A Systematic Review and Meta-Analysis of Stature Growth Complications in β-thalassemia Major Patients

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ABSTRACT

Background: Blood transfusion is a traditional treatment for β-thalassemia (β-thal) that improves the patients’ anemia and lifespan, but it may lead to iron overload in parenchymal tissue organs and endocrine glands that cause their dysfunctions as the iron regulatory system can’t excrete excess iron from the bloodstream.

Objective: To evaluate the prevalence of iron-related complications (short stature, growth retardation, and growth hormone deficiency) in β-thalassemia major (βTM) patients.

Methods: We performed an electronic search in PubMed, Scopus, and Web of Sciences to evaluate the prevalence of growth hormone impairment in β-thalassemia major (βTM) patients worldwide. Qualities of eligible studies were assessed by the Joanna Briggs Institute checklist for the prevalence study. We used Comprehensive Meta-Analysis (Version 2) to calculate the event rate with 95% CIs, using a random-effects model for all analyses.

Findings: Seventy-four studies were included from five continents between 1978 and 2019; 70.27% (Asia), 16.21% (Europe), 6.75% (Africa), 2.70% (America), 1.35% (Oceania), and 2.70% (Multicenter). The overall mean age of the participants was about 14 years. The pooled prevalence of short stature (ST) was 48.9% (95% CI 35.3–62.6) and in male was higher than female (61.9%, 95% CI 53.4–69.7 vs. 50.9%, CI 41.8–59.9). The pooled prevalence of growth retardation (GR) was 41.1% and in male was higher than in female (51.6%, 95% CI 17.8–84 vs. 33.1%, CI 9.4–70.2). The pooled prevalence of growth hormone deficiency (GHD) was 26.6% (95% CI 16–40.8).

Conclusion: Our study revealed that near half of thalassemia patients suffer from growth impairments. However, regular evaluation of serum ferritin levels, close monitoring in a proper institute, suitable and acceptable treatment methods besides regular chelation therapy could significantly reduce the patients’ complications.
INTRODUCTION

Thalassemia is the most prevalent inherited disease worldwide [1]. This disease is a diverse group of genetic abnormalities associated with reduced synthesis of hemoglobin chains. If the body is unable to produce sufficient amounts of these chains, an imbalance of hemoglobin chains will result in ineffective erythropoiesis and chronic hemolysis. This anemia starts in early childhood and continues throughout the whole life. If this chain deficiency presents in α-chain of Hb, this type of thalassemia is called α-thalassemia, but β-thal is the reduced synthesis of hemoglobin β-chain [2]. Homozygous β-thalassemia major (βTM) is an inherited autosomal recessive disease, with a contagion rate involving 23000 babies every year, mostly in low- or middle-income countries [3]. Chelating therapy, besides blood transfusion, has improved the lifespan of thalassemic patients [4]. However, both patients and governments tolerate lots of costs. These costs should be managed entirely to provide efficient cures for these patients [5]. Regular transfusions lead to hyper absorption and iron deposition in many organs as iron ligand proteins (ferritin or hemosiderin) [6].

The overload of iron in tissues is one of the most important causes of death among thalassemic patients [4]. Hepatic dysfunctions and endocrine problems are some complications of iron overload. Growth impairment is one of the most common complications in βTM. Chronic hypoxia resultant in anemia, growth hormone deficiency (GHD) (because of defective production of somatomedin by the liver and rapid destruction of RBCs) is the leading of growth retardation (GR), changes in appearance, bone deformity, and failure of pubertal development in thalassemia patients [1, 7].

Previous studies reported that patients with higher concentrations of iron deposition in their liver were shorter in height. They had less insulin-like growth factor-I (IGF-I) SDS than βTM patients with lower amounts of liver iron deposition [8]. Disproportionate trunk growth, which is one of the most common complications among β-thalassemic adults, is because of platyspondyly. Many factors like an iron deposition in red blood cells, the toxicity of desferrioxamine, or trace elements insufficiency, result in vertebrae deformity [9]. Also, GHD, gonadal failure, and hypothyroidism are more prevalent in these patients [1].

Due to our studies, there are no surveys available, including analyzing this vast majority of cases about short stature (ST), GR, and GHD of βTM patients. Most of the studies include lower populations than ours, so their conclusions are not as reliable as our results. Our research aims to analyze the vast majority of patients’ data and study their life complications to suggest new approaches for better managing these patients.

METHODS
PROTOCOL AND REGISTRATION

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for developing and reporting this article [10].

ELIGIBILITY CRITERIA

All cross-sectional, cohort, case-control, or prevalence studies were included in this systematic review and meta-analysis. All studies without full text in the English language were excluded.

All studies that report prevalence data on β-thalassemia transfusion-dependent patients regarding iron related complications include ST, GR, and GHD, which were included in this study. Studies that report incomplete data or full text was unavailable were excluded. These three complications were defined as below, and only issues according to these definitions are included.

Short stature; when the patient height is more than two standard deviations below the mean for age, gender, and ethnicity [11].

Growth hormone deficiency; GH deficiency is defined as the peak GH concentration obtained during a provocative test with cut-off values for deficiency varying from 0.5 to 5 ng/mL [12].
Growth retardation: when the height of the subject is lower than the Mid Parental Height (MPH) value of both parents [13].

INFORMATION SOURCES AND SEARCH
We did an electronic search of PubMed, Scopus, and Web of Sciences to December 31, 2019, without language restrictions. Search term combinations were “B-thalassemia transfusion-dependent,” “Beta-Thalassemia major,” “endocrine complication,” “iron-related complication,” “short stature,” “growth hormone,” and “growth retardation.” All reference lists from the included studies and relevant systematic reviews were hand-searched for additional studies (see Appendix 1 for full search strategy in PubMed database).

STUDY SELECTION
After the search was completed, all records were imported to EndNote V.8, and then duplicate records were removed. The titles, abstracts, and full-text records were screened based on the pre-mentioned inclusion and exclusion criteria. All records are screened by two independents reviewers. A third reviewer reviewed the record in case of discrepancy, and disagreement was resolved by consultation.

DATA COLLECTION PROCESS AND DATA ITEMS
Two independent reviewers extracted and tabulated all relevant data using a researcher-made checklist. The disagreement was resolved by consensus between all authors. The data extraction checklist includes items like author name, published year, country of origin, study design, source of data gathering, sample size, gender information, the mean age of participants, and prevalence data regarding complication. A third reviewer rechecked the extracted data.

QUALITY APPRAISAL
All the studies were checked in term of quality by two independent reviewers using a 9-items Joanna Briggs Institute checklist for a cross-sectional study [14]. The potential disagreement was resolved by consultation with a third reviewer. This checklist includes nine-question and four rating scores (Yes, No, Unclear, and Not applicable). Each question was scored 1 point for yes, 0 points for unclear and no. Then, studies were categorized as having a high risk of bias if the summary score was 0 to <4, moderate risk of bias if the summary score was between 4 to <7 points, and low risk of bias if the summary score was between 7 to 9 points [15, 16].

STATISTICAL ANALYSIS
Publication bias was assessed by visual inspection of funnel plots Egger’s test and Begg’s test. The standard error of prevalence was calculated from the reported percentage prevalence and sample size for each study. We used Comprehensive Meta-Analysis (Version 2) to calculate the event rate with 95% CIs, using a random-effects model for all analyses. If data is available, we also performed subgroup analyses based on region and gender to decrease heterogeneity. I² was also measured to assess heterogeneity between the included studies [17]. Although there was heterogeneity between the studies, this was negligible due to differences in context as well as the use of different source of data. However, a subgroup analysis based on regions and a meta-regression based on mean age of the participant were conducted to increase the reliability of the results.

RESULTS
STUDY SELECTION
The total search yielded 1024 records. After the removal of duplicates, 646 records were screened based on title and abstract. After that, 433 records were excluded, and 213 records entered full-text assessment for eligibility criteria. Finally, 74 studies included in the meta-analysis (Figure 1) [6, 7, 11, 18–88].
STUDY CHARACTERISTICS

General characteristics of the 74 included articles are listed in Table 1. The included studies were conducted in Asia (71.62%), Europe (16.21%), Africa (6.75%), America (2.7%), Oceania (1.35%), and Multicenter (2.7%). Among the included studies, the largest sample size was 3156, and the smallest sample size was 10. All final studies reported at least one of the outcomes considered. The overall mean age of the participants was about 14 years. Of 74 studies, ST, GR, and GH complications were reported in 46, 18, and 13 studies. The included articles were published between 1978 and 2019.

QUALITY APPRAISAL

The JBI tool for quality assessment of included studies yielded scores ranging from 2 to 9. The mean methodological quality was 6.9 out of 9. Fifty-six studies were classified as low risk of bias (75.67%), seventeen were a moderate risk of bias (22.97%), and one study was of a high risk of bias (1.35%). Details of the answers to the tool’s nine questions are given in Appendix 2.

We did not suspect any evidence of publication bias (Begg’s test $P = .711$ and Egger’s test $P = .602$). The visual inspection of the funnel plot did not show significant publication bias (Appendix 3).

SYNTHESIS OF RESULTS

The meta-analyses’ results on the prevalence of the different types of investigated complications in $\beta$TM patients are shown in Table 2.

SHORT STATURE

Forty-six studies encompassing 3832 participants reported the prevalence of ST. The pooled prevalence of ST was 48.9% (95% CI 35.3–62.6). Based on subgroup analyses by world region,
### Table 1 Summary characteristics of included studies.

| AUTHOR NAME, YEAR | COUNTRY | STUDY DESIGN | SOURCE OF DATA | SAMPLE SIZE | GENDER (MALE %) | AGE (MEAN ± SD) |
|-------------------|---------|--------------|----------------|-------------|-----------------|-----------------|
| Al akhras et al., 2016 | Egypt | Cross-sectional | Clinical data | 100 | 54 | 14.2 ± 1.37 |
| Aldemir-Kocabas et al., 2014 | Turkey | Case-control | medical record | 41 | 36.5 | 12.4 ± 5.4 |
| Aleem et al., 2000 | Saudi Arabia | Retrospective | Case records | 10 | NR | 13.6 |
| Altincik et al., 2016 | Turkey | Cross-sectional | Medical record | 45 | 48.8 | 12.39 ± 3.72 |
| Aydinok et al., 2002 | Turkey | Cross-sectional | Medical record | 37 | 56.7 | 14.8 ± 4.9 |
| Beshlawy et al., 2010 | Egypt | Cross-sectional | Clinical data and medical record | 30 | 60 | 13.8 ± 1.7 |
| Canatan et al., 2013 | Turkey | Cross-sectional | Questionnaire | 246 | 54.8 | 15.3 ± 8.6 |
| Chhabra et al., 2016 | India | Case-control | Questionnaire | 114 | 63 | 8-16 y |
| Law et al., 1998 | China | Cross-sectional | Clinical data | 71 | 46.4 | 2.1-25 |
| Dama et al., 2015 | India | Cross-sectional | Medical records | 125 | 58.4 | 6 Months-18 |
| Dayasiri et al., 2018 | Sri Lanka | Case-control | Questionnaire | 40 | NR | 17 |
| Dayer et al., 2012 | Iran | Case-control | Clinical data | 30 | NR | 14.1 |
| De Sanctis et al., 2017 | Multinational | Cross-sectional | Questionnaire | 3023 | NR | NR |
| De Sanctis et al., 2018 | Multinational | Cross-sectional | Questionnaire | 3156 | NR | NR |
| Dhouib et al., 2018 | Tunisia | Cross-sectional | Clinical data | 28 | 57.1 | 19 ± 4.54 |
| Domrongkit et al., 2003 | Thailand | Cross-sectional | Clinical data | 18 | 44.4 | 29.2 ± 2.5 |
| Doulgeraki et al., 2012 | Greece | Cross-sectional | Clinical data | 38 | 52.6 | 5-18 |
| Eshraghi et al., 2011 | Iran | Cross-sectional | Questionnaire | 130 | 43.1 | 20.95 ± 7.8 |
| Fahim et al., 2013 | Egypt | Case-control | Clinical data | 100 | NR | 7.35 ± 4.7 |
| Fica et al., 2005 | Romania | Cross-sectional | Clinical data and Medical records | 64 | 53.1 | 19.45 ± 6.82 |
| Garcia et al., 1993 | Spain | Cross-sectional | Clinical data | 10 | 40 | 18.9 ± 9.8 |
| Grundy et al., 1994 | England | Cross-sectional | Clinical data | 18 | 61.1 | 12.8 |
| Gulati et al., 2000 | India | Case-control | Clinical data | 84 | 67.8 | 6.6 ± 4.9 |
| Guriek et al., 2017 | Turkey | Cross-sectional | Clinical data | 24 | 37.5 | 7.1 |
| Habebe et al., 2013 | Saudi Arabia | Cross-sectional | Clinical data | 81 | 51.8 | 12.2 ± 6.85 |
| Hamidah et al., 2001 | Malaysia | Case-control | Clinical data | 66 | 54.5 | 2-24 |
| Hamidieh et al., 2018 | Iran | Cross-sectional | Clinical data | 20 | 30 | 10.8 ± 3.9 |
| Hattab et al., 2013 | Qatar | Cross-sectional | Clinical data | 54 | 57.4 | 11.6 ± 3.2 |
| Ibrahim et al., 2017 | Pakistan | Cross-sectional | Clinical data | 72 | 48.6 | 10-20 |
| Isik et al., 2014 | Turkey | Cross-sectional | Clinical data | 47 | 55.3 | 10.0 ± 4.5 |
| Jain et al., 1995 | India | Case-control | Clinical data | 25 | 72 | 10.3 ± 3.6 |
| Kanbour et al., 2018 | Qatar | Cross-sectional | Clinical data | 24 | 62.5 | 21.75 ± 8.05 |
| Karamifar et al., 2002 | Iran | Cross-sectional | Clinical data | 150 | 56 | 14.4 ± 2.8 |
| Karamifar et al., 2005 | Iran | Cross-sectional | Clinical data | 146 | 57.3 | 10-22 |
| Karamifar et al., 2010 | Iran | Case-control | Clinical data | 50 | 48 | 14.2 ± 4.8 |
| Karydis et al., 2004 | Greece | Cross-sectional | Clinical data | 15 | 73.3 | NR |
| Kattamis et al., 1970 | Greece | Cross-sectional | Clinical data | 74 | 52.7 | Less than 11 |

(Contd.)
| AUTHOR NAME, YEAR | COUNTRY | STUDY DESIGN | SOURCE OF DATA                  | SAMPLE SIZE | GENDER (MALE %) | AGE (MEAN ± SD) |
|-------------------|---------|--------------|---------------------------------|-------------|----------------|-----------------|
| Kwan et al., 1995 | China   | Cross sectional | Clinical data                  | 68          | 48.5           | 11.3 ± 3.8      |
| Lau et al., 1998  | China   | Cross sectional | Clinical data                  | 12          | 58.3           | 11.4            |
| Li et al., 2004   | China   | Cross sectional | Clinical data                  | 32          | 53.1           | 9.2 ± 4.5       |
| Low et al., 1995  | China   | Cross sectional | Clinical data                  | 15          | NR             | NR              |
| Low et al., 1997  | China   | Cross sectional | Clinical data                  | 41          | NR             | NR              |
| Mageddu et al., 1978 | Italy | Case control      | Clinical data                  | 50          | 46             | 2–13            |
| Mahachoklertwattana et al., 2011 | Thailand | Cross sectional | Clinical data                  | 20          | NR             | 11.7            |
| Masala et al., 2003 | Italy | Cross sectional   | Clinical data and medical records | 283         | 46.9           | 5–12            |
| Mettananda et al., 2019 | Sri Lanka | Case control      | Clinical data                  | 224         | 49.1           | 10.9 ± 3.6      |
| Mirhosseini et al., 2012 | Iran | Cross sectional   | Clinical data                  | 140         | 56.4           | 8–18            |
| Mirhosseini et al., 2013 | Iran | Cross sectional   | Clinical data                  | 140         | 56.4           | 8–18            |
| Moayeri et al., 2006 | Iran | Cross sectional   | Clinical data                  | 158         | 48.1           | 15.1 ± 4.8      |
| Mohseni et al., 2014 | Iran | Cross sectional    | Clinical data                  | 158         | 48.1           | 15.1 ± 4.8      |
| Mousa et al., 2016  | Egypt   | Cross sectional   | Clinical data                  | 38          | 57.8           | NR              |
| Nabavi zad et al., 2007 | Iran | Cross sectional  | Clinical data                  | 121         | 50.4           | NR              |
| Najafpour et al., 2008 | Iran | Cross sectional   | Medical records                 | 56          | 64.2           | 15.62 ± 4.44    |
| Oszan et al., 2001  | Turkey  | Cross sectional   | Clinical data                  | 20          | 40             | 1–14            |
| Perera et al., 2010 | Australia | Retrospective cohort | Clinical data                  | 29          | 34.4           | 29              |
| Poggi et al., 2010  | Italy   | Cross sectional   | Clinical data                  | 28          | 53.5           | 30 ± 6.2        |
| Roth et al., 1997   | Germany | Cross sectional   | Clinical data                  | 32          | 59.3           | 3 ± 36          |
| Safarinejad et al., 2008 | Iran | Case control      | Clinical data                  | 168         | 100            | 24 ± 4.6        |
| Safarinejad et al., 2010 | Iran | Case control      | Clinical data                  | 106         | 0              | 16.4 ± 2.2      |
| Saffari et al., 2012 | Iran | Cross-sectional   | Clinical data                  | 77          | 51.9           | 21.26 ± 4.53    |
| Saka et al., 1995   | Turkey  | Cross-sectional   | Clinical data                  | 54          | 46.2           | 10.4            |
| Shah et al., 2019   | Pakistan | Cross sectional  | Clinical data                  | 100         | 53             | 13.62 ± 3.78    |
| Shalitin et al., 2005 | Israel | Cross-sectional  | Medical records                 | 39          | 53.8           | 16.3            |
| Shamshir saz et al., 2003 | Iran | Cross-sectional questionnaires | Clinical data | 220         | 51.5           | 15.2 ± 3.1      |
| Sharma et al., 2016 | India   | Prospective       | Clinical data                  | 89          | 57.3           | 13.6            |
| Soliman et al., 2009 | Qatar | Cohort            | Clinical data                  | 272         | NR             | 13–21           |
| Soliman et al., 2011 | Qatar | Cross-sectional   | NR                              | 26          | NR             | 9.5 ± 4.2       |
| Vidergor et al., 2007 | Israel | Case control  | Medical records                 | 16          | 43.7           | NR              |
| Vichinsky et al., 2005 | USA | Cross-sectional  | Medical records                 | 30          | 46.6           | 8.7             |
| Vogiatzi et al., 2009 | North America | Cross-sectional | Clinical data Medical records | 236         | NR             | 6.1–75.4        |
| Wu et al., 2003     | Taiwan  | Cross-sectional   | Clinical data                  | 29          | 55.1           | 11.2 ± 4.3      |
| Yaman et al., 2013   | Turkey  | Retrospective     | Clinical data                  | 56          | 57.1           | 2–20            |
| Yassin et al., 2018  | Qatar   | Cross-sectional   | Clinical data                  | 52          | NR             | NR              |
| Yin et al., 2011     | China   | Cross-sectional   | Medical records                 | 231         | NR             | 5               |
the pooled prevalence of ST varied between regions, but these differences were not significant (Figure 2). Based on world region subgroup analyses, the pooled prevalence for males was higher than females (61.9%, 95% CI 53.4–69.7 vs. 50.9%, CI 41.8–59.9) (Figure 3).

Table 2 The pooled prevalence of endocrine complications in β-thalassemia transfusion-dependent patient.

| COMPLICATION | STUDIES (N) | SAMPLE SIZE (N) | PREVALENCE (%) | 95% CI | P-VALUE | I² (%) |
|--------------|-------------|----------------|----------------|--------|---------|--------|
| ST Gender    | Female      | 7              | 316            | 50.9   | 41.8–59.9 | 0.850  | 71.33  |
|              | Male        | 7              | 415            | 61.9   | 53.4–69.7 | 0.006  | 39.39  |
| Region       | Africa      | 2              | 138            | 68.1   | 47.8–83.2 | 0.079  | 0.00   |
|              | Asia        | 35             | 3128           | 49.2   | 44–54.4   | 0.773  | 85.74  |
|              | Europe      | 9              | 566            | 36.3   | 27.3–46.4 | 0.008  | 74.46  |
| Overall      |             | 46             | 3832           | 48.9   | 35.3–62.6 | 0.873  | 86.69  |
| GR Gender    | Female      | 6              | 414            | 33.1   | 9.4–70.2  | 0.377  | 96.02  |
|              | Male        | 6              | 292            | 51.6   | 17.8–84   | 0.938  | 94.81  |
| Region       | Africa      | 1              | 28             | 57     | 9.1–94.6  | 0.831  | 0.00   |
|              | America     | 1              | 30             | 27     | 2.7–83.3  | 0.454  | 0.00   |
|              | Asia        | 12             | 1015           | 42.1   | 25.5–60.7 | 0.410  | 95.02  |
|              | Europe      | 3              | 3316           | 39.3   | 12.7–74.2 | 0.566  | 98.37  |
| Overall      |             | 18             | 4418           | 41.1   | 27.5–56.4 | 0.253  | 95.39  |
| GH Region    | Africa      | 2              | 46             | 34.1   | 8.9–73.2  | 0.438  | 0.00   |
|              | Asia        | 8              | 855            | 27     | 14–45.5   | 0.017  | 92.36  |
|              | Europe      | 3              | 3200           | 21.6   | 6.8–50.9  | 0.057  | 97.96  |
| Overall      |             | 13             | 4101           | 26.6   | 16–40.8   | 0.002  | 98.11  |

Figure 2 Forrest plot of the pooled prevalence of ST in β-thalassemia transfusion-dependent patients.
GROWTH RETARDATION

Eighteen studies encompassing 4418 participants reported the prevalence of GR. The pooled prevalence of GR was 41.1% (95% CI 27.5–56.4). Based on world region subgroup analyses, the pooled prevalence of GR varied between regions, but these differences were not significant (Figure 4). Based on world region subgroup analyses, the pooled prevalence for males was higher than females (51.6%, 95% CI 17.8–84 vs. 33.1%, CI 9.4–70.2) (Figure 5).
GROWTH HORMONE DEFICIENCY

Thirteen studies encompassing 4101 participants reported the prevalence of GHD. The pooled prevalence of GHD was 26.6% (95% CI 16–40.8). Based on subgroup analyses by world region, the pooled prevalence of GHD varied between regions, but these differences were not significant (Figure 6). Not enough information was available for subgroup analysis by gender in this variable.

META-REGRESSION

Results of meta-regression showed a significant positive association between mean age of the participant and GH (Reg Coef = 0.096, p < 0.001) (Appendix 4, A). But this association is not observed in GR (Reg Coef = –0.017, p = 0.193) and ST (Reg Coef = 0.010, p = 0.128) (Appendix 4 B and C).

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**Table 1:**

| Study name            | Subgroup within study | Outcome | Event rate and 95% CI | Relative weight |
|-----------------------|-----------------------|---------|-----------------------|-----------------|
| Garcia et al, 1993    | Female                | GR      | 14.90                 |                 |
| Dama et al, 2014      | Female                | GR      | 17.11                 |                 |
| Kiwan et al, 1995     | Female                | GR      | 16.96                 |                 |
| Wu et al, 2003        | Female                | GR      | 16.88                 |                 |
| Low et al, 1996       | Female                | GR      | 17.10                 |                 |
| Masala et al, 2003    | Female                | GR      | 17.08                 |                 |
| Garcia et al, 1993    | Male                  | GR      | 11.40                 |                 |
| Dama et al, 2014      | Male                  | GR      | 17.90                 |                 |
| Kiwan et al, 1995     | Male                  | GR      | 17.84                 |                 |
| Wu et al, 2003        | Male                  | GR      | 17.26                 |                 |
| Low et al, 1996       | Male                  | GR      | 17.72                 |                 |
| Masala et al, 2003    | Male                  | GR      | 17.88                 |                 |

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**Figure 5** Forrest plot of the pooled prevalence of GR sub-grouped by gender in B-thalassemia transfusion-dependent patients.

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**Figure 6** Forrest plot of the pooled prevalence of GH in B-thalassemia transfusion-dependent patients.
DISCUSSION

As there is no permanent cure for TM patients, blood transfusion is still the best solution for reducing these problems. There are no unique means in the human body for eliminating the overload of iron, which consequent from a blood transfusion. There is 200 to 250 mg iron in every unit of the packed cell. The amounts of daily iron which is accumulated in different organs of TM patients is approximately 0.3 to 0.6 mg/kg [89]. Introducing iron-chelating therapy besides using noninvasive techniques same as T2 MRI, has been improved different functional complications in βTM patients [90]. However, there is no consensus on treating endocrine disorders resulting from iron overload thoroughly [89].

Also, a systematic review reported that only 54 % of βTM patients utilize chelation therapy regularly. So, this kind of treatment is not well-accepted by the people [91]. Overload of iron leads to severe heart failure complications, hepatic disorders, endocrine dysfunction, skeletal deformities, and growth impairment. The secondary effect of that on the growth hormone-insulin-like growth factor axis leads to ST, GR, and GHD due to deposition of iron in the pituitary gland [91, 92].

This study is the first systematic review and meta-analysis about growth impairments in βTM patients in the world. The prevalence rate of ST, GR, and GHD was 48.9%, 41.1%, 26.6%, respectively. Several studies proved that ST is one of the most common endocrine disorders in βTM patients as we did [1, 11, 30, 76].

Short stature is a multifactorial complication. However, one of the causes is the shortening of patients’ trunks disproportionately due to delayed-chelating therapy and hypogonadism [93]. The pituitary gonadotropes are incredibly vulnerable to oxidative stress caused by iron deposition in the hypothalamus and pituitary gland [9]. De Sanctis et al. evaluated the prevalence rate of ST among 3023 βTM patients in 16 countries and reported that 53% were short. These authors also reported that by comparing endocrinopathies of βTM with intermediate β-thal, endocrine disorders like ST in βTM patients are overloaded by iron [3].

We found that 41.1% of βTM patients all around the world are growth retarded. Some explanations containing hyper-metabolism, chronic anemia, hypoxia (especially in under-treated children), defects in secretion of gonadotropin, deposition of iron in thyroid, gonads, pituitary and adrenal glands, diabetes, liver disease, zinc and folic acid deficiency, emotional factors, nutritional deficiencies, and deferoxamine-induced bone dysplasia are suggested [1, 51, 94, 95]. Oxidative stress with iron overload can make the anterior part of the pituitary dysfunctional. Furthermore, Growth Hormone-Insulin-Like Growth Factor-1 (GH-IGF1) axis disorders result in growth deceleration [96].

Our understandings of GHD in βTM patients were confirmed by many studies like Yassin, Gulati, and Hamidiah et al [8, 37, 41]. They all have accordance with our results. Yassin suggests that the higher deposition of iron in the liver, the higher prevalence of complications like GHD [8]. Also, an increase in the somatostatinergic tone on GH release justifies impaired GH secretion [9]. GHD is also affected by increasing hypothyroidism and delayed puberty. With the longer life span of these patients, the probability of GHD increases [55].

Based on our analyses, the pooled prevalence of ST and GR for males was higher than females. The probable reason is females can endure iron toxicity better than males due to chronic oxidative stress [97, 98].

Taher et al., have claimed that geographical differences affect an iron overload in βTM patients [89]. One of the main reasons is that βTM patients can have different genetic predispositions to the toxicity of iron deposited in the endocrine gland and serum ferritin. Also, the amount of iron overload in a patient depends on how much the patient is under observation, follow-up, and treatment, how often they are under chelation therapy, and when the first desferrioxamine therapy was started [84]. But our findings indicate no significant differences in ST, GR, and GHD deficiencies of βTM patients among various populations.

In addition to our results, several studies had different ideas about the noticeable effect of serum ferritin levels on growth impairments. Hashemi et al. reported in a survey containing seventy transfusion-dependent thalassemic as that in patients with ST, the mean serum ferritin level was
considerably more than patients of standard height [99]. This point is also defined by other studies like Hamidah et al. conducting an issue on 26 pre-pubertal βTM or HbE-β thal who were transfusion-dependent (serum ferritin was higher in patients under the third percentile of height [4,567.0 vs. 2,271.0, \( P = 0.01 \)) and Shalitin et al. who somehow got the same result while acknowledging that if the patients do not begin chelation therapy before puberty with high quality, they appear shorter in height [77, 100].

Nevertheless, Grundy and coworkers are the opponents of this idea, reporting no relationships between the SD scores and the well or poorly chelated patients. They suggested genetic factors, racial and socioeconomic means, and urbanism as the most probable reasons for ST [36].

Some factors like; age (the older the patient gets, the more prevalent the ST is), hemoglobin level, age of the first chelation therapy, and genotype impacts on prevalence of endocrine dysfunction in βTM patients [11, 87, 101, 102]. βthal patients start transfusing blood at an earlier age; therefore, this genotype is related to iron overload and more endocrine complications. The growth impairments generally happen in patients with β°β° genotype more severe than those with β°β+ and β+β+ [103]. Therefore, clinical complications of the diseases are directly related to the genotype of βTM patients.

**CONCLUSION**

Many βTM patients are suffering from GR, ST, and GHD all around the world. Among, the prevalence of ST was more common, especially in patients older than seven years old. By noticing the control of patients’ serum ferritin levels, GH can be diagnosable. With close monitoring in a proper institute, suitable and acceptable treatment methods besides regular chelation therapy and follow-up, the patients can significantly reduce their complications.

**RECOMMENDATION FOR FUTURE RESEARCH**

The results of our study show that the number of studies conducted to investigate these complications is low in some countries where βTM is common. Therefore, further studies in this field are recommended. Using high transfusion and modern chelation in low and middle-income countries can generally prevent the disease from occurring, so, the cooperation of international organizations, especially the WHO, seems to be essential for setting up a central laboratory for low- and middle-income countries. It is necessary to investigate the reasons for families avoiding diagnostic tests, and training and educational courses should be developed following these reasons. It is difficult to counter the misconceptions that prevent such tests, but it requires round-the-clock efforts, and the support of health care professionals is crucial, and the development of such supportive strategies requires further study.

**ADDITIONAL FILES**

The additional files for this article can be found as follows:

- **Appendix 1.** Full search strategy for PubMed database. DOI: https://doi.org/10.5334/aogh.3184.s1
- **Appendix 2.** Quality appraisal of included studies. DOI: https://doi.org/10.5334/aogh.3184.s2
- **Appendix 3.** Funnel plot for ST complication. DOI: https://doi.org/10.5334/aogh.3184.s3
- **Appendix 4.** Meta-regression of GH (A), GR (B), and ST (C) based on Mean age of the participants in the included studies. DOI: https://doi.org/10.5334/aogh.3184.s4

**ETHICS AND CONSENT**

This article uses the secondary data of published studies and does not contain studies with human participants or animals.

**COMPETING INTERESTS**

The authors have no competing interests to declare.
AUTHORS CONTRIBUTIONS

EM and MAZ contributed to the design, data acquisition, and supervision. MAZ contributed to search the bibliographic databases. SKH and AR contributed to screening the records, data extraction, quality appraisal and drafting of the manuscript. MAZ contributed to the acquisition of data, analysis, and interpretation. EM was the study supervisor and contributed to all aspects of the study. All authors approved the final manuscript before submission.

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