Received: 19 January 2024 | Revised: 8 March 2024 | Accepted: 8 March 2024

DOI: 10.1002/jha2.882

eJHaem

British Society for Haematology

SHORT REPORT

Systematic review and evidence gap assessment of the clinical, quality of life, and economic burden of alpha-thalassemia

Khaled M. Musallam[1] | Vip Viprakasit[2] | Louise Lombard[3] | Keely Gilroy[3] | Amey Rane[3] | Lydia Vinals[4] | Candice Tam[5] | Maria Rizzo[5] | Thomas D. Coates[6]

[1]Center for Research on Rare Blood Disorders (CR-RBD), Burjeel Medical City, Abu Dhabi, United Arab Emirates

[2]Department of Pediatrics & Thalassemia Center, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

[3]Agios Pharmaceuticals, Cambridge, Massachusetts, USA

[4]Cytel, Toronto, Ontario, Canada

[5]Cytel, London, UK

[6]Cancer and Blood Disease Institute, Children's Hospital Los Angeles and USC Keck School of Medicine, Los Angeles, California, USA

Correspondence
Khaled Musallam, Center for Research on Rare Blood Disorders (CR-RBD), Burjeel Medical City, 28th Street, Mohammad Bin Zayed City, PO Box 92510, Abu Dhabi, United Arab Emirates.
Email: khaled.musallam@inhweb.org

Funding information
Agios Pharmaceuticals

Abstract

A recent evidence gaps assessment of the clinical, health-related quality of life, and economic burden associated with α-thalassemia is lacking. We conducted a systematic literature review (SLR) following the methodological and reporting requirements of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and the Cochrane Handbook for Systematic Reviews, using available literature over the past decade. This SLR identified a considerable evidence gap with regard to understanding the current burden of α-thalassemia as evident from paucity of studies published in the past 10 years. The limited data available still indicate that patients with α-thalassemia experience substantial morbidity and quality of life/economic burden that is generally comparable to patients with β-thalassemia.

KEYWORDS
complications, cost, HRQOL, management, morbidity, thalassemia

1 | INTRODUCTION

The thalassemias are a group of inherited disorders of hemoglobin synthesis that result from mutations in globin genes that lead to a deficit in the production of the α-globin (α-thalassemia) or β-globin (β-thalassemia) chains of adult hemoglobin and subsequent ineffective erythropoiesis and anemia of varying severity [1]. Approximately, 5% of the global population carries the α-thalassemia trait, with clinically significant forms having the highest prevalence in Southeast Asia [2]; although prevalence is also increasing in large multiethnic cities in the United States and Europe due to immigration [3, 4]. Globally, more than 5000 children are born each year with the severe form of α-thalassemia, α-thalassemia major or hemoglobin Bart's hydrops fetalis (four α-globin genes deleted/inactivated), but they are usually stillborn with only a few children who survive facing a lifelong requirement for transfusions. The annual number of births for α-thalassemia intermedia or hemoglobin H disease (three α-globin genes deleted/inactivated) is approximately 10,000 [5, 6]. In addition to deletional forms, there are various non-deletional mutations causing hemoglobin H disease which are typically associated with a more severe anemia and transfusion-dependence [1]. To date, most research has focused on the burden of β-thalassemia. However, recent evidence suggests that α-thalassemia,

once perceived as a benign condition, is associated with serious comorbidities, especially in non-deletional forms [7–9]. Moreover, while data on the global economic burden of α-thalassemia are limited, a considerable portion of the burden is borne by countries with limited resources [1].

This systematic literature review (SLR) characterized the clinical, health-related quality of life (HRQoL), and economic burden associated with α-thalassemia and assessed evidence gaps, based on available literature over the past decade to reflect contemporary understanding of the disease during a period when conventional management options and international guidelines were widely available [10].

2 | METHODS

The SLR followed the methodological and reporting requirements of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [11] and the Cochrane Handbook for Systematic Reviews of Interventions [12]. Literature searches for studies in α-thalassemia were part of a broader search including all thalassemia subtypes in MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the Health Technology Assessment Database, the National Health Service Economic Evaluations Database, and EconLit. Studies published from January 2010 to October 2022 were included if they reported results for α-thalassemia exclusively or separately for subgroups of patients. Abstracts from relevant conferences from January 2017 to October 2022 were searched and bibliographies of existing SLRs were screened to ensure no relevant studies were missed. Two independent reviewers screened references, and a third resolved discrepancies. Data were extracted by one reviewer and validated by another. Studies in α-thalassemia were included if they reported clinical burden outcomes (complications, treatment patterns, and mortality) for adults. Limited publications were available on HRQoL (including quality of life, psychosocial burden, symptom burden, and other patient reported outcomes) and economic burden (healthcare resource utilization [HCRU], costs, or cost-effectiveness of treatments) for adults; therefore, studies in both adults and children on these topics were included. Study types included real-world evidence studies (such as observational and cross-sectional studies) and economic evaluations (such as cost-effectiveness models).

3 | RESULTS AND DISCUSSION

The broader search across all thalassemia subtypes returned 9946 hits. However, only 13 studies on α-thalassemia (including hemoglobin H disease [HbH: deletional and/or non-deletional] and α-thalassemia with unspecified genotype) met the inclusion criteria (Figure 1) [13–25]. Eight studies reported on clinical burden [14, 16–22], two studies each reported on HRQoL [24, 25] and HCRU/costs outcomes [13, 15], and one study reported on both clinical burden and HCRU/costs (Table 1) [23]. No economic evaluations such as cost-effectiveness studies were identified.

Three studies were in an α-thalassemia-only population [16, 22, 23] and 10 were in a mixed population (α-thalassemia and other types) reporting separate subgroup data [13–15, 17–21, 24, 25].

Eight studies were cross-sectional [15–17, 19, 20, 22, 24, 25], three were retrospective cohorts [13, 18, 21], one was a prospective cohort [23], and one was a case-control design [14]. Only two studies had more than 100 α-thalassemia patients, and five studies reported relevant outcomes in subgroups of 10 or fewer patients. Sample sizes ranged from 1 [15] to 1675 patients [14]. A total of 10 studies were conducted in Asia (Thailand = 5 [17, 19, 21, 24, 25]; mainland China = 1 [22], Hong Kong SAR = 1 [16]; Malaysia = 1 [18], United Arab Emirates [UAE] = 2 [13, 15]), two in the United States [14, 23], and one in Italy [20]. Eleven studies [15–25] reported on patients with HbH, while two [13, 14] reported on patients with α-thalassemia without specifying its genotype.

Complication rates and treatment patterns among patients with HbH are presented in Figure 2. Among patients with HbH and/or HbH/constant spring (CS), the most frequently reported complications as defined in these studies were iron overload (31%–66% [16, 19, 22]), hyperuricemia (60% [17]), cholelithiasis (28%–52% [19–21]), bone disease (0%–33% [19–21]), hepatic (9%–28% [16, 19, 21]), and endocrine complications (0%–17% [19–21]). The clinical burden of non-thalassemia-related complications (outside the scope of this SLR) that are commonly observed in the aging general population (e.g., malignancy) may also be observed in older adults with HbH [26].

An analysis [14] of the MarketScan Commercial, Medicare, and Multi-State Medicaid claims database in the United States showed that patients with non-transfusion-dependent α-thalassemia (α-NTDT) had higher rates of cardiovascular disease (7.2% vs. 4.7%), cerebrovascular disease (3.8% vs. 1.9%), pulmonary hypertension (1.1% vs. 0.3%), jaundice (1.0% vs. 0.2%), and liver disease (1.2% vs. 0.4%) compared with matched controls (matched on age, sex, follow-up period, and payer type) (all $p < 0.001$), and a higher number of overall comorbidities (mean [standard deviation]: 1.7 [1.5] vs. 1.1 [1.2]; $p < 0.001$).

In a cross-sectional study in Hong Kong, moderate-to-severe liver iron overload (53% vs. 25%, p = 0.03) was more frequent and median liver iron concentration (median [range]: 7.8 [1.7–17.7] vs. 2.9 [0.1–15.0] mg/g dry weight, $p = 0.002$) was significantly higher in adults with non-deletional versus deletional HbH NTDT, although these complications were prevalent in both groups [16].

In adults with HbH and/or HbH/CS, 56.0% [16] had a history of blood transfusions, 46.7%–87.0% [19, 20] had occasional transfusions, 6.0%–52.2% had received iron chelation therapy, [16, 19–22] and 10.0%–14.8% were splenectomized [16, 20, 21]. The probability of receiving at least one transfusion by the age of 20 years was 3% for patients with deletional HbH and 80% for those with non-deletional HbH ($p < 0.001$) [23]. No evidence was identified on treatment patterns of hematopoietic stem cell transplantation, hydroxyurea, or novel therapies.

Another study from the United States compared the natural history of 83 patients (median [range] age: 5.9 [0.1–72] years) with deletional HbH or HbH/CS [23]. During the study observation period, one death occurred in an adult in the HbH/CS group (median [range] follow-up:

TABLE 1 Overview of included studies.

Reference	Outcome	Study design	Country	α-Thalassemia subtype	β-Thalassemia subtype	Transfusion phenotype[a]	Age, years	*N* (total)	*N* (α-thalassemia)
Alshamsi et al. [13]	HCRU	Retrospective cohort	United Arab Emirates	α-Thalassemia intermedia, not further specified	β-Thalassemia major, β-thalassemia intermedia, and HbE/β-thalassemia	TDT	≤18: 68 (26.7%) >18: 187 (73.3%)	255	2
Langer et al. [14][b]	Clinical	Case-control	United States	α-Thalassemia, not further specified	β-Thalassemia	NTDT and TDT	≥18	25,098	1675
Alshamsi et al. [15]	HCRU	Cross-sectional	United Arab Emirates	HbH, not further specified	HbE/β-thalassemia and β-thalassemia	TDT	19–52	161	1
Chan et al. [16]	Clinical	Cross-sectional	Hong Kong	Deletional and non-deletional HbH	NA	NTDT	≥18	80	80
Chaloemwong et al. [17]	Clinical	Cross-sectional	Thailand	Deletional and non-deletional HbH	HbE/β-thalassemia and β-thalassemia	NTDT and TDT	≥15	112	10
Ngim et al. [18]	Clinical	Retrospective cohort	Malaysia	HbH, not further specified	HbE/β-thalassemia and β-thalassemia	NTDT and TDT	≥18	69	2
Ekwattanakit et al. [19]	Clinical	Cross-sectional	Thailand	Deletional and non-deletional HbH	HbE/β-thalassemia and β-thalassemia	NTDT	≥18	57	23
Ricchi et al. [20]	Clinical	Cross-sectional	Italy	Deletional HbH	β-Thalassemia	NTDT	17–78	96	15
Winichakoon et al. [21]	Clinical	Retrospective cohort	Thailand	Deletional and non-deletional HbH	HbE/β-thalassemia and β-thalassemia	NTDT	≥15	100	54
Zhou et al. [22]	Clinical	Cross-sectional	China	Non-deletional HbH	NA	Not specified	≥18	50	50
Lal et al. [23]	Clinical HCRU	Prospective cohort	United States	Deletional and non-deletional HbH	NA	Not specified	0–72	86	86
Torcharus and Pankaew [24]	HRQoL	Cross-sectional	Thailand	HbH, not further specified	HbE/β-thalassemia and β-thalassemia	TDT	2–18	49	5
Thavorncharoensap et al. [25]	HRQoL	Cross-sectional	Thailand	HbH, not further specified	HbE/β-thalassemia and β-thalassemia	NTDT and TDT	5–18	315	130

Abbreviations: HbE, hemoglobin E; HbH, hemoglobin H disease; HCRU, healthcare resource use; HRQoL, health-related quality of life; NA, not applicable; NR, not reported; NTDT, non-transfusion-dependent thalassemia; TDT, transfusion-dependent thalassemia.

[a]Transfusion phenotype of total study population.

[b]Conference abstract.

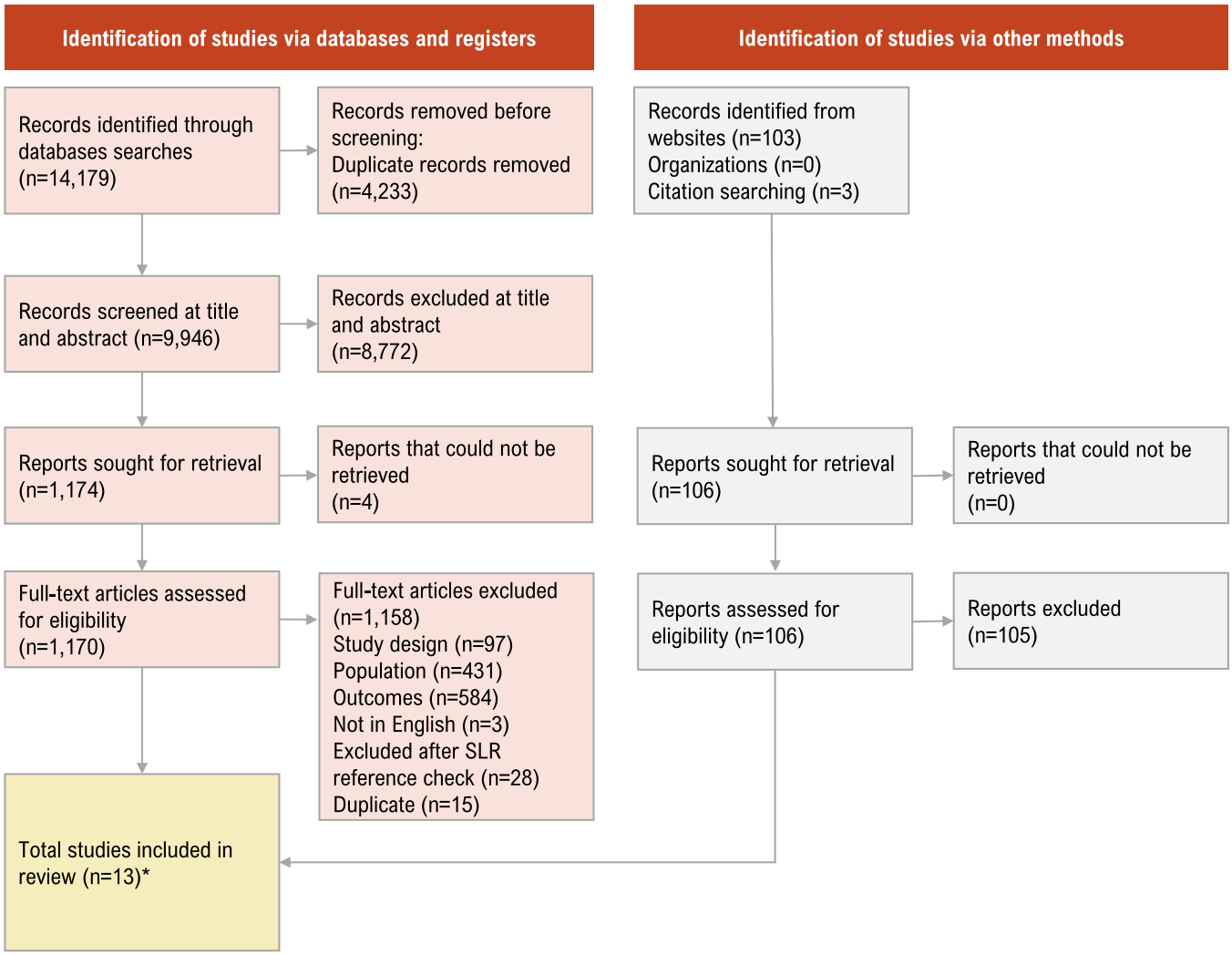

FIGURE 1 Literature flow diagram. *One of the included studies was a conference abstract. HCRU, healthcare resource utilization; HRQOL, health-related quality of life.

9.7 [0.3–18.2] years) and none occurred in the HbH group (median [range] follow-up: 2.6 [0.1–14.6] years) [23].

HRQoL burden was similar in children/adolescents with HbH compared with those with β-thalassemia across two studies in Thailand [24, 25]. One study was conducted in children with transfusion-dependent α-thalassemia (n = 5) and β-thalassemia (n = 44); however, there were only five patients with transfusion-dependent α-thalassemia which is too few to draw meaningful conclusions [24]. In another study in NTDT and transfusion-dependent thalassemia, there were no differences in any Pediatric Quality of Life Inventory subdomain among patients with HbH (n = 130), HbE/β-thalassemia (n = 165), and homozygous β-thalassemia (n = 15) (all $p > 0.100$) [25].

Two studies conducted in the UAE reported HCRU/costs data for patients with thalassemia receiving regular transfusions [13, 15]. These studies included only three [13, 15] patients with α-thalassemia combined, which is too few to draw meaningful conclusions. In a US study, adults and children with HbH/CS (n = 23) had significantly more annual clinic visits (by a factor of 1.7) and hospital admissions (by a factor of 3.9) than those with deletional HbH (n = 60; $p < .001$) [23].

This SLR identified only 13 studies reporting relevant burden data for α-thalassemia in an exhaustive search across thalassemia. Data sparsity for HRQoL and economic burden/costs highlights an evidence gap in adult and pediatric patients with α-thalassemia. Evidence on clinical outcomes was generally limited to small sample sizes and cross-sectional/retrospective studies, which challenges interpretation. Nonetheless, a range of complications was prevalent despite common use of conventional therapies, potentially signaling an unmet need for treatment optimization through management guidelines or novel therapies.

The limited data for α-thalassemia underscore the need to further characterize its clinical, HRQoL, and economic burden through longitudinal follow-up studies and disease registries. These would allow for a better understanding of the specific associations between risk factors and outcomes, tailoring conventional management, and establishing evidence-based guidelines. This would also allow targeted

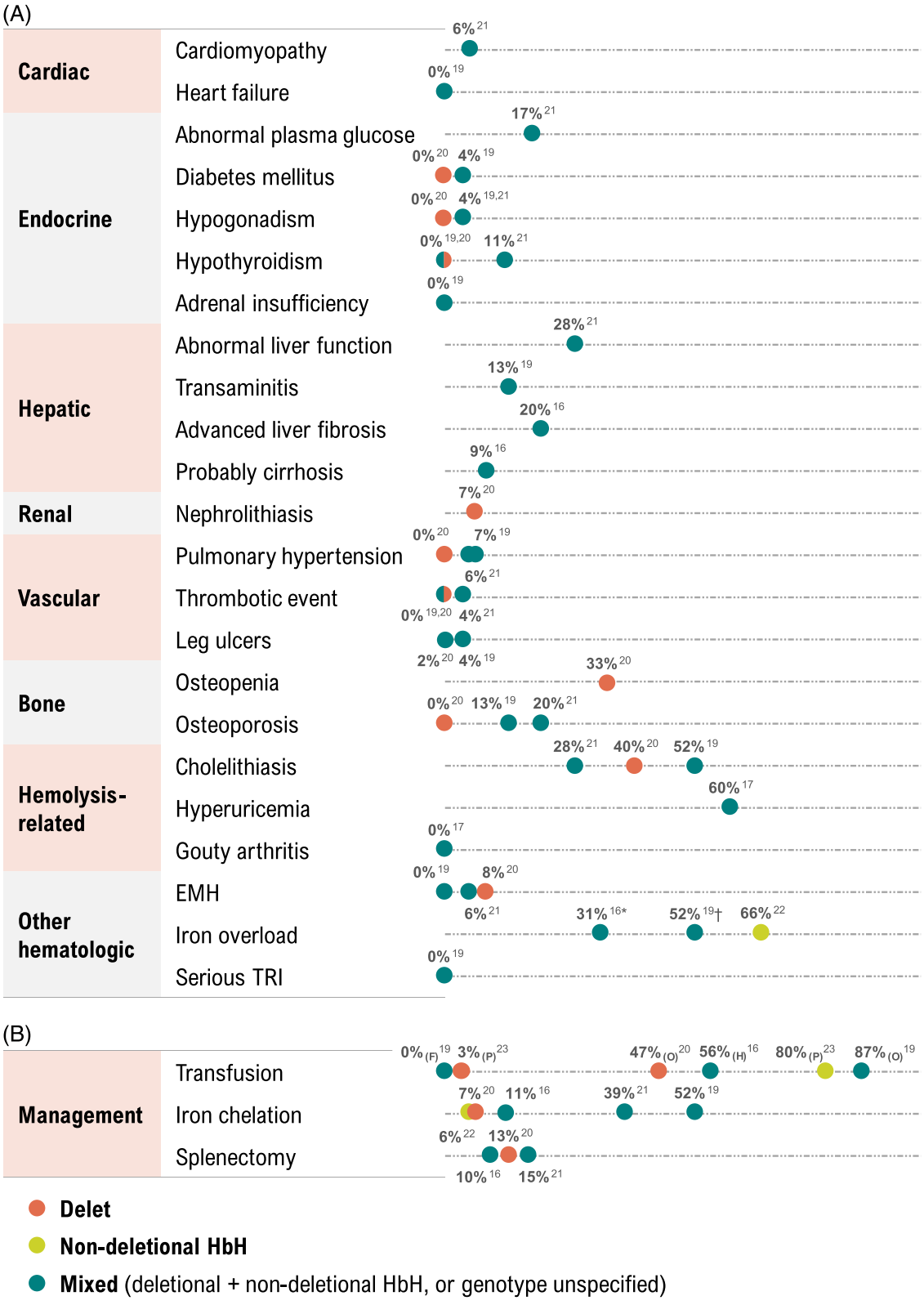

FIGURE 2 Complication rates (A) and treatment patterns (B) among patients with hemoglobin H disease. Each box represents the prevalence rate reported in an individual study on a 0%–100% percentage scale. Data are presented for deletional, non-deletional, and mixed (deletional + non-deletional, or genotype unspecified) subgroups; based on what was reported in individual studies. For transfusions, data are presented as the prevalence rate for frequent (F), historical (H), or occasional (O) transfusions; or as a probability (P) of receiving at least one transfusion by age 20 year; based on what was reported in individual studies. *Defined as liver iron concentration ≥7 mg Fe/g dry weight (moderate-to-severe). †Defined as liver iron concentration ≥5 mg Fe/g dry weight or serum ferritin ≥800 ng/mL. EMH, extramedullary hematopoiesis; HbH, hemoglobin H disease, IE, ineffective erythropoiesis; TRI, transfusion-related infection.

development of novel therapies to address the underlying pathophysiologies leading to the greatest burden. Additional research is particularly important as the global prevalence patterns continue to shift, and more healthcare systems are affected by this condition [3, 4].

AUTHOR CONTRIBUTIONS

Khaled M. Musallam, Vip Viprakasit, and Thomas D. Coates contributed to data interpretation and critical review of the manuscript; Louise Lombard, Keely Gilroy, Amey Rane, Lydia Vinals, Candice Tam, and Maria Rizzo designed and conducted the study, contributed to data interpretation, and developed and reviewed the manuscript.

ACKNOWLEDGMENTS

The authors thank Colleen Dumont, BSc from Cytel (MA, USA) for her medical writing and editorial review support for the study. The sponsor Agios Pharmaceuticals was involved in the design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

CONFLICT OF INTEREST STATEMENT

Khaled M. Musallam has been or is a consultant for Novartis, Celgene Corp (Bristol Myers Squibb), Agios Pharmaceuticals, CRISPR Therapeutics, Vifor Pharma, and Pharmacosmos; and received research funding from Agios Pharmaceuticals and Pharmacosmos. Vip Viprakasit is supported by the Department of Research Development, Faculty of Medicine Siriraj Hospital. He received research grants from Agios, GPO (Thailand), Bristol Myers Squibb and Silence for clinical research studies. Louise Lombard, Keely Gilroy, and Amey Rane are employees of and own stock in Agios Pharmaceuticals. Thomas D. Coates provides advisory support to Agios Pharmaceuticals, Bristol Myers Squibb, and Chiesi. Lydia Vinals and Maria Rizzo are employees of Cytel Inc. Candice Tam was employed by Cytel Inc during the conduct of this work.

FUNDING INFORMATION

Agios Pharmaceuticals.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

The authors have confirmed ethical approval statement is not needed for this submission.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

ORCID

Khaled M. Musallam https://orcid.org/0000-0003-3935-903X

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How to cite this article: Musallam KM, Viprakasit V, Lombard L, Gilroy K, Rane A, Vinals L, et al. Systematic review and evidence gap assessment of the clinical, quality of life, and economic burden of alpha-thalassemia. eJHaem. 2024;1–7. https://doi.org/10.1002/jha2.882