide valuable insights for allocating healthcare resources. Through the identification of specific challenges faced by patients, the healthcare systems can allocate resources in a prioritized manner to enhance support for paediatric

and adolescents with thalassemia. Furthermore, this study may assist in the enhancement healthcare policy and spearhead advocacy initiatives to improve the accessibility to care and support services. This study may identify gaps in current care practices and areas for innovation that may inspire new interventions aimed at improving quality of life and overall outcomes for thalassemia patients.

1.5 Research Questions

i. Is there a regional distribution of thalassemia in Sabah?

ii. What are the factors contributing to mothers having more than one thalassemia child in Sabah?

iii. How is the quality of life among pediatric and adolescent patient with thalassemia in Sabah?

iv. What are the factors contributing to the quality of life of pediatric and adolescent patient with thalassemia in Sabah?

1.6 Objectives of study

1.6.1 General Objectives

To determine the prevalence pattern of thalassemia, factors contributing to multiple thalassemia children in affected families, and quality of life of β-TM cases in Sabah.

1.6.2 Specific objectives

i. To map the spatial pattern of thalassemia prevalence over five years in Sabah by districts

ii. To identify the factors and reasons contributing to mothers having more than one β-TM child in Sabah

iii. To determine the quality of life among pediatric and adolescent patients with β-TM in Sabah

iv. To identify the factors contributing to the quality of life of the pediatric and adolescent patients with β-TM in Sabah

1.7 Hypothesis

Ho 1: The thalassemia prevalence pattern in Sabah does not follows a regional distribution.

H_A 1: The thalassemia prevalence pattern in Sabah follows a regional distribution.

Ho 2: Sociodemographic characteristics does not contribute to mothers having more than one β-TM children in Sabah.

H_A 2: Sociodemographic characteristics contributes to mothers having more than one β-TM children in Sabah.

Ho 3: Paediatric and adolescent patients with β-TM in Sabah have high score of quality of life.

H_A 3: Paediatric and adolescent patients with β-TM in Sabah have low score of quality of life.

Ho 4: Sociodemographic and clinical characteristics does not contribute to quality of life of paediatric and adolescent patients in Sabah

H_A 4: Sociodemographic and clinical characteristics contributes to quality of life of paediatric and adolescent patients in Sabah

1.8 Operational definition

Prevalence pattern refers to the distribution of thalassemia in Sabah within 5 years, which expressed in rate.

Quality of life refers to individual subjective perception of their overall well-being and various aspects of life which encompasses physical, emotional, social and school functioning.

Paediatrics refer to thalassemia children from new-born through 12 years of age.

Adolescents refer to thalassemia children above 12 years old up till 18 years of age.

1.9 Chapter summary

In summary, this chapter identifies a critical research problem: the lack of specific epidemiological data and impacts of the thalassemia to patients' QOL in Sabah, highlighting the need to address this gap to improve disease management and patient care in the region. This study seeks to answer key research questions related to the prevalence, familial experiences of having more than one thalassemia children's, quality of life of thalassemia paediatrics and adolescents in Sabah, which further guiding the research direction and methodology. The significance of this study is emphasized through its potential contributions to existing knowledge and its ability to inform healthcare policies and strategies in Sabah. By addressing both clinical and psychosocial aspects, the study offers a holistic view of thalassemia's impact. The

chapter also discusses the scope and limitations of the study, focusing on patients in Sabah and acknowledging constraints such as data availability and potential selection bias in the qualitative component.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

The literature review chapter provides a comprehensive review of the existing research on thalassemia This review encompasses a brief introduction on the thalassemia disease which include the clinical manifestations, classification, management and the complications and other themes highlighting the distribution and prevalence of the thalassemia in different regions, and the quality of life of paediatric and adolescents living with thalassemia. Understanding the prevalence pattern and QOL of children and adolescents affected by thalassemia is crucial for optimizing healthcare interventions and improving patient outcomes.

This literature review aims to systematically examine existing research on the prevalence pattern of thalassemia and QOL of thalassemia-affected children and adolescents. A comprehensive search was conducted across multiple electronic databases, including Google Scholar and PubMed using relevant keywords such as “thalassemia”, “prevalence”, “factors of thalassemia”, "quality of life", "children", "paediatrics," and "adolescents." The initial search yielded a total of 342 articles. After screening titles and abstracts for relevance, 75 articles were selected for full-text review. Studies focusing on the prevalence of thalassemia, as well as those assessing QOL using PedsQL^{TM} instruments in children and adolescents, were included. Key information was extracted from each selected study, including study design, participant characteristics (e.g., age, gender), prevalence rates of thalassemia, predisposing factor of thalassemia, measures of QOL, factors associated with QOL and relevant findings.

2.2 Thalassemia disease

Thalassemia result from mutations in the α (HBA1/HBA2) and β globin (HBB) genes, which disrupt the balanced production of globin chains and consequently impair erythropoiesis. Thalassemia is primarily characterized as α-thalassemia and β-thalassemia, depending on which globin chain is damaged and the underlying molecular abnormalities. Additionally, there are thalassemia subtypes caused by co-inheritance of thalassemia trait and structural haemoglobin variations, including haemoglobin S, C, and E. Common forms are haemoglobin E/ β-thalassemia, S/β-thalassemia, and haemoglobin C/β-thalassemia. In addition to these, there are several classic types of thalassemia, including silent carrier, thalassemia trait, HbH disease, and thalassemia major. Both α-thalassemia silent carrier and α-thalassemia trait are asymptomatic. HbH disease consists of non-deletional and deletional variants, with the non-deletional type being more severe due to interference with transcription of the normal α chain gene (Harewood & Azevedo, 2021).

Thalassemia presents diverse laboratory characteristics and clinical manifestations. Initially, thalassemia was classified based on clinical severity, including thalassemia major (TM), thalassemia intermedia (TI), and thalassemia minor. However, Viprakasit and Ekwattanakit (2018), argue that this classification disregarded several clinical thalassemia syndromes, namely α-thalassemia and hemoglobinopathies like Hb E/-thalassemia. Subsequently, a classification based on clinical management, peculiarly the need for regular blood transfusion, has been widely accepted. Thalassemia is classified into transfusion dependent (TDT) and non-transfusion dependent (NTDT). TDT refers to patients requiring regular blood transfusion and may experiences adverse effects such iron overload, infection and immunological reactions, which require further treatments. TDT includes patients with transfusion-dependent or

Hb H hydrops fetalis, Hb H disease, β-thalassaemia major, severe Hb E/β thalassaemia and surviving Hb Bart's hydrops fetalis (Cappellini *et al.*, 2021). NTDT represents a milder form of thalassemia where regular blood transfusions are not required. However, NTDT patients may occasionally require transfusions during concurrent illnesses, such as infection and pregnancy. In later stages of life, NTDT patients may need regular blood transfusion due to complications such as splenomegaly. NTDT includes of Hb E/β thalassaemia, Hb H disease and β-thalassaemia intermedia (Viprakasit and Ekwattanakit, 2018; Angastiniotis and Lobitz, 2019).

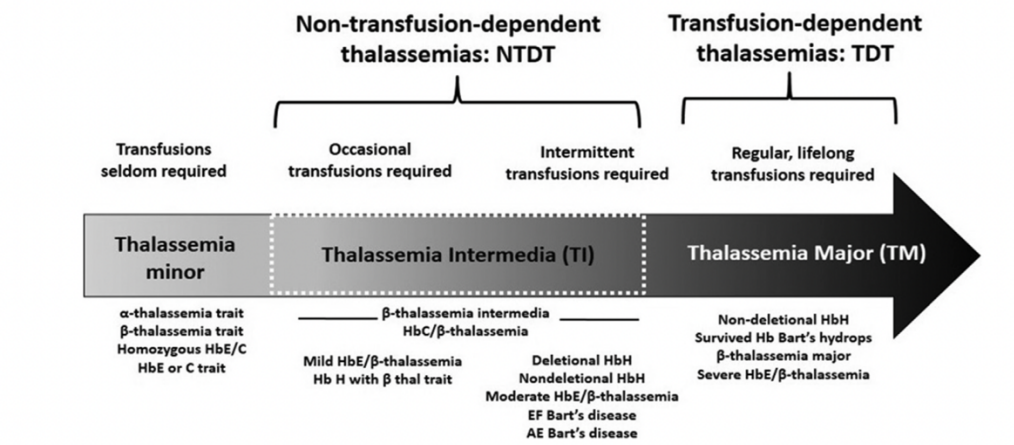

Figure 1 Classification of thalassemia based on the requirement of blood transfusion. The classification based on the severity, thalassemia intermedia (TI) and thalassemia major (TM) are shown in the arrow. (Viprakasit, V. and Ekwattanakit, S., 2018: 195)

Thalassemia is a genetic disorder and inherited in an autosomal recessive pattern. In autosomal recessive condition, an individual inherits two abnormal genes, known as recessive alleles (one from each parent), and considered homozygous for the recessive allele. Thus, will be affected by the disease. It is necessary for both parents to carry at least one disease allele capable of transmission to their child (Gulani and Weiler, 2023). Each parent has a 50% chance of passing on the disease allele. When both parents are carriers, there's a 25% chance that their child will be affected by the

disease, a 50% chance of being a carrier, and a 25% chance of being completely unaffected (*Introductory Biology CK-12 Foundation*, 2023).

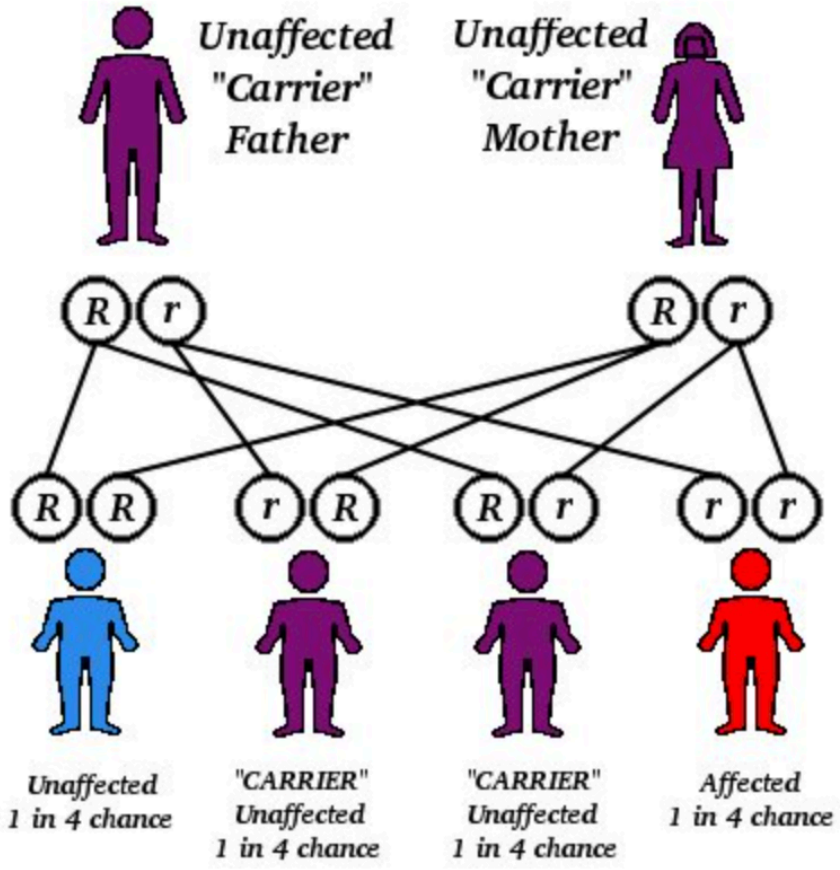

Figure 2 Mode of thalassemia inheritance, follow autosomal recessive pattern (Bhattacharya, 2012: 5)

Thalassemia patients require life-long blood transfusion due to anemia, as well as iron chelation therapy. Patients with thalassemia may present with physical changes, such growth retardation, facial skull deformities, enlarged spleen and delayed sexual development (Nienhuis and Nathan, 2012; Hoffbrand and Moss, 2016). On the contrary, patients must cope with ongoing routine of frequent visits to hospitals for blood transfusion and administration of iron chelation therapy at home throughout their lives. Patients also may require multiple hospital admissions due to complications associated with their treatments. While patients with thalassemia can live and reach older age,

living with a chronic illness has a negative impact on their well-being and quality of life.

2.3 Epidemiology

2.3.1 Worldwide regional distribution

Thalassemia is a prevalent health concern in various regions, including the Mediterranean, the Indian subcontinent, the North Africa, the Middle East, and Southeast Asia, including Malaysia (Williams and Weatherall, 2012). According to WHO Bulletin, approximately 20% of the world population are carriers of α^{+}-thalassemia, and 5.2% are carriers of significant variant, including β-thalassemia and α^{0}-thalassemia (Modell & Darlison, 2008). The prevalence and carrier rates of thalassemia vary significantly across different regions and populations.

In Mediterranean region, countries such as Afghanistan, Egypt, Iran, Iraq, Jordan, and United Arab Emirates (UAE) have higher carriers' rate of β-thalassemia rates ranging from 3% to 9%. In Iran, a countrywide study shown the average prevalence rate of thalassemia carriers is approximately 4%. However, thalassemia prevention efforts in Iran have been successful, as evidenced by the decrease in the number of newborns with thalassemia from 1,087 cases in 1989 to 239 cases in 2009 (Miri et al., 2013). In Egypt, the carrier rate for β-thalassemia in several study has been estimated to range between 5.3% and 9% (El-Beshlawy and Youssry, 2009). In contrast, α-thalassemia is less common in Egypt; one study, based on neonatal samples and molecular analysis, found that 3.1% had one α-globin gene deleted, and 4.2% had two α-globin genes deleted (Youssry et al., 2018). In UAE, the prevalence of thalassemia carriers is 4.56%. However, this study was conducted in Dubai, with the number of

subjects from other emirates being too small to draw definitive conclusions about the prevalence in those areas (Belhoul, Abdulrahman and Alraei, 2013).

In Europe, countries such as Cyprus and Greece shown significant higher carrier rate of β-thalassemia than other countries. The β-thalassemia carrier rate in Cyprus is estimated between 12% to 15% (Kyrri *et al.*, 2013) while the α-thalassemia carrier rate is around 20% (Kyriacou *et al.*, 2000). In Greece, the regional distribution is uneven, and there are known localised areas with high incidence. The prevalence of β-thalassaemia carriers ranges from 7% to 8% (Loukopoulus, 2011). However, in Chalkidiki peninsula, the prevalence of β-thalassaemia carriers higher than another region which exceeds 10% (Kalleas *et al.*, 2012). While in Italy, the prevalence of β-thalassaemia carriers is 6% and other countries such Albania, Azerbajian and Bulgaria shows lower β-thalassemia carriers' rate (Gil Bellis and Alain Parant, 2021).

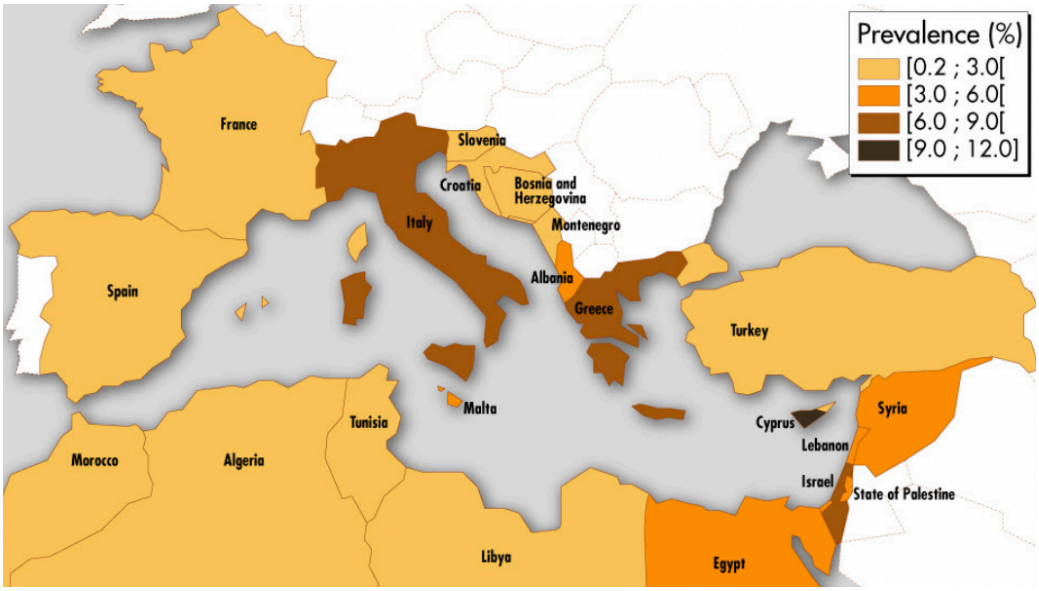

Figure 3 Prevalence of β-thalassemia carrier in Mediterranean and Europe.
(Gil Bellis and Alain Parant, 2021; 4)

In South Asia, Southeast Asia and East Asia, the thalassemia is highly prevalence and varies significantly across different countries and regions. The prevalence of β-thalassemia in India varies between 2.6% and 7.3%, with differences

observed across different regions (Choudhuri *et al.*, 2015; Mukhopadhyay *et al.*, 2015; Maji *et al.*, 2020). Certain indigenous populations exhibit considerably greater predominance (Yadav, Panchal and Menon, 2022). In Pakistan, the most common thalassemia is β-thalassemia, with the prevalence of β-thalassemia carriers approximately 3% to 5% (Bashir, Ehsan and Jafri, no date; Ali et al., 2012; Sadiq et al., 2018). A study done in Sindh, Pakistan showed there is regional and ethnic distribution of β-thalassemia patients (Kandhro *et al.*, 2017). However, the prevalence rate in Pakistan could be higher as many individuals living in unregistered villages lack access to the thalassemia center (Asif and Hassan, 2014). In Bangladesh, reported prevalence of thalassemia is limited. According to the only published report, 4.1% of Bangladeshi schoolchildren had the β-thalassemia trait (Khan *et al.*, 2005).

In Southeast Asia, α-thalassemia and β-thalassemia are both common in Thailand and Indonesia, while α-thalassemia is most prevalent in Vietnam compared to β-thalassemia. In Thailand, prevalence of β-thalassemia carrier estimated are range from 3% to 9%, 15% to 20% for α^+ thalassemia and 2.5% to 10% for α^0-thalassemia (Fucharoen and Winichagoon, 1987). Recent study done in Northern region Thailand showed 3.1% of people have α^0-thalassemia, 25.9% have α^+ thalassemia and 0.6% have β-thalassemia (Chaibunruang *et al.*, 2018). A separate study found that the prevalence of thalassemia varies among different ethnic groups in the region (Tritipsombut *et al.*, 2012). The prevalence of thalassemia carrier in Indonesia is approximately 3% to 10% for β-thalassemia and 2.6% to 11% for α-thalassemia (Wahidiyat *et al*., 2021). In Vietnam, the rate of β-thalassemia patients is 2.24%, whereas α-thalassemia patients is 10.73% (Tran *et al.*, 2023).

The occurrence of thalassemia in China exhibits significant regional disparities, with certain provinces displaying elevated carrier frequencies for both α-thalassemia

and β-thalassemia. According to a meta-analysis study, the combined prevalence of α- and β-thalassemia in Mainland China was 7.88% and 2.21%. Based on their analysis, the prevalence of thalassemia was found to be highest in the southern region of China and to decline towards the northern region (Lai *et al.*, 2017) .

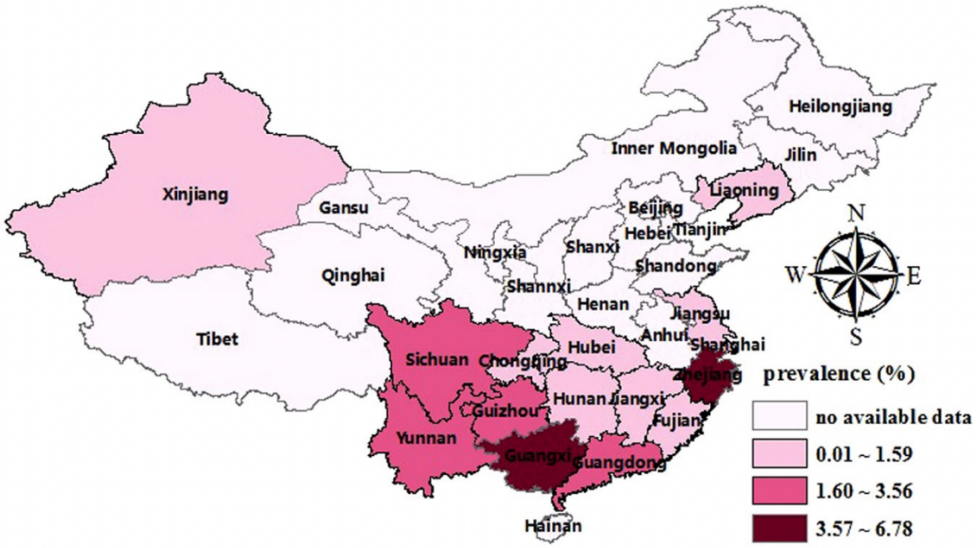

Figure 4 Geographical variation in the occurrence of β-thalassemia across various areas of mainland China (Lai *et al.*, 2017: 8)

2.3.2 Malaysia

In Malaysia, there are about 3.1% and 1.8% carriers of α^{+}-thalassemia and α^{0}-thalassemia, respectively (Fucharoen and Weatherall, 2016). For β-thalassemia, there are about 4.5% carriers among the Malays and Chinese in Malaysia (Fucharoen and Weatherall, 2016). In 2018, the Malaysian National Thalassemia Registry recorded a total of 7984 patients of various type of thalassemia. In Sabah, the estimated number of cases with transfusion-dependent β-thalassemia major cases in Sabah was greater than 1000 (Mohd Ibrahim, 2019; Teh et al., 2014). Among these patients in Sabah, over 86% have the Filipino β-deletion, with the mutation being most prevalent in the Kadazandusun group (Teh *et al.*, 2014). The indigenous population in Sabah, consisting

of more than 30 diverse ethnic groups, accounts for about 60% of the region's estimated 2.6 million people, with kadazandusuns (consists of two main ethnics, Kadazan and Dusun) being the largest group (25%), followed by Bajau (15%), Murut (3%) and other minority ethnic groups such as Sungai, Rungus, Kedayan, Lundayeh, Suluk, Brunei, and others (Population and Housing Census, 2010).

The gene defects causing α- and β-thalassemia in Malaysia are heterogeneous, and some mutations are specific to ethnic groups (Tan *et al.*, 2004; Wee *et al.*, 2005). The single -globin deletion-$\alpha^{3.7}$ is the most prevalent gene mutation among Malays in Peninsular Malaysia, while the South-East Asian deletion ($--^{SEA}$) is the most common gene mutation among the Chinese population. Among the Indian population in Malaysia, the most common mutation is -$\alpha^{3.7}$ deletion, which has the lowest prevalence of thalassemia compared to the Malay and Chinese populations (Ahmad et al., 2012; Wee et al., 2005). Among the indigenous population in Sabah and Sarawak, the commonest defect is the Filipino β-deletion, which is a rare mutation present only among the indigenous populations in Sabah (Tan *et al.*, 2010; Teh *et al.*, 2014) and Sarawak (Tan *et al.*, 2015), but not present in West Malaysia (Tan et al., 2004).

Overall, the commonest α-thalassemia gene mutation in Malaysia is the -$\alpha^{3.7}$ deletion, with the highest prevalence observed among the indigenous population in Sabah (25.6%) compared to Malays (15.5%) and Chinese (4.4%) in Peninsular Malaysia (Ahmad *et al.*, 2013). In an earlier study conducted only in Peninsular Malaysia, the prevalence of -$\alpha^{3.7}$ deletion among the Malays, Chinese, and Indian was lower, at 10.7%, 10%, and 7.4%, respectively (Wee *et al.*, 2005).

2.4 Predisposing factors for thalassemia

2.4.1 Consanguineous marriage

In countries where thalassemia is highly prevalent, such as Saudi Arabia (Al-Gazali, Hamamy and Al-Arrayad, 2006) , Iran (Asadi-Pooya, Doroudchi and Turk, 2004), and India (Ishaq *et al.*, 2012), high consanguineous marriage rates play a significant role in the increase occurrence of thalassemia births. Consanguinity, which refers to the act of marrying close relatives, result in an increase frequency of recessively inherited disease such thalassemia (Hamamy, 2012). In Iran, for example, several studies have shown that 50% to 70% of thalassemia major results from parents with first- or second-cousin marriages (Asadi-Pooya, Doroudchi and Turk, 2004; Rajaeefard *et al.*, 2015; Zamani, Khazaei and Rezaeian, 2015). In Malaysia, there are no specific report on consanguineous marriages. However, Ngim (2013) suggested that the high prevalence of thalassemia among Kadazadusun ethnic group in Sabah could be influenced by the practice of marriage between relatives, which is not an uncommon among the indigenous communities in Sabah.

2.4.2 Thalassemia screening

Despite the initiation of thalassemia screening program 25 years ago, thalassemia major is still being inherited by families who already have children affected by the disease. The prevalence of families with more than one thalassemia child varies worldwide, ranging from 18% to 32% (Karimi, Johari and Cohan, 2010; Khan *et al.*, 2012; Haghpanah *et al.*, 2013; Miri-Aliabad *et al.*, 2021). In Malaysia, 28% of the families have more than one thalassemia children (Ngim *et al.*, 2013).

Screening and prenatal diagnosis are effective preventive measures that can reduce the incidence of β-thalassaemia births by 80% to almost 100% (Angastiniotis *et al.*, 1995; Cao, Galanello and Rosatelli, 1998). Globally, screening programmes area

implemented through various culturally acceptable approaches. In countries such as Iran, Saudi Arabia, Cyprus, Turkey and Palestine, premarital screening is mandatory and is followed by counselling (Cousens *et al.*, 2010). In other countries, thalassemia screening is offered as a voluntary option and can be conducted in high schools, before marriage, when planning for pregnancy or during pregnancy (Cousens *et al.*, 2010).

However, Saffie and Howard (2015), revealed that premarital screening programs in Middle Eastern was ineffective in reducing high-risk marriages, which can be primarily attributed to suboptimal timing of the premarital screening, a lack of awareness about genetic diseases, and the influence of social and religious factors. In Bangladesh, the acceptance of premarital screening is significantly influenced by factors such as education level, religious belief, social norm, government policy and attitude of the couple (Rahman, 2014). In Oman, young individuals are reluctant to undergo premarital screening due to the concern that the positive results would prohibit the continuance of their marriage, and they did not want to interfere with what they perceived as God's plan (Al Kindi et al., 2012).

Despite the mandatory premarital screening in Iran, it was found that 78.6% parents with children affected by thalassemia major did not undergo premarital screening due to unregistered marriage (Miri-Moghaddam *et al.*, 2012). While in non-mandatory premarital screening countries, such Pakistan, found that only 29% of parents were aware of the premarital screening test (Ghafoor et al. 2016). While a study in India reported that 84.3% of parents were aware of the premarital screening test (Ishaq *et al.*, 2012). Although the percentages differ greatly, both studies concluded parental awareness regarding screening test is insufficient, indicating a high numbers of thalassemia parents who unaware of their carrier status. Studies by Miri-Moghaddam et al. (2012) and Jain et al. (2020) found that 71.2% and 86.4% of parents, respectively,

were unaware of their carrier status until the first child with thalassemia was born. However, a recent study by Miri-Aliabad et al. (2021) in Iran reported only 29.6% of parents had no information about their carrier status compared to the 71.2% reported in an earlier study done by Miri-Moghaddam et al. in 2012. This showed an improvement in awareness level regarding carrier status over the years.

In Malaysia, thalassemia screening began in 2004 as a voluntary and targeted program, focusing on family members (including siblings, parents, aunts, uncles, and cousins) of an index case (either individuals with thalassemia major or carriers) and antenatal women, while premarital screening was also provided as screening initiative ('National Thalassaemia Screening Program', 2016). In 2016, school-based thalassemia screening involved 16 years old student was implemented to strengthen the existing prevention programme ('National Thalassaemia Screening Program', 2016). However, as premarital thalassemia screening is not a mandatory requirement in Malaysia, there are still high chances of couples who are carriers of thalassemia are unaware of their status as evidenced by a study conducted in Johor, Malaysia found 70% of the thalassemia parents were unaware of their carrier status before married (Ngim *et al.*, 2015). Although thalassemia screening is accessible in Malaysia, it does not appear to be a priority within the community. Ezzati et al. (2017) revealed main reason for Malays declining premarital thalassemia screening was their apprehension about discovering the test result and its potential impact on their lives. In another study, it was discovered that 9.2% of parents of school children declined to have their child screened, with the primary reason being their belief that their children were not at risk of contracting the disease (Mat, Yaacob and Zakaria, 2020).

2.4.3 Prenatal diagnosis and pregnancy termination

Prenatal diagnosis and pregnancy termination in some countries are not permitted. Countries like Egypt, Iraq, Laos and Philippines have strict prohibition on termination of pregnancy. However, some countries like Indonesia, Malaysia, Iran, and India allow termination of pregnancy under some medical circumstances, such as to save women's life or protect her health. A study done by Khan et al. (2012) in India found that only 28% of parents who had at least one pregnancy after the birth of their first child with thalassemia underwent prenatal diagnosis. Out of the five foetuses diagnosed with thalassemia major, four parents agreed to terminate the pregnancy. On the other hand, Miri-Moghaddam et al. (2012) found in their study that 25% of parents underwent prenatal diagnosis, but 16 mothers refused to terminate the pregnancy despite the foetus having thalassemia major. Financial limitations contributed to the decision against prenatal diagnosis (Khan *et al.*, 2012; Miri-Moghaddam *et al.*, 2012), as many of the families had low socioeconomic status. Additionally, some parents were not adequately advised regarding prenatal diagnosis (Khan *et al.*, 2012). In Malaysia, a report done by the Ministry of Health (*Report management of thalassemia*, 2003), indicated that some physicians opposed the termination of pregnancy due to moral values, which created a crisis in counselling their patients regarding screening and terminating pregnancy. In a study done by Moghaddam et al. (2012), it was found that thalassemia carrier mothers were not referred for prenatal diagnosis due uncertainty regarding the gestational age. Pregnancy termination is only allowed within specific gestational age limits according to the respective national law.

Ngim et al. (2013) in their cross-sectional study evaluating the acceptability of prenatal diagnosis and abortion among parents whose children were affected by thalassemia major, found that 71.6% of Malaysian parents favoured for prenatal

diagnosis. The acceptance rate for prenatal diagnosis among Malaysian was lower compared to Iranian, where 90.3% of parents favoured prenatal diagnosis (Karimi, Johari and Cohan, 2010). This difference could be attributed to Iranian having more knowledgeable about thalassemia due to the implementation classes regarding thalassemia in high school. However, only 39.8% of those who supported prenatal diagnosis expressed a willingness to terminate an affected pregnancy (Ngim et al., 2003). The main reason for Malaysian parents refusing termination of pregnancy was religious prohibition, especially among the Muslims (Ngim *et al.*, 2013). This finding is similar to the study by Karimi et al. (2010), where the decision regarding termination of pregnancy was influenced by religious beliefs.

2.4.4 Sociodemographic and knowledge about thalassemia

Studies conducted by Karimi et al. (2010), Naseem et al. (2008), and Al-Sabbah et al. (2017) highlight the importance of educating mothers about thalassemia to reduce the number infants born with thalassemia. They found that higher levels of maternal education were associated with smaller family sizes, increased usage of prenatal diagnosis, and higher likelihood of terminating affected pregnancies. These findings suggest that maternal education plays a significant role in making informed decisions regarding pregnancy and thalassemia. While a study by Ngim et al. (2015) found a strong correlation between parental age and the choice to terminate affected pregnancy and higher education mothers showed a borderline significant association with termination of affected pregnancy.

A qualitative study conducted in Iran by Zahra Moudi and Miri-Moghaddam (2017) explored the reasons why some mothers chose to continue affected pregnancies. The study identified several subthemes, including, belief in accuracy of the diagnosis, lack of understanding, concerns about the consequences to family, opinions of other

family members, future reproductive capabilities, inclination towards having a sizable family, preference for a male foetus, moral considerations, and religious conviction (Zahra Moudi and Miri-Moghaddam, 2017). These factors may also contribute to the decision-making process among Malaysian parents, although further research is needed to explore the specific reasons in the Malaysian context.

2.5 Health related QOL of thalassemia patients

QOL is subjective evaluation of various aspects of life, including health, emotional well-being, and social functioning, as perceived by an individual (Varni, Seid and Kurtin, 2001). According to Calman (1984), a person's quality of life is influenced by their past experiences, present lifestyle, future expectations, aspirations, and hopes. QOL is predisposed by an individual's experience, current lifestyle, future expectations, dreams and hopes. Hence, QOL is a measure of the differences between an individual's life expectations and their current experiences. Health-related quality of life (HRQOL), as defined by Hays & Reeve (2010), refers to an individual's level of functioning and their perceived well-being across the physical, mental, and social aspects of health. Meanwhile, Karimi and Brazier (2016) appraised HRQOL as merely focus on the impact of health status on individual's quality of life. In epidemiological studies or clinical practice, QOL is an important indicator in evaluating treatments/interventions outcomes.

Over the past decades, considerable numbers of QOL measuring tools have been developed (Solans *et al.*, 2008) and there is a wide range of QOL measuring tools used in studies assessing the quality of life among children with thalassemia. Some commonly used tools include KINDL, Child Health and Illness Profile (CHIP), Paediatric Quality of Life Inventory (PedsQL), and KIDSCREEN-52. Kenzik et

al.(2014) noted that no single instrument was found to be superior to the others in terms of psychometric properties.

In Malaysia, the range of total mean score of QOL among thalassemia children using the PedsQL is 65.35 to 80.12 (Ismail, Michael J Campbell, *et al.*, 2006; Ismail *et al.*, 2013; Sazlina, Asauji and Juni, 2015; Shafie *et al.*, 2020). In Thailand, the total mean scores range from 74.35 to 78.5 (Surapolchai, Satayasai and Udomsubpayakul, 2010; Thavorncharoensap *et al.*, 2010; Torcharus and Pankaew, 2011). In the Middle East, the total mean scores using PedsQL range from 59.15 to 77.75, with Jordan showing the lowest mean score (Caocci *et al.*, 2012; Gharaibeh and Gharaibeh, 2012a; Jafari-Shakib *et al.*, 2016). India has the highest mean scores for QOL among thalassemia children and adolescents, with a range of 82 to 83.7 (Dhirar *et al.*, 2016; Sharma *et al.*, 2017).

2.5.1 Factors associated with QOL

Factors associated with the QOL of thalassemia patients are diverse and include sociodemographic and clinical factors as summarized in Table 2.1. Age at the time of first diagnosed, family income, (Surapolchai, Satayasai and Udomsubpayakul, 2010; Thavorncharoensap *et al.*, 2010), and the total number of hospital visit (Dhirar *et al.*, 2016) have been found to be significantly associated with QOL. Clinical factors that were found to associated with QOL are the type of treatment received (Thavorncharoensap *et al.*, 2010; Dhirar *et al.*, 2016), delayed the start of iron chelation (Caocci *et al.*, 2012), the frequency of treatment (Dhirar *et al.*, 2016),and complications (Gharaibeh & Gharaibeh, 2012).

In Malaysia, there have been limited studies on QOL of paediatric patients with thalassemia. Ismail *et al*. (2006) conducted the first study in Malaysia investigating the QOL of children aged 5 to 18 years old with thalassemia, including β-TM, β-