Acta Biomed 2025; Vol. 96, N. 1: 16746 DOI: 10.23750/abm.v96i1.16746

Prevalence of hypoparathyroidism among patients with thalassemias: A systematic review and meta-analysis

Sezaneh Haghpanah[1], Zahra Ghahramani[1], Mehran Karimi[2], Seyed Reza Abdipour Mehrian[3], Erfan Taherifard[1,4], Shadi Moshksar[5], Vincenzo De Sanctis[6], Sam Rahbin[7], Mani Ramzi[1]*

[1]Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran; [2]Hematology Oncology Clinic, American Hospital Dubai, Dubai, UAE; [3]Clinical Research Development Center, Amir Oncology Teaching Hospital, Shiraz University of Medical Sciences, Shiraz, Iran; [4]MPH Department, Shiraz University of Medical Sciences, Shiraz, Iran; [5]Poostchi Ophthalmology Research Center, Department of Ophthalmology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran; [6]Pediatric and Adolescent Outpatient Clinic, Private Accredited Quisisana Hospital, Ferrara, Italy; [7]Interdisciplinary Undergraduate Program in Neuroscience, Vanderbilt University, Nashville, Tennessee, USA

Abstract. *Background:* Thalassemia, the most prevalent hereditary anemic disease worldwide, significantly impacts public health, causing substantial morbidity and mortality. Clinically, β-thalassemia can be classified in transfusion-dependent thalassemia (TDT) and non–transfusion-dependent thalassemia (NTD). Hypoparathyroidism (HPT) is a common complication in TDT patients, with varying prevalence rates across different populations. *Objectives:* This meta-analysis aimed to determine the prevalence of HPT among TDT and NTDT patients through a comprehensive review of studies. *Methods:* A systematic review and meta-analysis of studies reporting HPT prevalence in thalassemia patients since 2000 was conducted. Data on prevalence rates, study characteristics, and patient demographics were extracted and meta-analyzed. Subgroup analyses were performed based on geographic regions. *Results:* Overall, 3453 patients with thalassemias from 25 studies were included in this meta-analysis, of which 69 were NTDT patients. A pooled HPT prevalence of 11.3% (95% CI: 8.1-15.5%) was detected. The highest prevalence was observed in Europe at 19.1%, followed by Asia at 9.8%, and Africa at 6.2%. The mean age of participants was 19.0 (±1.1) years, with a nearly equal distribution of genders. No significant correlation was found between parathyroid hormone (PTH) levels and other biochemical parameters. *Conclusions:* This meta-analysis shows a prevalence of 11.3% for HPT in thalassemia patients. Although, parathyroid dysfunction is primarily considered a disease of the second or third decade it could **be** seen in the earlier stage of life. Severity of disease, differences across populations**,** management of iron overload, adherence to iron chelation therapy, quality of healthcare systems, differences in diagnostics criteria and splenectomy may affect the distribution of HPT. These data should be dynamically updated as studies are published. (www.actabiomedica.it)

Key words: thalassemia, endocrine disorders, parathyroid hormone, hypoparathyroidism

Introduction

Thalassemia is a heterogeneous group of genetic disorders with defective synthesis of one or more globin chains. The most clinically relevant types of thalassemia are α and β, resulting from the decrease of one of the two types of polypeptide chains (α or β) that form the normal adult human hemoglobin molecule (Hb A, α2β2). Clinically, β-thalassemia can be classified in transfusion-dependent thalassemia (TDT) and non–transfusion-dependent thalassemia (NTD) according to the severity of phenotype caused by the

α: β-globin unbalance ratio deriving from a wide spectrum of mutations in a homozygous or compound heterozygous state (1, 2). In addition to the characteristic of hematological abnormalities, TDT β-thalassemia is associated with a wide range of systemic complications, including endocrine disorders (3), collectively known as thalassemic endocrine disease (TED) (4). Management of TDT patients typically involves regular transfusion therapy, to suppress extramedullary hematopoiesis maintaining normal well-being, and iron chelation to mitigate the effects of iron overload. Advances in transfusion protocols, iron chelation strategies, and the monitoring of iron burden have significantly improved patient survival rates, leading to an increased proportion of adult subjects. However, in countries with strained economies not all patients can benefit from the latest health care developments. Consequently, the prevalence of disease-related morbidities has risen, particularly among older patients (5). Overt or symptomatic hypoparathyroidism (HPT), one of the complications of TED, is present in a significant percentage of patients. HPT is typically characterized by low serum albumin-corrected calcium or ionized calcium (below the lower limit of the normal range; respectively <8.5 mg/dl or 2.12 mmol/l) and 1,25- dihydroxyvitamin D [1,25(OH)2D] levels, increased serum phosphorus concentration, and low or inappropriate, for the degree of hypocalcemia, intact parathyroid hormone (PTH) levels. However, the clinical utility of the ionized calcium measurement is limited by the technical issues. The 24-h urine calcium level may be low-normal before calcium and vitamin D metabolites or analogs supplementation is started and can be found increased during treatment (6-10). In the general population, the most common cause of HPT is parathyroid gland injury or inadvertent removal during thyroid surgery (11, 12), whereas in patients with TDT**,** it is mainly attributed to iron overload, secondary to multiple blood transfusions and suboptimal chelation therapy (3, 4). Chronic anemia and magnesium deficiency could be other additional factors causing parathyroid dysfunction (3, 4). Other factors, like individual susceptibility to iron toxicity effects, damage secondary to persisting iron overload in the years preceding iron chelation therapy, and the severity of the hematological phenotype of the disease could also play a role in the development of HPT. Reports in the literature indicate that parathyroid dysfunction due to iron overload generally occurs in 2nd or 3rd decade of patients with TDT (3, 4,13). The prevalence of overt or symptomatic HPT in NTDT patients with suboptimal iron chelation therapy varies from 0.5 to 7.6% (14). However, asymptomatic hypocalcemia seems to be more common. In a recent study, the prevalence of "under-recognized asymptomatic" HPT was 38% (14). These patients had also significantly lower median plasma FGF-23 levels than the controls. FGF-23 is a phosphaturic hormone secreted by osteoblasts and osteocytes in response to elevated serum phospate (14). This systematic review and meta-analysis aimed to determine the prevalence of HPT in the last two decades in patients with thalassemias in different continents.

Methods

The present systematic review and meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (15). Our study was registered at the International Prospective Register of Systematic Reviews (PROSPERO) with the confirmed code CRD42023401008. The study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1402.619).

Search strategy

The systematic search of the databases was done in February 2024. Two independent authors searched the Web of Science (formerly ISI Citation Indexes), Scopus, PubMed, and Google Scholar for papers staring from 2000. A combination of the following Medical Subject Headings (MeSH) terms and keywords was used to conduct comprehensive literature searches: ("Beta-Thalassemia" OR "Thalassemia Major" OR "Thalassemia Intermedia") AND ("Hypoparathyroidism" OR "Endocrinopathies" OR "Parathyroid Disease"). Moreover, we hand-searched the reference lists of the relevant articles and previously performed reviews for additional pertinent studies. Articles were categorized and screened using Endnote and Rayyan by two independent reviewers.

Inclusion and exclusion criteria:

The eligible studies were selected based on specific criteria, including: (a) subjects with TDT or NTDT, (b) number or percentage of HPT and (c) patients with primary HPT. We excluded studies that met the following characteristics: (a) case reports; (b) review articles or non-original articles; (c) conference abstracts, letters, book chapters, editorials, and/or brief reports; (d) publications in a non-English language; (e) studies published before 2000 or after February 2024; (f) studies intentionally selecting patients based on serum ferritin levels; (g) studies with a low score (less than five) based on quality assessment, according to the Newcastle-Ottawa scale (NOS); and (h) studies not reporting the reference for normal PTH values. The flow diagram of this systematic review and meta-analysis is reported in Figure 1 (15).

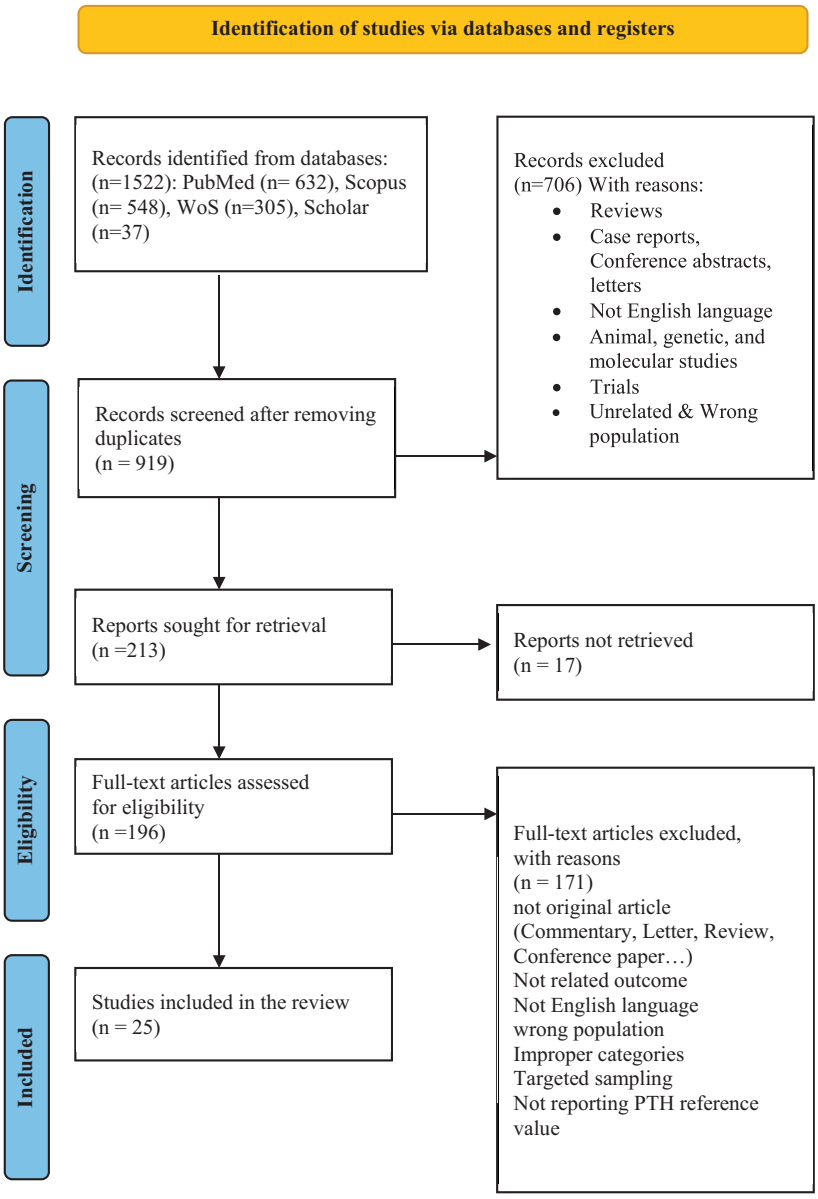

Figure 1. PRISMA flow diagram of study selection process for the review, detailing identification, screening, eligibility, and inclusion stages.

Data extraction

Two researchers independently extracted the data from the eligible papers and inserted them into an Excel sheet, including the name of the first author, publication year, the timeline in which the study was conducted, country, continent, type of study, type of disease (TDT or NTDT), the mean age of the patients, total number of thalassemia patients, mean serum ferritin level, the mean level of pre-transfusion hemoglobin (Hb), serum calcium (Ca), serum phosphate (P), vitamin D (25-OHD), liver iron concentration (LIC), alkaline phosphatase (ALP) and number of patients with HPT. Any disagreement in the selection of articles was resolved consulting a third author. When there were several reports from a study, we only considered the most comprehensive results for prevalence meta-analyses.

Study quality assessment

Two independent authors assessed the quality of the included studies based on the NOS checklist (16). This scale encompasses three items: selection, comparability, and outcome. According to the NOS checklist, the quality score was considered to be at least five for inclusion in our meta-analysis

Statistical analysis

We utilized comprehensive meta-analysis software (Biostat, Inc., NJ, USA) version 3 for our quantitative analyses. We followed the methodologies outlined by Wan et al. (17) and Hozo et al. (18) to determine the mean and standard deviation (SD) values and variation when appropriate. The random effects model with the DerSimonian–Laird method was employed to compute pooled estimates. The pooled prevalence of HPT was reported with relative frequencies and confidence intervals (95% CI). Additionally, mean values and SDs were utilized to report pooled estimates for age, as well as levels of PTH, Ca, P, 25-OHD, LIC, ALP, serum ferritin, and pretransfusion hemoglobin level. Subgroup analysis based on the continent of study was also conducted. Furthermore, sensitivity analysis employing the leave-one-out method was implemented. Heterogeneity among studies was assessed using the I^2 statistic and Cochran's Q test. The potential publication bias was evaluated through Egger's test and funnel plot analysis of standard error by logit event rate. A P-value less than 0.05 was considered statistically significant.

PTH Linear Meta-Regression

The PTH linear meta-regression analysis was conducted using Stata software to examine potential correlations between various biochemical findings. The clinical parameters analyzed included PTH, 25-OHD, LIC, ALP, serum ferritin, and pre-transfusion Hb levels. Linear regression models were used to explore the relationships between PTH levels and the other biochemical markers. A scatter plot matrix was presented to visually assess the bivariate relationships between pairs of these variables.

Results

Literature search and study characteristics

Our initial search yielded a total of 1,522 articles, which were subsequently screened for duplicates, resulting in 919 no duplicated reports. After assessing titles and abstracts, 706 articles were excluded based on predetermined criteria. This selection allowed us to assess 213 full-text articles that underwent to a further evaluation. 171 reports were furtherly excluded due to: (a) targeted sampling and (b) the absence of laboratory cutoffs for parathyroid function tests or not reporting HPT prevalence. Finally, a total of 25 studies (19-43) satisfied all the inclusion criteria and showed sufficient quality to be included in our analysis (Figures 1 and 2).

Main outcomes and subgroup analysis

Overall, 3,453 patients with thalassemia from 25 studies were included in this meta-analysis of which 69 patients from 2 articles were NTDT. The mean age ± SD of the participants was 19.0 years (±1.1), 50.4% were males and 49.6% females (Table 1). The pooled prevalence of HPT was equal to 11.3% (95% CI: 8.1-15.5%) and the I2 statistics of 88.57 was

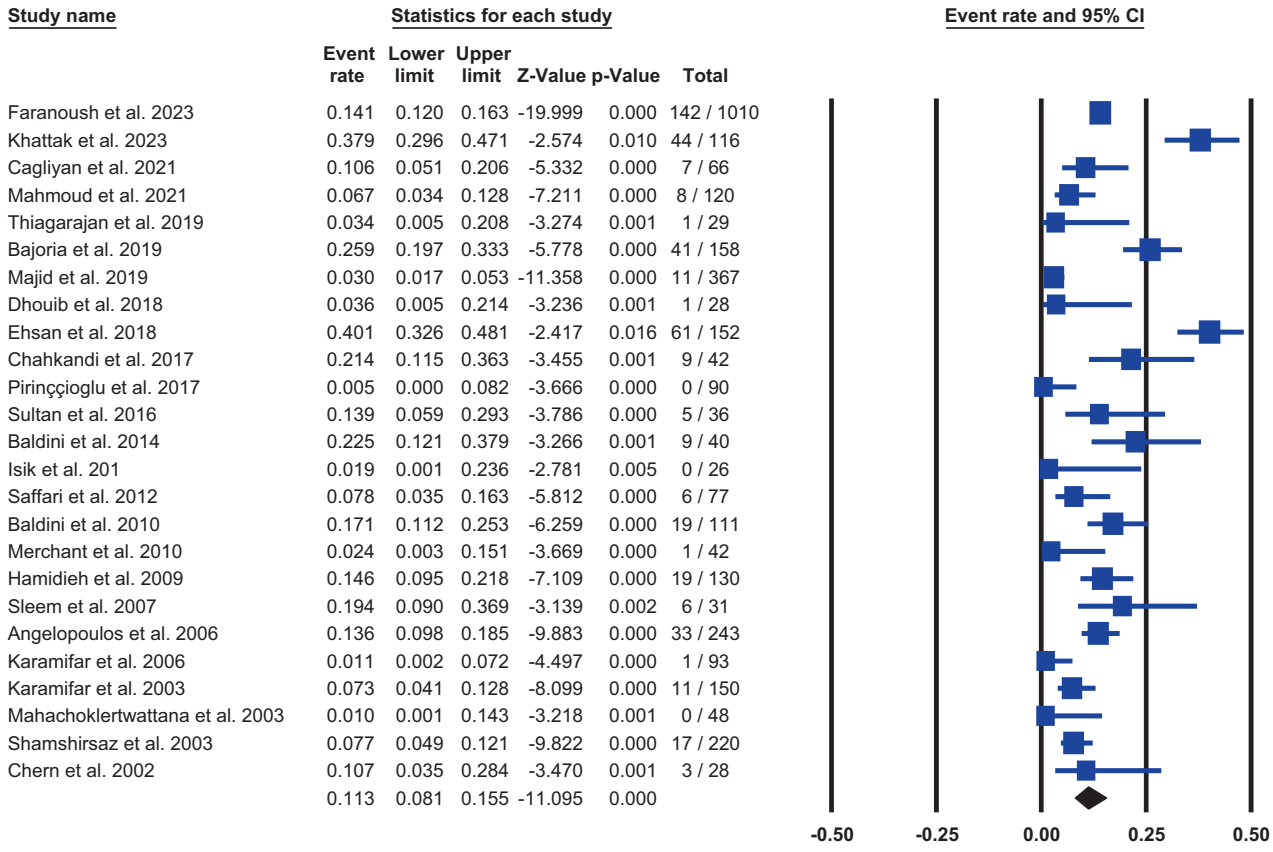

Figure 2. The forest plot for the overall prevalence of hypoparathyroidism among TDT and NTDT patients.

indicative for a significant heterogeneity (P = <0.001) (Figure 2). The I2 analysis calculated for each continent was as follows: Asia (n=19): 9.8% (95% CI: 6.3-15.0%), I2 statistics: 90.35, P= < 0.001; Africa (n=2): 6.2% (95% CI: 3.3-11.5%), I2 statistics: 0, P=0.544; Europe (n=4): 19.1% (95% CI: 13.4-26.5%), I2 statistics: 70.12, P= 0.018.

Significant heterogeneity persisted overall and across different continents after subgroup analysis, except for Africa, where homogeneity was observed, albeit based only on two included articles (Figure 3).

Reported iron chelation therapy

Out of 1,433 patients with thalassemias, included in 16 articles, reported data on chelation therapy, The distribution of iron chelating agents was as follows: 919 patients (64.13%) received desferrioxamine (DFO), 241 patients (16.82%) received deferasirox (DFX), 161 patients (11.24%) received more than one chelating agent, and 56 patients (3.91%) received deferiprone (DFP). Additionally, 56 patients (3.91%) did not undergo any chelation therapy.

Reported levels of biochemical parameters

The mean serum ferritin (± SD) was 2,869.4 ng/mL (±2,21.6) (n=18), 35.2 (± 3.7) pg/mL for PTH (n=13), 8.8 (± 0.1) m/dL for serum calcium (n=5), 4.6 (± 0.2) mg/dL for serum phosphate or (n=14), 20.5 (±1.9) ng/mL for vitamin D (n=10), 117.4 (± 9.1) U/l for ALP (n=7), and 9.1 (± 0.2) g/dL for pre-transfusion hemoglobin level (n=12).

Sensitivity analysis and publication bias

Figure 4 shows the outcomes of the sensitivity analysis for the overall pooled prevalence of HPT in

Table 1. Summary of demographic and laboratory characteristics of the included articles

Ref. number and year of publication	Female (%)	Age (yrs)	Continents	HPT (%)	Patients (n)
(19)	50.79	28.48 ± 7.76	Asia	14.06	1010
(20)	29.31	12.79±1.80	Asia	37.93	116
(21)	56.06	25.8 ± 6.6	Asia	10.61	66
(22)	45	n=28: 11.60 ± 3.21 n=92: 11.0 ±1.2	Africa	6.67	120
(23)	34.48	5 ± 1.4	Asia	3.45	29
(24)	60.13	n=106: 36.0±10.29 n=52: 39 ±7.93	Europe	25.95	158
(25)	44.14	median 11 (7-13)	Asia	55.31	367
(26)	42.86	19 ± 4.54	Africa	3.57	28
(27)	NaN	NaN	Asia	40.13	152
(28)	38.89	7.16 ± 4.06 (females) 7.61 ± 4.26 (males)	Asia	21.43	90
(29)	45.24	14.38 ± 6.63	Asia	0	42
(30)	60	n=20: 33.1± 6.5 n=20: 33.5 ±7.3	Europe	13.89	40
(31)	NaN	10.0 ± 4.5	Asia	22.5	26
(32)	52.78	12.56 ± 5.9	Asia	0	36
(33)	48.05	21.26 ± 4.53	Asia	7.79	77
(34)	59.46	32.6 ± 6	Europe	17.12	111
(35)	35.71	17.1 ± 4.2	Asia	2.38	42
(36)	53	mean age:18 (2-42)	Asia	14.62	130
(37)	48.39	19 ± 3	Asia	19.35	31
(38)	55.97	25.26 ± 6.25	Europe	13.58	243
(39)	56.99	19.45 ± 5.40	Asia	1.08	93
(40)	44	14.4 ± 2.8	Asia	7.33	150
(41)	43.75	n=16: 13.2 ± 2.6 n=32: 12.8 ± 2.5	Asia	0	48
(42)	49.5	15.2 ± 3.1	Asia	7.73	220
(43)	42.86	16.1 ± 4.5	Asia	10.71	28

patients with TDT. No significant impact from any of the included articles was observed. Moreover, the funnel plot demonstrates an asymmetry consistent with Egger's test findings (P=0.038), suggesting a notable potential for publication bias among the articles included (Figure 5).

Correlations of biochemical parameters

Univariate linear regression analysis showed no significant correlations between Vit D, LIC, ALP, serum ferritin, pre-transfusion Hb, and serum PTH level (Table 2 and Figure 6).

Group by Continent	Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Africa	Mahmoud et al. 2021	0.067	0.034	0.128	-7.211	0.000
Africa	Dhouib et al. 2018	0.036	0.005	0.214	-3.236	0.001
Africa		0.062	0.033	0.115	-7.881	0.000
Asia	Faranoush et al. 2023	0.141	0.120	0.163	-19.999	0.000
Asia	Khattak et al. 2023	0.379	0.296	0.471	-2.574	0.010
Asia	Cagliyan et al. 2021	0.106	0.051	0.206	-5.332	0.000
Asia	Thiagarajan et al. 2019	0.034	0.005	0.208	-3.274	0.001
Asia	Majid et al. 2019	0.030	0.017	0.053	-11.358	0.000
Asia	Ehsan et al. 2018	0.401	0.326	0.481	-2.417	0.016
Asia	Chahkandi et al. 2017	0.214	0.115	0.363	-3.455	0.001
Asia	Pirinççioglu et al. 2017	0.005	0.000	0.082	-3.666	0.000
Asia	Sultan et al. 2016	0.139	0.059	0.293	-3.786	0.000
Asia	Isik et al. 2014	0.019	0.001	0.236	-2.781	0.005
Asia	Saffari et al. 2012	0.078	0.035	0.163	-5.812	0.000
Asia	Merchant et al. 2010	0.024	0.003	0.151	-3.669	0.000
Asia	Hamidieh et al. 2009	0.146	0.095	0.218	-7.109	0.000
Asia	Sleem et al. 2007	0.194	0.090	0.369	-3.139	0.002
Asia	Karamifar et al. 2006	0.011	0.002	0.072	-4.497	0.000
Asia	Karamifar et al. 2003	0.073	0.041	0.128	-8.099	0.000
Asia	Mahachoklertwattana et al. 2003	0.010	0.001	0.143	-3.218	0.001
Asia	Shamshirsaz et al. 2003	0.077	0.049	0.121	-9.822	0.000
Asia	Chern et al. 2002	0.107	0.035	0.284	-3.470	0.001
Asia		0.098	0.063	0.150	-9.052	0.000
Europe	Bajoria et al. 2019	0.259	0.197	0.333	-5.778	0.000
Europe	Baldini et al. 2014	0.225	0.121	0.379	-3.266	0.001
Europe	Baldini et al. 2010	0.171	0.112	0.253	-6.259	0.000
Europe	Angelopoulos et al. 2006	0.136	0.098	0.185	-9.883	0.000
Europe		0.191	0.134	0.265	-6.723	0.000

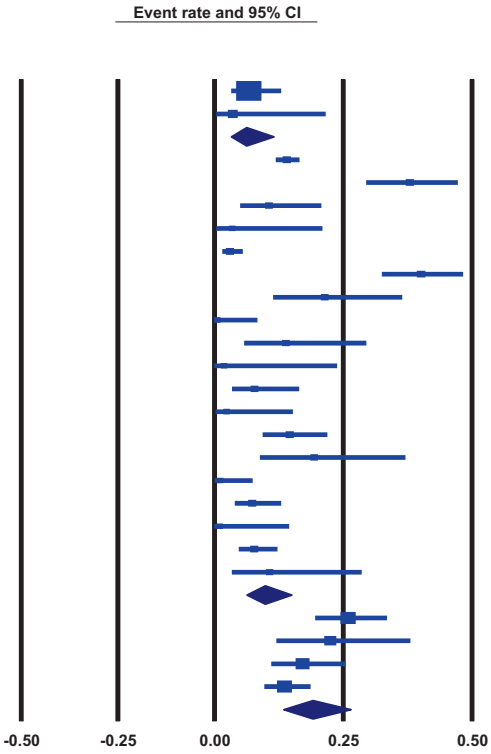

Figure 3. Subgroup analysis of pooled prevalence of hypoparathyroidism in patients with TDT and NTDT in different continents.

Discussion

Thalassemias, the most prevalent hereditary anemic disease worldwide, have a significant impact on public health. They affect millions of individuals and lead to substantial morbidity and mortality, especially in regions with high prevalence (44). The prevalence of HPT varies among different populations and disease cohorts. For instance, a 2017 review reported prevalence rates of HPT, following neck surgery, to be 22, 23, and 6.4 per 100,000 in Danish, American, and Norwegian populations, respectively (45). In a study focused on Iranian patients with TDT, the prevalence of reported HPT was 10% (46). Similarly, in a study involving 100 TDT patients, Manne et al. (47) found that 18% of them had HPT (47). Higher percentages were reported by Mostafavi et al. (22.7%) (48) and Adil et al. (35.3%) (49). The pooled prevalence of HPT among TDT and NTDT patients through a comprehensive synthesis of available evidence from multiple studies worldwide since 2000, has documented a lower prevalence of 11.3% (95% CI: 8.1-15.5%). Although, cell surface transferrin receptors could play a role in protecting parathyroid glands against inorganic iron. Iron overload induces lysosomal and sarcolemmal membrane damage through free radical formation and lipid peroxidation and subsequent damage of parathyroid glands (4-6). The incidence rate of HPT in TDT has been thought to be linked to entity of iron overload and adhesion to chelation therapy (19, 23, 24, 28, 38). Moreover, the severity of disease (TDT vs. NTDT), the availability of diagnostic tools, the adherence to clinical guidelines, the overall quality of healthcare systems (13), and splenectomy could be an additional factors. In the subgroup analysis, we found that among thalassemic patients, the highest prevalence of HPT was observed in Europe, with a rate of 19.1% followed by Asia (9.8%), and Africa (6.2%). These results be attributed to pattern changes in the epidemiology of thalassemias due

Study name	Statistics with study removed				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Faranoush et al. 2023	0.107	0.073	0.155	-9.817	0.000
Khattak et al. 2023	0.106	0.077	0.145	-11.725	0.000
Cagliyan et al. 2021	0.113	0.081	0.157	-10.753	0.000
Mahmoud et al. 2021	0.116	0.083	0.160	-10.712	0.000
Thiagarajan et al. 2019	0.116	0.083	0.159	-10.853	0.000
Bajoria et al. 2019	0.107	0.075	0.149	-10.902	0.000
Majid et al. 2019	0.124	0.091	0.167	-11.015	0.000
Dhouib et al. 2018	0.116	0.083	0.159	-10.855	0.000
Ehsan et al. 2018	0.107	0.079	0.144	-12.290	0.000
Chahkandi et al. 2017	0.109	0.077	0.151	-10.932	0.000
Pirinççioglu et al. 2017	0.118	0.085	0.161	-10.896	0.000
Sultan et al. 2016	0.112	0.080	0.155	-10.844	0.000
Baldini et al. 2014	0.109	0.077	0.151	-10.955	0.000
Isik et al. 2014	0.116	0.083	0.159	-10.913	0.000
Saffari et al. 2012	0.115	0.082	0.159	-10.731	0.000
Baldini et al. 2010	0.110	0.077	0.153	-10.721	0.000
Merchant et al. 2010	0.117	0.084	0.160	-10.835	0.000
Hamidieh et al. 2009	0.110	0.078	0.154	-10.667	0.000
Sleem et al. 2007	0.110	0.078	0.152	-10.925	0.000
Angelopoulos et al. 2006	0.110	0.077	0.155	-10.503	0.000
Karamifar et al. 2006	0.119	0.086	0.163	-10.819	0.000
Karamifar et al. 2003	0.116	0.083	0.160	-10.699	0.000
Mahachoklertwattana et al. 2003	0.117	0.084	0.160	-10.900	0.000
Shamshirsaz et al. 2003	0.115	0.082	0.159	-10.686	0.000
Chern et al. 2002	0.113	0.081	0.156	-10.843	0.000
	0.113	0.081	0.155	-11.095	0.000

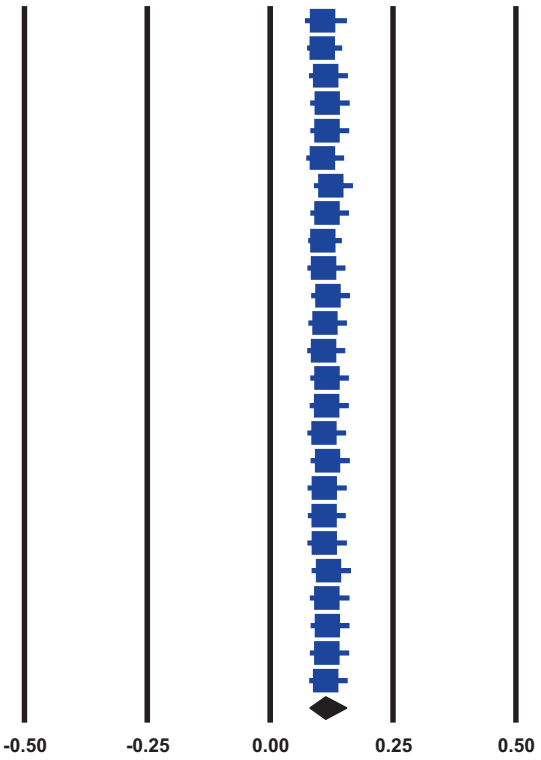

Figure 4. Sensitivity analysis for the overall prevalence of hypoparathyroidism among thalassemia patients.

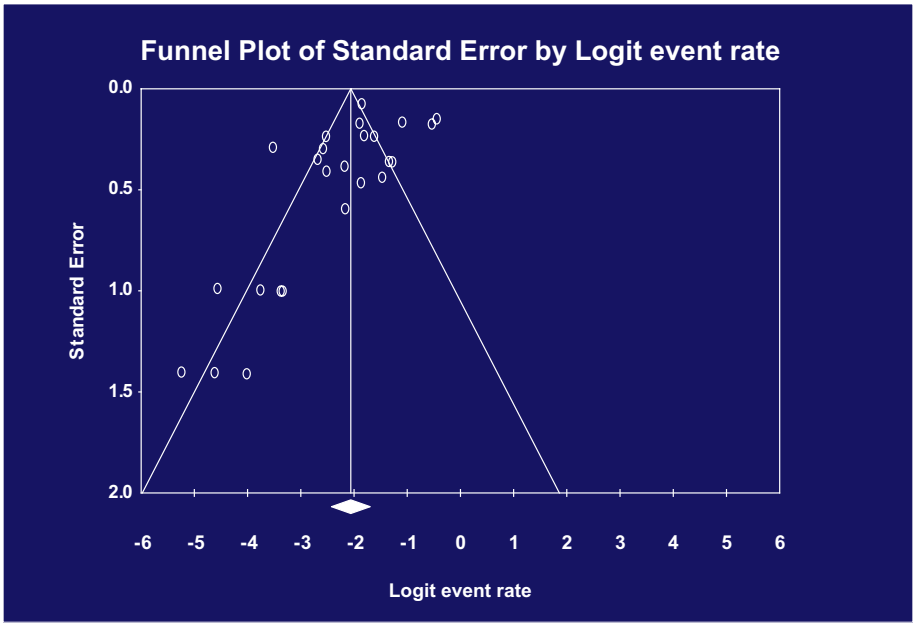

Figure 5. Funnel plot of the included studies assessing the prevalence of hypoparathyroidism in patients with thalassemias.

Table 2. Association of biochemical markers with parathyroid hormone in patients with thalassemia

Biomarker	Coefficient	Standard Error	P-value (Coefficient)	95% Conf. Interval (Lower)	95% Conf. Interval (Upper)
Vit D	-0.796	0.681	0.267	-2.295	0.703
LIC	-0.967	0.689	0.394	-9.717	7.783
ALP	0.013	0.041	0.763	-0.083	0.109
Serum ferritin level	0.002	0.003	0.437	-0.004	0.009
Pretransfusional Hb level	-1.323	4.723	0.786	-12.007	9.361

Abbreviations: LIC: liver iron concentration; ALP: alkaline phosphatase: Hb: hemoglobin

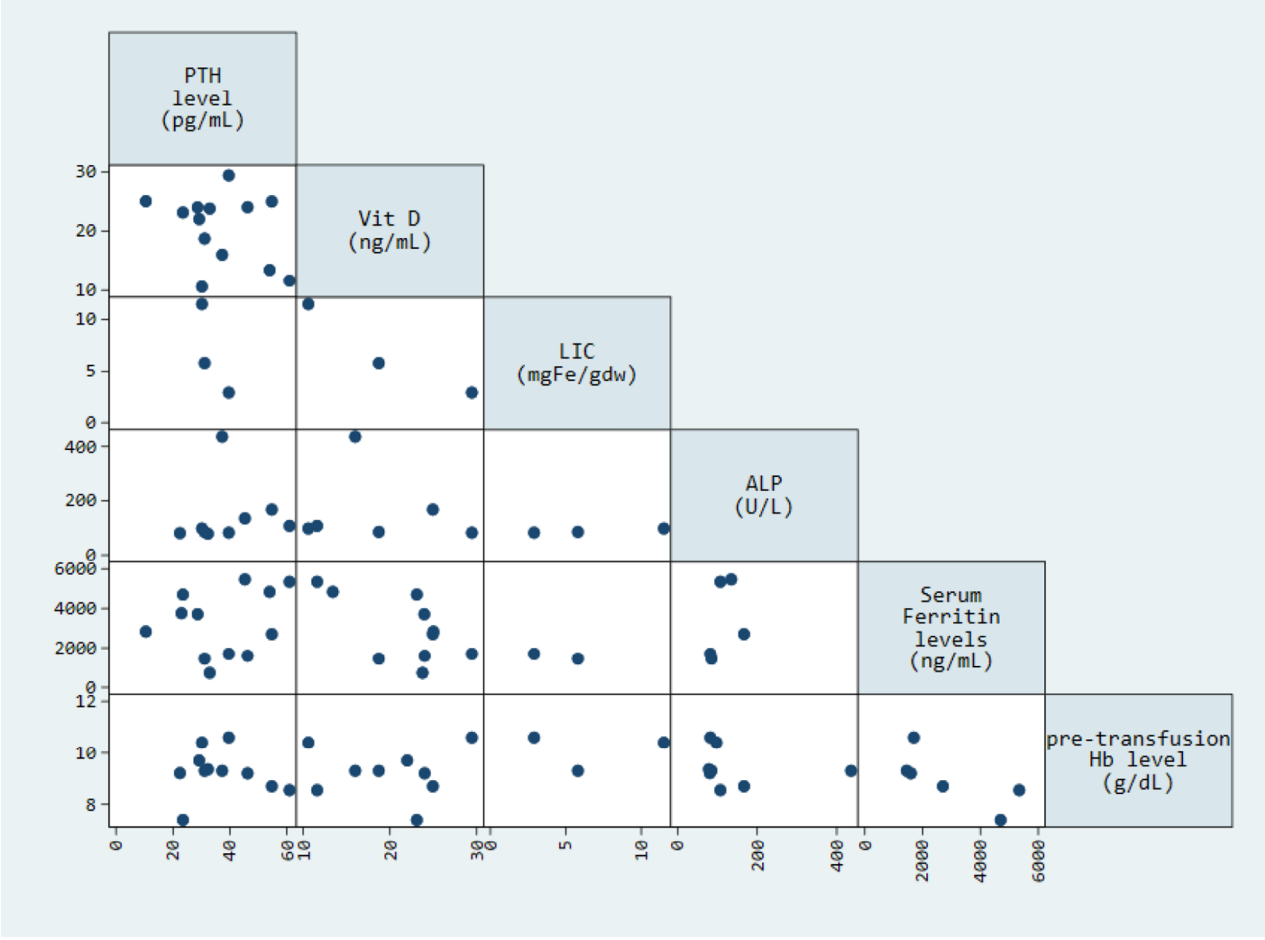

Figure 6. Scatter plot matrix of clinical parameters: The matrix displays pairwise scatter plots of PTH, vitamin D, LIC, ALP, serum ferritin, and pre-transfusional Hb levels.

to migration, which has increased the prevalence in regions traditionally believed to have a low prevalence of hemoglobinopathies (50,51). However, the detection of asymmetry in the funnel plot, along with the notable results from Egger's test (P=0.038), indicate a considerable publication bias among the included articles. This bias has the potential to skew the portrayal of study results. To address this issue in future research,

steps can be taken, such as promoting study protocol registration to enhance transparency and utilizing additional tools to assess bias. The sensitivity analysis performed on the overall pooled prevalence of HPT in thalassemic patients revealed that none of the studies had a significant impact, underscoring the stability and consistency of the results. We found that the mean age (± SD) of the participants was 19.0 (± 1.1), 50.4% male and 49.6% female. However, some studies have shown that PTH due to iron overload may develop earlier (23,25,31,32,35,40,42,43). PTH linear meta-regression demonstrated no significant correlation between PTH and other biochemical markers despite their anticipated association. This unexpected outcome could potentially be attributed to various factors, such as methodological differences in the studies, variations in sample populations, or underlying complexities in the interactions between PTH and these biochemical markers. Our study has several limitations: First, a significant heterogeneity was detected in the pooled analyses of prevalence. This heterogeneity may be due to differences in the number of cases or basic characteristics. Second, there were insufficient data to conduct a complete evaluation of all regions worldwide. Third, it was not possible to analyze the prevalence of asymptomatic HPT because the data reported in the literature were scanty. Lastly, the majority of the articles were on TDT patients, precluding any comparisons between TDT and NTDT groups.

Conclusion

Our meta-analysis shows an HPT prevalence of 11.3% in thalassemia patients. The reason why some patients develop parathyroid dysfunction, and others do not is not exactly known. Although, parathyroid dysfunction is primarily considered a disease of the second or third decade it could be seen in the earlier stage of life. Enhanced adherence to chelation and consistent diagnostics is vital for improved HPT management in thalassemia. These data should be dynamically updated as studies are published.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Funding: None.

Ethics: Not applicable.

Authors' Contribution: S.H., Z.G., M.K., and M.R. contributed to the conception and design of the study. Z.G., S.M., S.R., E.T., and S.R.A.M. were involved in data collection and analysis. S.R.A.M., E.T., S.H., and Z.G. contributed to data interpretation and manuscript drafting. V.D.S. M.K., and M.R. provided critical revisions for important intellectual content. All authors reviewed and approved the final version of the manuscript.

Declaration on the Use of AI: None.

References

1. Langer AL. Beta-Thalassemia: University of Washington, Seattle, Seattle (WA); 1993 1993.
2. Fibach E, Rachmilewitz EA. Pathophysiology and treatment of patients with beta-thalassemia - an update. F1000Res. 2017;6:2156. doi:10.12688/f1000research.12688.1.
3. De Sanctis V, Elsedfy H, Soliman AT, et al. Endocrine profile of β-thalassemia major patients followed from childhood to advanced adulthood in a tertiary care center. Indian J Endocrinol Metab. 2016;20(4):451-9. doi:10.4103/2230-8210.183456.
4. Carsote M, Vasiliu C, Trandafir AI, et al. New Entity—Thalassemic Endocrine Disease: Major Beta-Thalassemia and Endocrine Involvement. Diagnostics. 2022;12(8):1921. doi:10.3 3907 diagnostics 120811921.
5. Pinto VM, Poggi M, Russo R, Giusti A, Forni GL. Management of the aging beta-thalassemia transfusion-dependent population – The Italian experience. Blood Rev. 2019;38:100594. doi:10.1016/j.blre.2019.100594.
6. Mannstadt M, Bilezikian JP, Thakker RV, et al. Hypoparathyroidism. Nat Rev Dis Primers. 2017;3(1):17055. doi:10.1038/nrdp.2017.55.
7. Wei K, Yin Z, Xie Y. Roles of the kidney in the formation, remodeling and repair of bone. J Nephrol. 2016;29(3):349-57. doi:10.1007/s40620-016-0284-7.
8. Bilezikian JP. Hypoparathyroidism. J Endocrinol Metab. 2020;105(6):1722-36. doi:10.1210/clinem/dgaa113.
9. Bilezikian JP, Brandi ML, Cusano NE, et al. Management of Hypoparathyroidism: Present and Future. J Endocrinol Metab. 2016;101(6):2313-24. doi:10.1210/jc.2015-3910.
10. Abate EG, Clarke BL. Review of Hypoparathyroidism. Front Endocrinol (Lausanne). 2017;7. doi:10.3389/fendo.2016.00172.

11. Clarke BL, Brown EM, Collins MT, et al. Epidemiology and Diagnosis of Hypoparathyroidism. J Endocrinol Metab. 2016;101(6):2284-99. doi:10.1210/jc.2015-3908.
12. Harsløf T, Rolighed L, Rejnmark L. Huge variations in definition and reported incidence of postsurgical hypoparathyroidism: a systematic review. Endocrine. 2019;64(1): 176-83. doi:10.1007/s12020-019-01858-4.
13. De Sanctis V, Soliman AT, Canatan D, et al. An ICET-A survey on Hypoparathyroidism in Patients with Thalassaemia Major and Intermedia: A preliminary report. Acta Biomed. 2017;88(4):435. doi:10.23750%2Fabm.v88i4.6837.
14. Tangngam H, Mahachoklertwattana P, Poomthavorn P, et al. Under-recognized Hypoparathyroidism in Thalassemia. J Clin Res Pediatr Endocrinol. 2018;10(4):324-30. doi:10.4274/jcrpe.0020.
15. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71.
16. Luchini C, Stubbs B, Solmi M, Veronese N. Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale. World J Meta-Anal. 2017;5(4):80-4. doi:10.13105/wjma.v5.i4.80.
17. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14 (1): 135. doi:10.1186/1471-2288-14-135.
18. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5(1):13. doi:10.1186/1471-2288-5-13.
19. Faranoush M, Faranoush P, Heydari I, et al. Complications in patients with transfusion dependent thalassemia: A descriptive cross-sectional study. Health Sci Rep. 2023;6(10):e1624. doi:10.1002/hsr2.1624.
20. Khattak MB, Shad H, Munir A, Khan MA, Afridi MA, Ali K. Relationship of Hypoparathyroidism with Patients of Beta Thalassemia Major in a Tertiary Care Hospital. Medical Forum Monthly. 2023; p. 49-52
21. Cagliyan GA, Yaylalı GF, Soyer N, Hacioglu S, Cagliyan O, Guler N. Relationship Between Endocrinopathies and Ferritin Levels in Adult Turkish Patients with Beta Thalassemia Major: A Single-Center Experience. J Clin Pract Res. 2021;43(1):37-42. doi:10.14744/etd.2020.33427.
22. Mahmoud RA, Khodeary A, Farhan MS. Detection of endocrine disorders in young children with multitransfused thalassemia major. Ital J Pediatr. 2021;47(1):165. doi:10.1186/s13052-021-01116-2.
23. Thiagarajan N, Delhi Kumar C, Sahoo J, Krishnamurthy S. Effect of vitamin D and calcium supplementation on bone mineral content in children with thalassemia. Indian Pediatr. 2019;56:307-10. PMID:31064900.I.
24. Bajoria R, Rekhi E, Almusawy M, Chatterjee R. Hepatic hemosiderosis contributes to abnormal vitamin D-PTH axis in thalassemia major. J Pediatr Hematol Oncol. 2019;41(2): e83-e9. doi:10.1097/MPH.0000000000001261.
25. Majid H, Jafri L, Ahmed S, Talati J, Moiz B, Khan AH. Unique classification of parathyroid dysfunction in patients with transfusion dependent thalassemia major using Nomogram-A cross sectional study. Ann Med Surg (Lond). 2019;45:22-6. doi:10.1016/j.amsu.2019.07.016.
26. Dhouib NG, Ben Khaled M, Ouederni M, et al. Growth and Endocrine Function in Tunisian Thalassemia Major Patients. Mediterr J Hematol Infect Dis. 2018;10(1):e2018031. doi:10.4084/MJHID.2018.031.
27. Ehsan L, Rashid M, Alvi N, et al. Clinical utility of endocrine markers predicting myocardial siderosis in transfusion dependent thalassemia major. Pediatr Blood Cancer. 2018; 65(10):e27285. doi:10.1002/pbc.27285.
28. Pirinççioğlu AG, Gökalp D, Söker M. Parathyroid functions in thalassemia major patients. Ann Clin Endocrinol Metab. 2017;1(1):015-9. doi:10.29328/journal.hcem.1001003.
29. Chahkandi T, Norouziasl S, Farzad M, Ghanad F. Endocrine disorders in beta thalassemia major patients. Int J Pediatr. 2017;5(8):5531-8. doi:10.22038/ijp.2017.21937.1834.
30. Baldini M, Forti S, Orsatti A, et al. Bone disease in adult patients with beta-thalassaemia major: a case-control study. Intern Emerg Med. 2014;9(1):59-63. doi:10.1007/s11739-011-0745-x.
31. Isik P, Yarali N, Tavil B, et al. Endocrinopathies in Turkish children with Beta thalassemia major: results from a single center study. Pediatr Hematol Oncol. 2014;31(7):607-15. doi:10.3109/08880018. 2014.898724.
32. Sultan S, Irfan SM, Ahmed SI. Biochemical Markers of Bone Turnover in Patients with beta-Thalassemia Major: A Single Center Study from Southern Pakistan. Adv Hematol. 2016;2016:5437609. doi:10.1155/2016/5437609.
33. Saffari F, Mahyar A, Jalilolgadr S. Endocrine and metabolic disorders in β-thalassemiamajor patients. Caspian J Intern Med. 2012;3(3):466. PMID: 24009916.
34. Baldini M, Forti S, Marcon A, et al. Endocrine and bone disease in appropriately treated adult patients with beta-thalassemia major. Ann Hematol. 2010;89(12):120713. doi:10.1007/s00277-010-1007-0.
35. Merchant R, Udani A, Puri V, D'Cruz V, Patkar D, Karkera A. Evaluation of osteopathy in thalassemia by bone mineral densitometry and biochemical indices. Indian J Pediatr. 2010;77(9):987-91. doi:10.1007/s12098-010-0158-2.
36. Hamidieh AA, Moradbeag B, Pasha F, Jalili M, Hadjibabaie M, Keshavarznia M. High prevalence of hypoparathyroidism in patients with beta-thalassemia major. IJHOSCR. 2009: 17-20. doi: not available.
37. Sleem GAA, Al-Zakwani IS, Almuslahi M. Hypoparathyroidism in adult patients with beta-thalassemia major. Sultan Qaboos Univ Med J. 2007;7(3):215-8. PMID: 21748106.
38. Angelopoulos NG, Goula A, Rombopoulos G, et al. Hypoparathyroidism in transfusion-dependent patients with beta-thalassemia. J Bone Miner Metab. 2006;24(2):138-45. doi:10.1007/s00774-005-0660-1.
39. Karamifar H, Karimi M, Amirhakimi G, Badiei M. Endocrine function in thalassemia intermedia. Int J Biomed Sci. 2006;2 (3):236-40. PMID: 23674986.

40. Shahriari M, Sadjadian N. Prevalence of endocrine complications in beta-thalassaemia major in the Islamic Republic of Iran. EMHJ. 2003;9(1-2):55-60. doi:10.26719/2003.9.1-2.55.
41. Mahachoklertwattana P, Chuansumrit A, Sirisriro R, Choubtum L, Sriphrapradang A, Rajatanavin R. Bone mineral density, biochemical and hormonal profiles in suboptimally treated children and adolescents with beta-thalassaemia disease. Clin Endocrinol (Oxf). 2003;58 (3):273-9. doi:10.1046/j.1365-2265.2003.01707.x.
42. Shamshirsaz AA, Bekheirnia MR, Kamgar M, et al. Metabolic and endocrinologic complications in beta-thalassemia major: a multicenter study in Tehran. BMC Endocr Disord. 2003;3(1):4. doi:10.1186/1472-6823-3-4.
43. Chern JP, Lin K-H. Hypoparathyroidism in transfusion-dependent patients with β-Thalassemia. J Pediatr Hematol Oncol. 2002;24 (4):291-3. PIMD:11972098.
44. Tuo Y, Li Y, Li Y, et al. Global, regional, and national burden of thalassemia, 1990–2021: A systematic analysis for the global burden of disease study 2021. eClin Med. 2024;72:102619. doi:10.1016/j.eclinm.2024.102619.
45. Edafe O, Balasubramanian SP. Incidence, prevalence and risk factors for post-surgical hypocalcaemia and hypoparathyroidism. Gland Surg. 2017;6 (Suppl 1):S59-s68. doi:10.21037/gs.2017.09.03.
46. Azami M, Rahmati S, Sayehmiri K. Prevalence of Hypoparathyroidism in Patients with Thalassemia Major in Iran. J Babol Univ Med Sci. 2016;18 (9):39-48. doi:10.22088/jbums.18.9.39.
47. Manne N, Yadav SK, Gupta BK, Singhal S, Dubey A. Prevalence of hypoparathyroidism, growth retardation in patients of β-thalassemia major. IJCBR. 2020;7(2):158-63. doi:10.18231/j. ijcbr.2020.034.
48. Mostafavi H, Afkhamizadeh M, Rezvanfar M. Endocrine disorders in patients with thalassemia major. Iran J Endocrinol Metab. 2005;7(2):143-7. doi:not available.
49. Adil A, Sobani ZA, Jabbar A, Adil SN, Awan S. Endocrine complications in patients of beta thalassemia major in a tertiary care hospital in Pakistan. J Pak Med Assoc. 2012;62(3):307-10. doi: not available.
50. Kattamis A, Forni GL, Aydinok Y, Viprakasit V. Changing patterns in the epidemiology of β-thalassemia. Eur J Haematol. 2020;105(6):692-703. doi:10.1111/ejh.13512.
51. Yadav SP, Sachdeva A, Arya SC, Khanna VK, Arya AD. Prevalence of Hypoparathyroidism in Children and Young Adults with Thalassemia Major. Blood. 2005;106(11): 3850. doi:10.1182/blood.V106.11.3850.3850.

Correspondence:
Received: 20 November 2024
Accepted: 28 December 2024
Zahra Ghahramani, MD
Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.
E-mail: z.ghrmn@gmail.com
ORCID: 0000-0003-2224-3778