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A systematic review of the prevalence and phenotypic characteristics of hemoglobin Malay in Southeast Asia

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Abstract:

BACKGROUND: Hemoglobin (Hb) Malay is a β-globin variant associated with a β^{++}-thalassemia phenotype, resulting from a point mutation at codon 19 of the β-globin gene. Data on its prevalence and phenotypic characteristics remain fragmented.

AIMS: This study aimed to determine the prevalence of Hb Malay and describe its phenotypic spectrum across different regions.

METHODS: A systematic literature search was conducted using Medline (PubMed), CINAHL (EBSCOhost), and ScienceDirect. Relevant studies published from database inception to 2024 were screened according to predefined eligibility criteria. Meta-analysis was performed using Review Manager (RevMan) version 5.4. Pooled prevalence estimates were calculated, and outcomes were reported with corresponding 95% confidence intervals.

RESULTS: Twenty-two studies involving 19,956 participants were included. Due to substantial heterogeneity among studies (I^2 = 86%, P < 0.001), a random-effects model was applied. The overall pooled prevalence of Hb Malay was 3.53%. The highest prevalence was observed in Indonesia (12.18%), followed by Thailand (3.43%), Malaysia (3.02%), and Singapore (0.75%).

CONCLUSION: This study represents the first comprehensive meta-analysis of Hb Malay prevalence and phenotypic characteristics over 30 years (1990–2024). Although Hb Malay is a relatively rare Hb variant largely confined to Southeast Asia, its clinical relevance is significant, particularly when coinherited with other β-thalassemia mutations, which may modify disease severity and increase transfusion requirements. These findings provide valuable evidence to inform regional thalassemia screening strategies and support targeted genetic counselling programmes.

Keywords:

Hemoglobin Malay, prevalence, Southeast Asia, β++-thalassemia

Introduction

Thalassemia is the most prevalent inherited hematological disorder in Southeast Asia and results from reduced or absent hemoglobin (Hb) synthesis, leading to an imbalance in globin chain production.[1] β-Thalassemia arises from mutations affecting the single β-globin gene, which disrupt β-globin chain synthesis either completely (β^0) or partial residual production (β$^+$ or β^{++}, so-called "silent" thalassemia).[2,3] The extent of β-globin production, and hence the β^0, β$^+$, or β^{++} phenotype, is determined by the location and nature of the underlying mutation. As a result, the clinical and hematological spectrum of β-thalassemia ranges from asymptomatic silent carriers to clinically significant disorders, including transfusion-dependent β-thalassemia major and β-thalassemia intermedia.[4]

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The diagnosis of thalassemia and abnormal Hb variants is based on integrated laboratory evaluation, including red blood cell indices as a first-line screening tool, followed by Hb analysis with HbA_2 and HbF quantification using capillary electrophoresis or high-performance liquid chromatography, which remain the standard methods for routine β-thalassemia screening.[5-7] In β-thalassemia carriers, HbA_2 levels are typically elevated above normal, often exceeding 3.5%, with mean values around 5.2% reported in recent analyses, making elevated HbA_2 a robust marker of β-thalassemia trait.[8]

Notably, Hb Malay carriers demonstrate a wider range of HbA_2 levels compared with classical β-thalassemia carriers, as reported in several studies.[9,10] Local investigations and unpublished data further suggest that a proportion of Hb Malay carriers fall within the borderline HbA_2 range of 3.4%–3.9%.[4] Hb Malay migrates similarly to Hb A and therefore cannot be reliably identified using either CE or HPLC.[11] Consequently, definitive diagnosis of Hb Malay requires molecular techniques.[4] Because Hb Malay is electrophoretically indistinguishable from Hb A, posing a diagnostic challenge, particularly in centres without access to molecular testing facilities.[4] Hb Malay is a structural Hb variant associated with a β^{++}-thalassemia phenotype, caused by a mutation in the β-globin gene that substitutes serine for asparagine at codon 19.[9,12]

Globally, thalassemia represents the most common monogenic disease. According to the WHO, about 5.2% of the global population carry a clinically significant Hb disorder, most commonly sickle cell disease and thalassemia. In 2008, it was estimated that 5.2% of the world's population were thalassemia carriers, with around 1.1% of couples being at risk of having a child affected by a Hb disorder.[13] Hb Malay is prevalent among Southeast Asian populations. In Malaysia, a 2017 study reported a prevalence of 5.5%, corresponding to 132 identified cases,[14] while 226 cases were documented in southern Thailand between 2015 and 2022.[15] Overall, Hb Malay accounts for approximately 15% of all β-thalassemia mutations in Malaysia, 16% in southern Thailand, and 2% in central Thailand.[12]

Several Southeast Asian countries have independently reported the prevalence of Hb Malay among different ethnic groups, demonstrating marked variability between populations. However, to date, no comprehensive analysis has systematically evaluated the prevalence of Hb Malay. Therefore, this systematic review aims to consolidate and update available data on the global prevalence of Hb Malay from 1990 to 2024 globally with particular emphasis on Malaysia, Thailand, Singapore, and Indonesia. The findings are expected to support evidence-based healthcare policies, guide large-scale screening programmes, and enhance genetic counselling strategies in regions where Hb Malay is prevalent.

Methods

Eligibility criteria

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[16] The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (Registration Number: CRD42025637325).

Studies were eligible for inclusion if they reported the prevalence of Hb Malay worldwide. Cross-sectional studies, analytical observational studies, and articles available only in abstract form, published in English and conducted at either community or healthcare institution levels, were included for prevalence analysis. Case reports, case series, conference papers, editorials, letters to the editor, commentaries, and systematic reviews were excluded from prevalence estimation but were included for descriptive analysis of phenotypic characteristics.

Search strategy and study selection

A comprehensive systematic search was conducted in Medline (PubMed), CINAHL (EBSCOhost), and ScienceDirect. The search terms included combinations of the keywords "thalassemia," "hemoglobin," "Hb Malay," and "Southeast Asia." Search strategies were adapted to suit the syntax and requirements of each database. All relevant studies published from database inception until 2024 were retrieved. The search was limited to full-text articles published in English. In addition, reference lists of all included studies were manually screened to identify any additional eligible publications.

All records identified through the search were imported into EndNote software, and duplicate entries were removed. Two independent reviewers screened the titles and abstracts of the retrieved articles for eligibility. Full-text articles of potentially relevant studies were then reviewed in detail to confirm inclusion. Any discrepancies between the reviewers were resolved through discussion, and where consensus could not be reached, a third reviewer was consulted. The study selection process is summarised in a PRISMA flow diagram, detailing the number of studies included and excluded, along with reasons for exclusion.

Data extraction and quality assessment

Data extraction was performed using a standardized data collection form. Extracted information included the first author, β-thalassemia phenotype, study location,

study design, specific ethnic groups studied, sample size, number of Hb Malay cases, and other relevant clinical or laboratory characteristics.

Data synthesis

Data synthesis was performed in two stages: qualitative (descriptive) synthesis and quantitative synthesis (meta-analysis). For the qualitative synthesis, all studies that met the inclusion criteria were reviewed to summarise study characteristics and phenotypic descriptions of Hb Malay. This included study setting, population characteristics, ethnic groups, diagnostic methods used, β-thalassemia phenotype, and reported laboratory findings. These data were narratively synthesised to describe the geographical distribution and phenotypic variability of Hb Malay across Southeast Asia.

For the quantitative synthesis, studies that reported sufficient data on the prevalence of Hb Malay were included in the meta-analysis. Pooled prevalence estimates were calculated using Review Manager (RevMan) software, version 5.4. The Cochrane Collaboration, Copenhagen, Denmark. Given the substantial heterogeneity observed among studies, a random-effects model was applied. Heterogeneity was considered substantial when I^2 exceeded 50%, according to the Cochrane Handbook for Systematic Reviews of Interventions.[17] Prevalence estimates were presented with corresponding 95% confidence intervals (CIs).

Subgroup analyses were performed based on country and region, where data were available, to explore potential sources of heterogeneity. Publication bias was assessed visually using funnel plots when an adequate number of studies were available. The results of the study selection process, including the number of studies identified, screened, excluded, and included in both qualitative and quantitative syntheses, are summarised in the PRISMA flow diagram [Figure 1].

Results

A total of 206 articles were identified through electronic database searches using various search terms. After removal of 11 duplicate records, 195 articles remained for screening. Of these, 119 articles were excluded following title and abstract screening. Full-text assessment was conducted for 76 articles, after which 51 studies were excluded (50 did not report the primary outcome of interest, and one was available only as an abstract). Consequently, 25 studies were assessed in detail, with a further three excluded as case reports.

Ultimately, 22 studies were included in the systematic review and meta-analysis. Of these, 20 were cross-sectional studies, one was an observational study, and one was an abstract. The studies were conducted across multiple countries, including 10 from Malaysia, eight from Indonesia, three from Thailand, and one from Singapore.

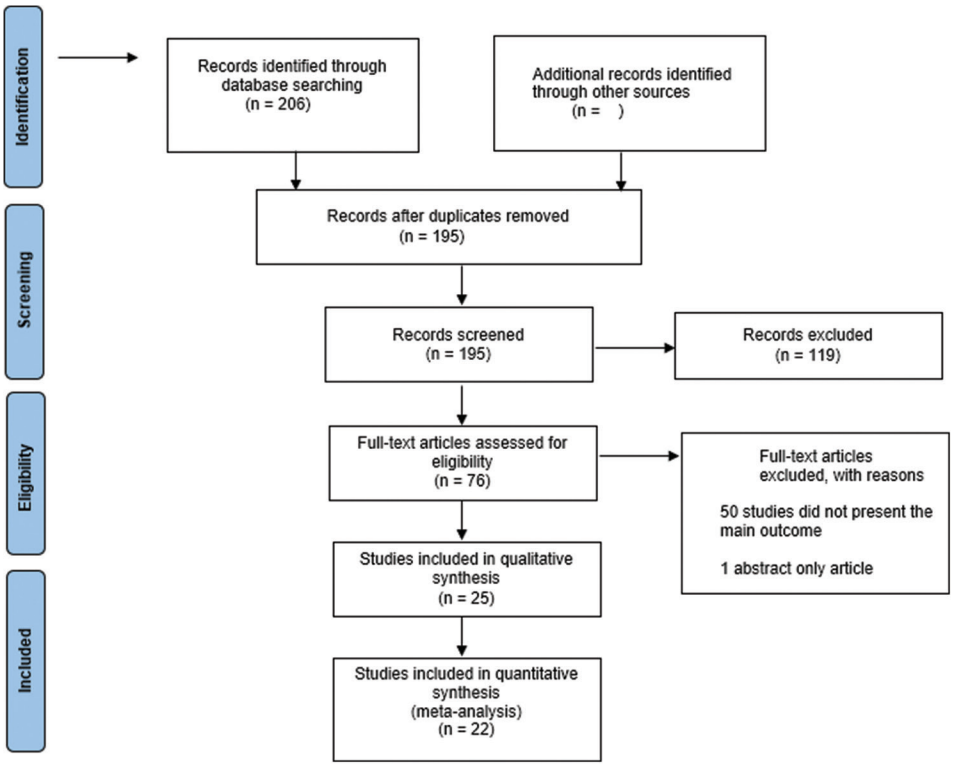

Figure 1: Flow diagram shows the included studies for systemic review and meta-analysis on the prevalence hemoglobin Malay in Southeast Asia

Sample sizes ranged from 14 participants to 13,391 participants.[15,18] In total, the review encompassed 19,956 participants.

Among the included studies, 19 were conducted in hospital-based settings, while seven studies[2,9,13,14,16,19,20] were community-based. The review demonstrated modest variation in the prevalence of Hb Malay across Southeast Asia. The lowest prevalence (0.75%) was reported in a hospital-based study,[21] whereas the highest prevalence (25.7%) was observed in a community-based study.[14] The pooled prevalence of Hb Malay across all included studies was 3.53% (95% CI: 2.48–4.58). A total of 22 studies were included in the estimation of pooled prevalence [Figure 2].

The forest plot in Figure 3 illustrates the prevalence of Hb Malay across different Southeast Asian countries. Due to substantial heterogeneity among studies (I^2 = 86%), a random-effects model was applied. This heterogeneity is likely attributable to differences in study settings (community versus hospital-based), ethnic composition, and methodological approaches. Indonesia showed the highest pooled prevalence (12.18%), largely driven by community-based studies from South Sumatra. Thailand and Malaysia demonstrated comparable pooled prevalences of 3.43% and 3.02%, respectively, supported by large and ethnically diverse cohorts. Singapore reported the lowest prevalence (0.75%); however, this estimate is based on a single hospital-based study and should be interpreted cautiously.

Table 1 summarises the hematological phenotype of Hb Malay carriers reported across Southeast Asian populations. Hb Malay is associated with mild anemia and consistent microcytosis and hypochromia. Hb levels are generally within the mild anemic or low-normal range. HbA_2 levels show a wider and often borderline-to-mildly elevated range compared with classical β-thalassemia carriers, while Hb F levels are typically low but variable, particularly in compound heterozygous states.

Discussion

Hb Malay is a structural or thalassemic Hb variant, similar to HbE. It is a relatively common β-globin variant in Malaysia, caused by a nucleotide substitution at codon 19, which leads to a β^{++}-thalassemia phenotype. Detecting Hb Malay is difficult because it co-migrates with Hb A on routine CE or HPLC, making it indistinguishable by these methods alone. Clinically, Hb Malay often presents with thalassemia-like features based on suggestive red cell indices and an elevated HbA_2 level. However, definitive confirmation requires molecular testing. Techniques such as multiplex amplification refractory mutation system PCR (M-ARMS PCR) and DNA sequencing are commonly

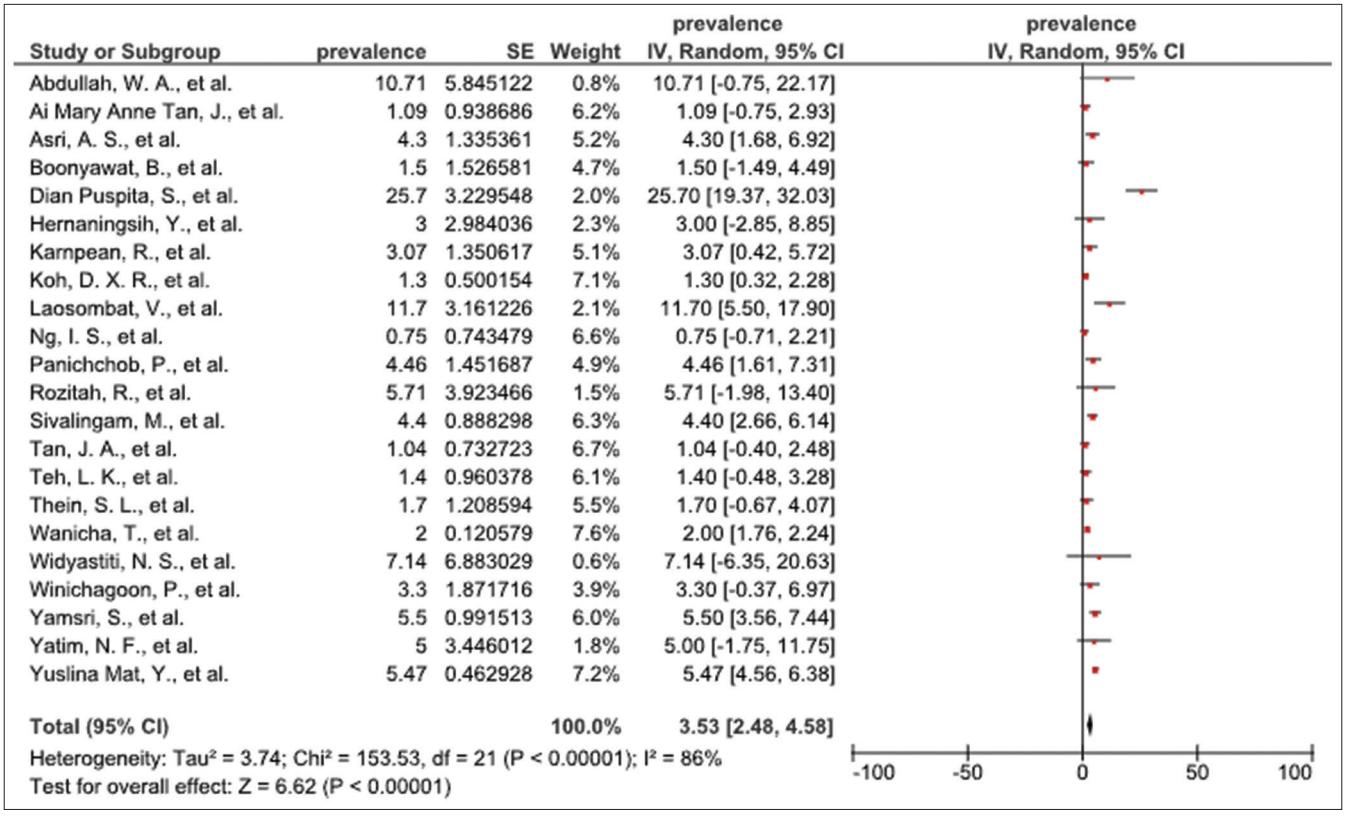

Figure 2: Forest plot for the prevalence of hemoglobin Malay using random effect model

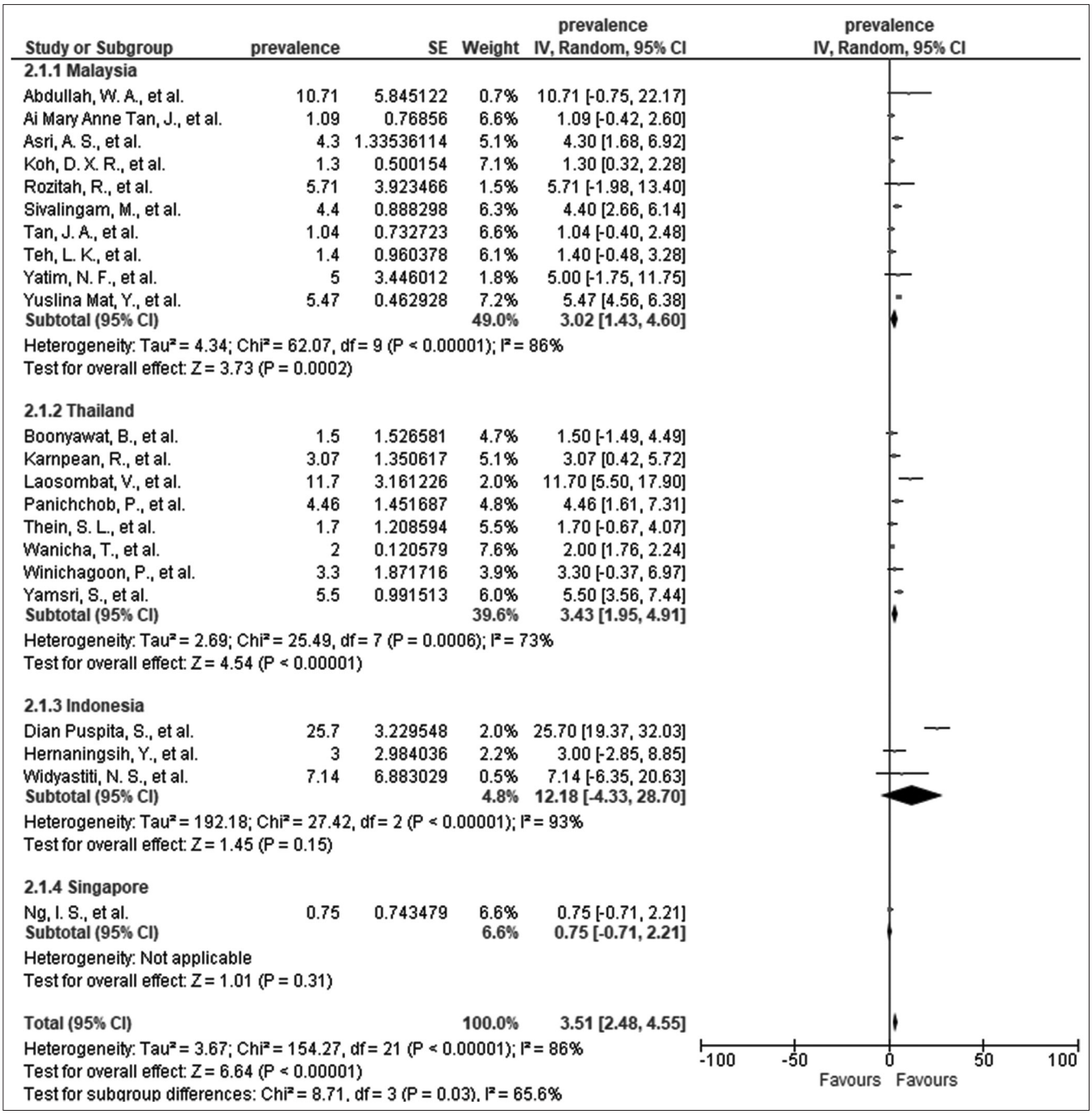

Figure 3: Forest plot for the prevalence of hemoglobin Malay grouped according to country

used. In addition, rapid dedicated genetic testing kits such as the ViennaLab SEA panel can also assist in confirming the presence of the Hb Malay variant.[11] Co-inheritance of Hb Malay with other defective β-globin alleles, whether in homozygous or compound heterozygous states, may result in transfusion-dependent thalassemia (TDT) or non-TDT phenotypes.[22,23] While homozygous Hb Malay and compound heterozygous Hb Malay/Hb E have generally been associated with non-TDT phenotypes,[24,25] cases of compound Hb Malay/β^0-thalassemia presenting as TDT have also been reported.[9,26] In line with World Health Organization recommendations, characterization of mutation spectra remains a cornerstone of β-thalassemia control strategies, enabling effective carrier detection, genetic counseling, prenatal diagnosis, and population screening.[11]

Molecular pathogenesis of hemoglobin Malay

Hb Malay arises from a point mutation at codon 19 (AAC → AGC) of the β-globin (HBB) gene, resulting in substitution of asparagine by serine at position 19 of the β-globin chain. This mutation disrupts normal

Table 1: Phenotypic characteristics of heterozygous hemoglobin Malay across Southeast Asia

Study	Hb (g/dL)	MCV (fL)	MCH (pg)	HbA2/E (%) HPLC	Hb F (%) HPLC	References
1	11.6±1.7 (8.7–15.5)	70.7±6.3 (53.2–82.8)	22.5±2.1 (16.7–25.5)	4.01±0.44 (3.5–5.5)	0.76±1.24 (0–5.4)	Asri, A. S., *et al.* (2024)[11]
2	12.3 (8.3–15.5)	71.2 (53.4–81.3)	22.0 (16.0–25.0)	-	0.2 (0–3.9)	Dian Puspita, S., *et al.* (2022)[14]
3	11.5±1.1	72.1±6.0	23.6±1.5	5.6±0.2	1.3±0.8	Karnpean, R., *et al.* (2022)[20]
4	12.8±1.2	72.3±5.6	22.1±1.5	4.9±0.5 (4.4–6.1)	-	Koh, D. X. R., *et al.* (2017)[10]
5*	11.0±0.9	71.5±4.0	23.1±1.5	4.5±0.4	0.1±0.7	Wanicha, T., *et al.* (2024)[15]
6	12.0±1.6	70.2±5.1	23.4±2.5	4.4±0.4	1.3±1.4	Yamsri, S., *et al.* (2015)[9]

*These data represent heterozygous females only. Values are expressed as mean±SD (Range). Hb=Hemoglobin, HbA2/E=Hemoglobin A2/E, HPLC=High performance liquid chromatography, MCV=Mean corpuscular volume, MCH=Mean corpuscular hemoglobin, SD=Standard deviation

Hb structure and stability, affecting oxygen-binding properties. Importantly, the codon 19 mutation introduces a cryptic 5′ splice donor site within exon 1, which competes with the canonical splice site during mRNA processing. This aberrant splicing leads to the generation of unstable or non-functional transcripts, thereby reducing effective β-globin production to approximately 60% of normal levels. The resulting imbalance between α-and β-globin chains contributes to ineffective erythropoiesis and a quantitative β^{++}-thalassemia phenotype.

Proteomic characteristics of hemoglobin Malay

At the proteomic level, the asparagine-to-serine substitution alters the local conformation of the β-globin chain, influencing subunit interactions, heme incorporation, and tetramer assembly. Although structurally subtle, these changes may affect Hb function under physiological stress. Proteomic analyses have demonstrated altered globin chain stability and distribution, particularly in compound heterozygous states, with elevated Hb F levels commonly observed as a compensatory response. Advanced techniques such as mass spectrometry and two-dimensional electrophoresis have revealed differences in globin abundance, solubility, and posttranslational modifications. Consistent with electrophoretic findings, Hb Malay comigrates with Hb A on CE, underscoring the need for molecular confirmation. Additional evidence suggests that Hb Malay may exhibit reduced thermal stability and increased susceptibility to oxidative stress, potentially contributing to shortened erythrocyte survival. Recent data indicate that Hb Malay carriers have higher Hb, MCV, MCH, and Hb A levels compared with β^0-thalassemia carriers, with HbA_2 values ranging from 3.5% to 5.5% and a proposed diagnostic cut-off of ≤4.6%.[11]

This study represents the first comprehensive evaluation of the prevalence of Hb Malay in Southeast Asia over 30 years (1990–2024). No eligible studies meeting the predefined inclusion and exclusion criteria were identified from other Southeast Asian countries, including Brunei, Myanmar, Vietnam, the Philippines, Timor-Leste, Laos, and Cambodia. Using a random-effects model, the pooled prevalence of Hb Malay across the included countries was estimated at 3.53% (95% CI: 2.48–4.58).

When analysed by country, Indonesia demonstrated the highest pooled prevalence of Hb Malay at 12.18%. This elevated prevalence is likely attributable to the high carrier frequency of β-thalassemia trait in South Sumatra, reported to be as high as 15%.[27] In contrast, the prevalence of Hb Malay in Thailand (3.43%) and Malaysia (3.02%) was relatively similar. Singapore recorded the lowest prevalence at 0.75%; however, this estimate was derived from a single study, and additional data are required to accurately determine the true national prevalence. To date, no cases of Hb Malay have been reported in other Southeast Asian countries.[28]

In Malaysia, the pooled prevalence of Hb Malay was 3.02% (240/4,933), which slightly lower to the findings from a local study reporting a prevalence of 5.5% (132/2,413).[26] The slightly lower estimate observed in this meta-analysis may be explained by the inclusion of studies with larger sample sizes. Consistent with previous reports, the majority of Hb Malay cases were identified among individuals of Malay ethnicity, with only isolated cases reported among those of Chinese descent. A large-scale study conducted at the Institute of Medical Research, Malaysia, in 2018 further demonstrated that 96% of Hb Malay cases occurred among Malays, followed by smaller proportions among Dusun (1.5%), Chinese (0.8%), Bajau (0.8%), and Orang Asli (0.8%) populations.[22]

Co-inheritance of hemoglobin Malay with other hemoglobinopathies

The clinical significance of Hb Malay is most evident when co-inherited with other hemoglobinopathies common in Southeast Asia.

1. Hb Malay and Hb E: Compound heterozygosity for Hb Malay and Hb E typically results in a thalassemia intermedia phenotype, characterised by microcytic anemia, elevated Hb F, and splenomegaly, with most

patients remaining transfusion-independent. Studies from Thailand have reported a high frequency of this genotype, highlighting the diagnostic importance of molecular testing
2. Hb Malay and β-thalassemia: Coinheritance with β^0-thalassemia mutations leads to additive impairment of β-globin synthesis and often manifests as thalassemia intermedia. Clinical severity is influenced by residual β-globin production and modifying genetic factors, including co-existing α-thalassemia and Hb F-modulating polymorphisms
3. Hb Malay and α-thalassemia: When Hb Malay is inherited alongside α-thalassemia, the resulting globin chain imbalance can exacerbate ineffective erythropoiesis, producing a spectrum of disease severity ranging from mild anemia to Hb H-like features. These patients may experience increased hemolysis, iron overload, and splenomegaly, necessitating careful monitoring and individualized management, including iron chelation and, in selected cases, splenectomy.

Strengths and limitations

Several limitations should be acknowledged. Data were available only from selected Southeast Asian countries, limiting the generalisability of prevalence estimates to the wider region. In addition, ethnic-specific analyses could not be performed for most countries due to insufficient reporting, with detailed ethnic data largely confined to studies from Malaysia. Another limitation is the inability to analyse coinheritance of Hb Malay with other hemoglobinopathies, as most included studies did not report sufficient genotype-level data.

Conclusion

This meta-analysis is the first to systematically assess the prevalence of Hb Malay in Southeast Asia. The findings indicate that Hb Malay is present at relatively low prevalence in selected countries, with marked regional variation. The results provide valuable evidence to support the development of targeted screening strategies, educational initiatives, and genetic counselling programmes aimed at improving the detection and management of Hb Malay within affected populations.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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