Review Article

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Prevalence of Short Stature, Underweight and Delayed Puberty in Iranian Patients with Thalassemia Major: A Systematic Review and Meta-Analysis

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Abstract

Growth disorders are considered as one of the common complications of thalassemia major patients. The present study was conducted to examine the prevalence of short stature, underweight, and delayed puberty in patients with thalassemia major in Iran.

This review study was conducted based on systematic review and meta-analysis protocol (PRISMA) until 2017. To access relevant literature, two researchers independently searched Magiran, Medlib, Iranmedex, SID, PubMed, Scopus, ScienceDirect, Web of Science, as well as Google Scholar search engine. Pooled prevalence was calculated using a random effects model. Data were analyzed using Comprehensive Meta-Analysis Software (Version 2).

In 18 studies, including 2,446 Iranian thalassemia major patients, the prevalence of short stature was estimated to be 52.3% (95%CI: 45.7-58.8). The lowest prevalence of short stature was in the North of Iran (42.4% [95%CI: 34.7-50.4]) and Mazandaran province (31.8% [95%CI: 27.5-36.5]), and the highest prevalence was in the South (64.6% [95%CI: 51.2-72.1]) and Fars province (71.4% [95%CI: 49.8-86.3]). The prevalence of short stature among males and females was estimated to be 48.7% (95%CI: 39.3-58.1) and 40.4% (95%CI: 30.4-51.2), respectively, and male to female odds ratio was 1.21 (95%CI: 1.01-1.46, P=0.03). Prevalence of delayed puberty and underweight in Iranian thalassemia major patients were estimated to be 67.5% (95%CI: 46.8-83.1) and 47.6% (95%CI: 37.0-58.4), respectively.

The results of this meta-analysis showed that the prevalence of short stature, delayed puberty, and underweight in Iranian thalassemia major patients is very high. Therefore, new planning and policies seem necessary to minimize the complications in patients with thalassemia major

Key words: Delayed Puberty, Growth Disorders, Thalassemia

Introduction

Thalassemia is the most common hereditary disease in Iran and the world (1). Approximately, 95% of thalassemia patients are born in Asia, the Middle East, and India (2-3). Iran is one of the countries where thalassemia occurs frequently and around 18616 people suffer from this disease (3). Due to abnormalities in the structure of hemoglobin chains in red blood cells (RBCs), the RBCs in the bloodstream do not have a normal life and they are quickly destroyed (4). Symptoms of the disease start with anemia, which is associated with change in appearance, bone problems, weakness, and delayed

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growth (5). These patients are treated by monthly transfusion that decreases the acute symptoms of the disease. However, receiving blood causes many complications, including infections, alloimmunization, and excess iron deposition in various organs that can cause liver failure, heart failure, and endocrine disorders (6-11). To avoid these complications, chelation therapy is used for disposal of excess iron, but endocrine disorders are still observed (12). Growth disorder is one of the serious complications in people with thalassemia major. Growth hormone deficiency, gonadal failure, and hypothyroidism are common in patients with growth disorders (13).Patients with thalassemia often show constitutional growth and puberty delay by lowering the ultimate height compared to the target height. Short stature, mostly due to trunk shortening usually starts at the ages of 5-6 in boys and 8 in girls. But today, patients who perform blood transfusion and iron removal have a normal growth rate during the first 10 years of life. Treatment with deferoxamine has proved to improve the linear growth of these patients compared to other previous chelators. Linear growth is characterized by decreased growth rate until maturity: at this stage, the physiological growth rate is often weak and/or delayed and the growth failure becomes more apparent (14-17). Growth plate fusions are usually delayed until the end of the second decade of life, with the final height close to the height expressed in the SD score (SDS) at the onset of puberty (15-18).

Several studies have investigated the function of GHRH-GH-IGF-I and showed short stature deficiencies in a large number of patients. Neurosecretory GH (Growth Hormone) disorders with different prevalence are reported in thalassemia patients with short stature (19-22). While contradictory data is available about GH storage, it is found in natural (23) or reduced form with a wide range of changes (8-80%) in short patients due to defects in the pituitary gland and/or in the hypothalamus (22, 24).

Long-term recombinant human GH (rhGH) therapy is ineffective for reaching a normal height. These patients can benefit from rhGH over a short period of time, while longer-term treatment should be provided for adolescents with mental problems due to short stature. In these patients, the acceleration of linear growth may even be the main goal. In adolescents with delayed sexual maturity, the replacement of sex steroid can increase linear growth as much as it occurs on rhGH (25-26).

A review of documents showed that the frequency of short stature, underweight, and delayed puberty in patients with thalassemia major is varied in different regions of Iran (27-48). By examining all relevant documents and combining those using meta-analysis methods, systematic review and meta-analysis can provide a more complete picture of the dimensions of the problem in the community (49-51). Therefore, considering the importance of this issue, it seems necessary to estimate the prevalence of short stature, underweight, and delayed puberty in patients with thalassemia major in Iran by conducting a systematic review and meta-analysis.

Materials and Methods

1.1.Study protocol

This review study was conducted based on preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) (51). To conduct this study, 5 steps were designed, including search strategies, study collection and systematic review of them, inclusion and exclusion criteria assessment, qualitative evaluation, and finally statistical analysis of the data. In order to avoid bias in this study, two researchers conducted each of the mentioned steps independently. Finally, a third reviewer examined the agreed results.

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1.2.Search strategy

This study was conducted based on the review of all scientific literature published until April 2017, examining short stature, underweight, or delayed puberty in patients with thalassemia major in Iran. To identify the relevant studies, national and international databases, including: Magiran, Medlib, Iranmedex, SID (Scientific Information Database), PubMed, Scopus, Science Direct, Web of Science (ISI), as well as Google Scholar search engine were searched. In order to maximize the validity of search in databases, English and Persian keywords were searched based on MeSH searching. The MeSH keywords included Prevalence, Endocrine, Growth, Delayed puberty, Hemosiderosis, Iron Overload, Chelation Therapy, Thalassemia Major, and Iran. References used in the investigated papers were also used to find further studies. Appendix 1 shows the combined search in PubMed database.

1.3.Inclusion and exclusion criteria

In this study, the main criteria for inclusion was the cross-sectional studies, in which the prevalence of short stature, underweight, and delayed puberty in thalassemia major patients were reported. Exclusion criteria included: 1. selection of non-random sample size to estimate prevalence; 2. Being irrelevant to the topic; 3. Insufficient data such as lack of a report on the prevalence; 4. Population other than Iranian thalassemia major patients; 4. Case-control studies, reviews, case reports, letters to the editor, and 6. Duplicate studies.

1.4. Qualitative evaluation

For qualitative evaluation of studies, STROBE checklist was used (52). The authors adopted a simple method for scoring. Each item was scored from 0 to 2 from the checklist. Scoring was done by two researchers independently. The minimum and maximum score were 0 and 44, respectively. Score 1-15 was considered as poor quality, score 16-30 was considered as moderate quality, and score 31-44 was considered as good quality. Finally, high-quality articles that obtained a score higher than 16 were selected for the meta-analysis process.

1.5.Data extraction

The data were extracted using data extraction form (name of the first author, year of publication, year of study, place, number of participants, mean and standard deviation for age, the overall prevalence for short stature, underweight, and delayed puberty, prevalence of short stature, underweight, and delayed puberty in terms of gender and age). When a specific question was proposed or the articles' information was unclear, the authors were contacted by email.

Statistical analysis

The variance of each study was calculated according to the binomial distribution. Cochran's Q test and I^2 statistic were used to determine the heterogeneity of studies. Pooled prevalence was calculated using a random effects model considering the high heterogeneity of studies (53-54). Sensitivity analysis was performed to check the stability and reliability of the main effect size for short stature prevalence. To find the source of heterogeneity, sub-group analysis was conducted in terms of age, geographic regions and provinces of Iran. Meta-regression model was used to find the relationship between short stature prevalence and years of studies. To investigate the relationship between gender and short stature, male to female, odds ratio (OR) was used. Data were analyzed using Comprehensive Meta-Analysis Software (Version 2) and P-value less than 0.05 was considered significant in tests.

Results

2.1.Search results and study characteristics

In the first systematic search, 310 possible relevant studies were found and 180 articles were excluded from the study due to duplication. After screening the abstract

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of the remaining articles, 65 articles were excluded due to being irrelevant to the topic. 43 articles were excluded from the study due to the following reasons: 1. Not reporting the prevalence (N=16); 2. Population other than thalassemia major patients (N=15); 3. Non-Iranian studies (N=5), and 4. Case-control studies, reviews, case reports, letters to the editor (N=7). Finally, 22 high-quality studies (18, 7 and 6 studies were about short stature, delayed puberty and underweight, respectively) were included for quantitative process of meta-analysis (Figure 1).

In 22 studies, 2,699 patients with thalassemia major were studied. The mean age of the patients in the studies was 17.28% years (95%CI [Confidence Interval]: 15.13-19.44). Other characteristics of each study are shown in Table 1.

2.2.Total prevalence of short stature

In 18 studies including 2,446 Iranian thalassemia major patients, the prevalence of short stature was estimated to be 52.3% (95%CI: 45.7-58.8). The lowest and highest prevalence were related to studies in Babol (30.1%) and Shiraz (91.1%), respectively (Figure 2).

2.3.Sensitivity analysis

Sensitivity analysis based on removing one study at a time for prevalence of short stature data showed that the overall result is reliable (Figure 3).

2.4.Subgroup analysis for the prevalence of short stature

The subgroup analysis based on regions and provinces of Iran shows that the lowest prevalence of short stature was in the North of Iran (42.4% [95%CI: 34.7-50.4]) and Mazandaran province (31.8% [95%CI: 27.5-36.5]), and the highest prevalence was in the South of Iran (64.6% [95%CI: 51.2-72.1]) and Fars province (71.4% [95%CI: 49.8-86.3]), and the test result for subgroup analysis was significant (P<0.02) (Table 2).

Prevalence of short stature in patients with thalassemia major below and above 10 years of age was estimated to be 61.4% (95%CI: 48.8-72.6) and 48.7% (95%CI: 38.6-58.9), respectively, and the test result for subgroup analysis was not significant (P=0.30) (Table 2).

2.5.Meta-regression

Meta regression model for the relationship between prevalence of short stature and years of studies had a descending trend, but was not significant (P=0.08) (Figure 4).

2.6.Prevalence of short stature by gender

The prevalence of this disorder among males and females was estimated to be 48.7% (95%CI: 39.3-58.1) and 40.4% (95%CI: 30.4-51.2), respectively, and male to female OR was 1.21 (95%CI: 1.01-1.46, P=0.03) (Figure 5).

2.7.Total prevalence of delayed puberty

The prevalence of delayed puberty in the 7 studies including 1,000 patients with thalassemia major was estimated to be 67.5% (95%CI: 46.8-83.1). The lowest and highest prevalence of delayed puberty were related to studies of Rabani in 2000 in Tehran (26.7%) and Mostafavi in 2005 in Shiraz (88%), respectively (Figure 6-A).

2.8.Total prevalence of underweight

The prevalence of underweight was estimated to be 47.6% (95%CI: 37.0-58.4) in 6 studies including 759 patients with thalassemia major. The lowest prevalence was related to study of Asgharian in 2010 in Shiraz (26.2%) and the highest prevalence was related to study of Rajabian in 2006 in Mashhad (68.1%) (Figure 6-B).

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Table I: Studies included in meta-analysis

Ref	First author	Place	Year	Sample size	Age (Mean±SD)	Prevalence (%)		
						short stature	delayed puberty	underweight
27	Rostami P, 2011	Boshehr	2009	60	20.23±23.0	45		
28	Mostafavi H, 2005	Shiraz	2003	44	15.7±3.7	90.9	88	
29	Saffari F, 2008	Qazvin	2006	63	20.89±5.01		42.9	
30	Najafipour F, 2000	Tabriz	2006	56	15.6±4.44	51.8		
31	Rabani A, 2008	Tehran	2000	315			26.7	
32	Shiva S, 2012	Tabriz	2006	71	12.9±5.2	45.1		
33	Eshraghi P, 2011	Babol	2010	280	19.6±8.5	32.1		
34	Saffari F, 2012	Qazvin	2012	77	21.26±4.53	33.8		
35	Eshragi P, 2011	Babol	2009	130	20.95±7.8	31.3		
36	Salehzadeh F, 2002	Tehran	2002	48		66.7		
37	Nabavizadeh S, 2005	Yasoj	2002	121		67		**53.7**
38	Khalili D, 2007	Rasht	2001	392	11.1±4.4	41.8		**37**
39	Rajabian R, 2006	Mashhad	2004	47	18.1±2.6	68.1		**68.1**
40	Asgharian A, 2010	Shiraz	2007	62		61.4		**26.2**
41	Hashemizadeh H, 2013	Mashhad	2010	100		55		**51**
42	Mohammadi R, 2011	Ardebil	2010	37	15.43±5.97	64.9		**54**
43	Salak M, 2008	Isfahan	2008	100			69	
44	Nouri NM, 2008	Zahedan	2002	100			86	
45	Moayeri H, 2006	Tehran	2006	158	15.1±4.8	62	69	
46	Safarinejad MR, 2003	Tehran	2006	168	24.0±4.6	44.6		
47	Shamshirsaz AA, 2003	Tehran	1999	220	15.2±3.1	39.3	77	
48	Karamifar H, 2003	Shiraz	2008	50	14.22±4.27	58		

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Table II: The prevalence of short stature based on region, province and age

	Variable	Studies (N[a])	Sample (N[a])	Heterogeneity		95%CI[b]	Prevalence (%)
				I^2	P-Value		
Region	Center	5	671	87.39	<0.0001	37.6-60.1	**48.8**
	East	2	147	55.52	0.134	47.3-72.4	**60.5**
	North	6	966	79.48	<0.0001	34.7-50.4	**42.4**
	South	5	337	80.63	<0.0001	51.2-72.1	**64.6**
	Test for subgroup differences: Q=10.44, df(Q)=3, P=0.015						
Province	Ardabil	1	37	0	-	48.5-78.4	**64.9**
	Bushehr	1	60	0	-	33.0-57.6	**45.0**
	Fars	3	156	82.93	0.003	49.8-86.3	**71.4**
	Razavi Khorasan	2	147	55.52	0.134	47.3-72.4	**60.5**
	Guilan	1	392	0	-	37.0-46.7	**41.8**
	East Azarbaijan	2	127	0	0.453	39.5-56.7	**48.1**
	Kohgiluyeh and Boyer-Ahmad	1	121	0	-	58.2-74.8	**67.0**
	Mazandaran	2	410	0	-	27.5-36.5	**31.8**
	Qazvin	1	77	0	-	24.2-45.0	**33.8**
	Tehran	4	594	88.31	<0.0001	39.9-64.6	**52.4**
	Test for subgroup differences: Q=72.80, df(Q)=9, P<0.001						
Age	Under 10	1	62	0	-	48.8-72.6	**61.4**
	Over 10	8	913	87.90	<0.0001	38.6-58.9	**48.7**
	Both	9	1146	88.77	<0.0001	44.9-64.0	**54.6**
	Test for subgroup differences: Q=2.38, df(Q)=2, P=0.303						

[a] Number; [b] Confidence interval

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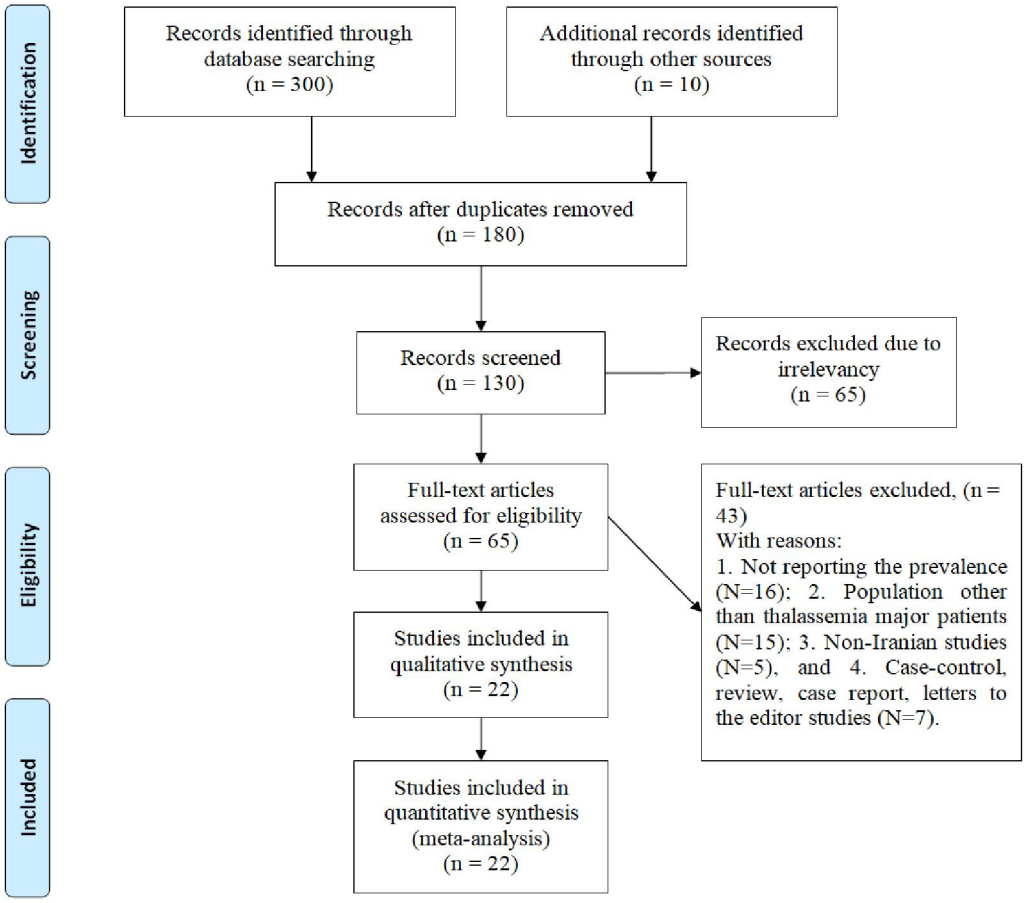
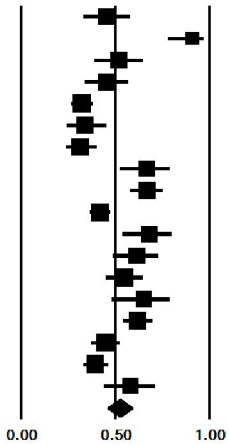


Fugure 1. The selection process of studies for meta-analysis process

Study name	Statistics for each study					Event rate and 95% CI	Relative weight
	Event rate	Lower limit	Upper limit	Z-Value	p-Value		
Rostami P, 2011	0.450	0.330	0.576	-0.773	0.439		5.42
Mostafavi H, 2005	0.909	0.781	0.965	4.391	0.000		3.34
Najafipour F, 2008	0.518	0.389	0.645	0.269	0.788		5.35
Shiva S, 2008	0.451	0.340	0.567	-0.824	0.410		5.59
Eshraghi P, 2012	0.321	0.269	0.378	-5.853	0.000		6.39
Saffari F, 2012	0.338	0.242	0.450	-2.790	0.005		5.57
Eshragi P, 2011	0.313	0.239	0.398	-4.156	0.000		5.98
Salehzadeh F, 2002	0.667	0.524	0.785	2.268	0.023		5.02
Nabavizadeh S, 2005	0.670	0.582	0.748	3.663	0.000		5.95
Khalili D, 2007	0.418	0.370	0.467	-3.232	0.001		6.53
Rajabian R, 2006	0.681	0.536	0.798	2.423	0.015		4.96
Asgharian A,2010	0.614	0.488	0.726	1.779	0.075		5.40
Hashemizadeh H, 2013	0.550	0.452	0.644	0.998	0.318		5.89
Mohammadi R, 2011	0.649	0.485	0.784	1.784	0.074		4.69
Moayeri H, 2006	0.620	0.542	0.692	2.987	0.003		6.16
Safarinejad MR, 2003	0.446	0.373	0.522	-1.397	0.162		6.22
Shamshirsaz AA, 2003	0.393	0.331	0.459	-3.149	0.002		6.33
Karamifar H, 2003	0.580	0.441	0.708	1.126	0.260		5.19
	0.523	0.457	0.588	0.678	0.498		



Meta Analysis

Figure 2: Prevalence of short stature in patients with thalassemia major in Iran. Random effects model

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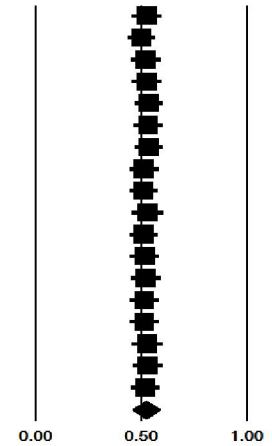
Study name	Statistics with study removed				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Rostami P, 2011	0.527	0.459	0.595	0.782	0.434
Mostafavi H, 2005	0.503	0.441	0.564	0.081	0.936
Najafipour F, 2008	0.523	0.455	0.591	0.671	0.502
Shiva S, 2008	0.528	0.459	0.596	0.784	0.433
Eshraghi P, 2012	0.536	0.471	0.600	1.080	0.280
Saffari F, 2012	0.534	0.466	0.601	0.984	0.325
Eshragi P, 2011	0.536	0.469	0.602	1.063	0.288
Salehzadeh F, 2002	0.514	0.448	0.580	0.424	0.671
Nabavizadeh S, 2005	0.511	0.447	0.576	0.347	0.728
Khalili D, 2007	0.532	0.459	0.604	0.861	0.389
Rajabian R, 2006	0.514	0.447	0.579	0.401	0.688
Asgharian A,2010	0.517	0.450	0.584	0.505	0.614
Hashemizadeh H, 2013	0.522	0.453	0.590	0.613	0.540
Mohammadi R, 2011	0.516	0.449	0.582	0.473	0.636
Moayeri H, 2006	0.516	0.449	0.582	0.459	0.646
Safarinejad MR, 2003	0.529	0.458	0.599	0.805	0.421
Shamshirsaz AA, 2003	0.533	0.462	0.602	0.908	0.364
Karamifar H, 2003	0.520	0.452	0.587	0.570	0.569
	0.523	0.457	0.588	0.678	0.498



Meta Analysis

Figure 3: Sensitivity analysis for prevalence of short stature in patients with thalassemia major in Iran. Random effects model

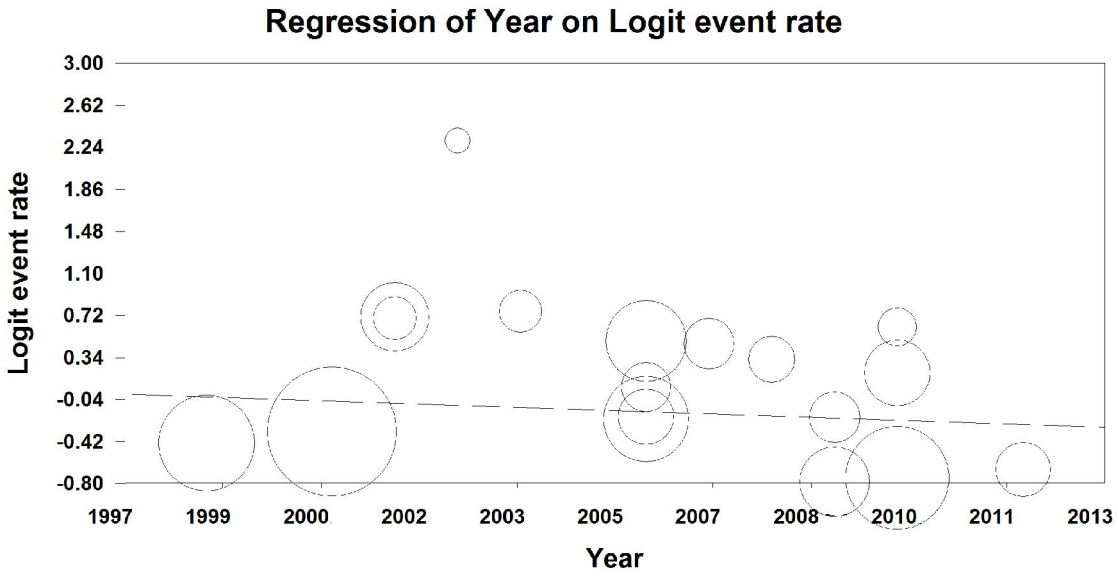


Figure 4. Meta-regression of the prevalence of short stature based on years of studies. Larger circles show larger sample size.

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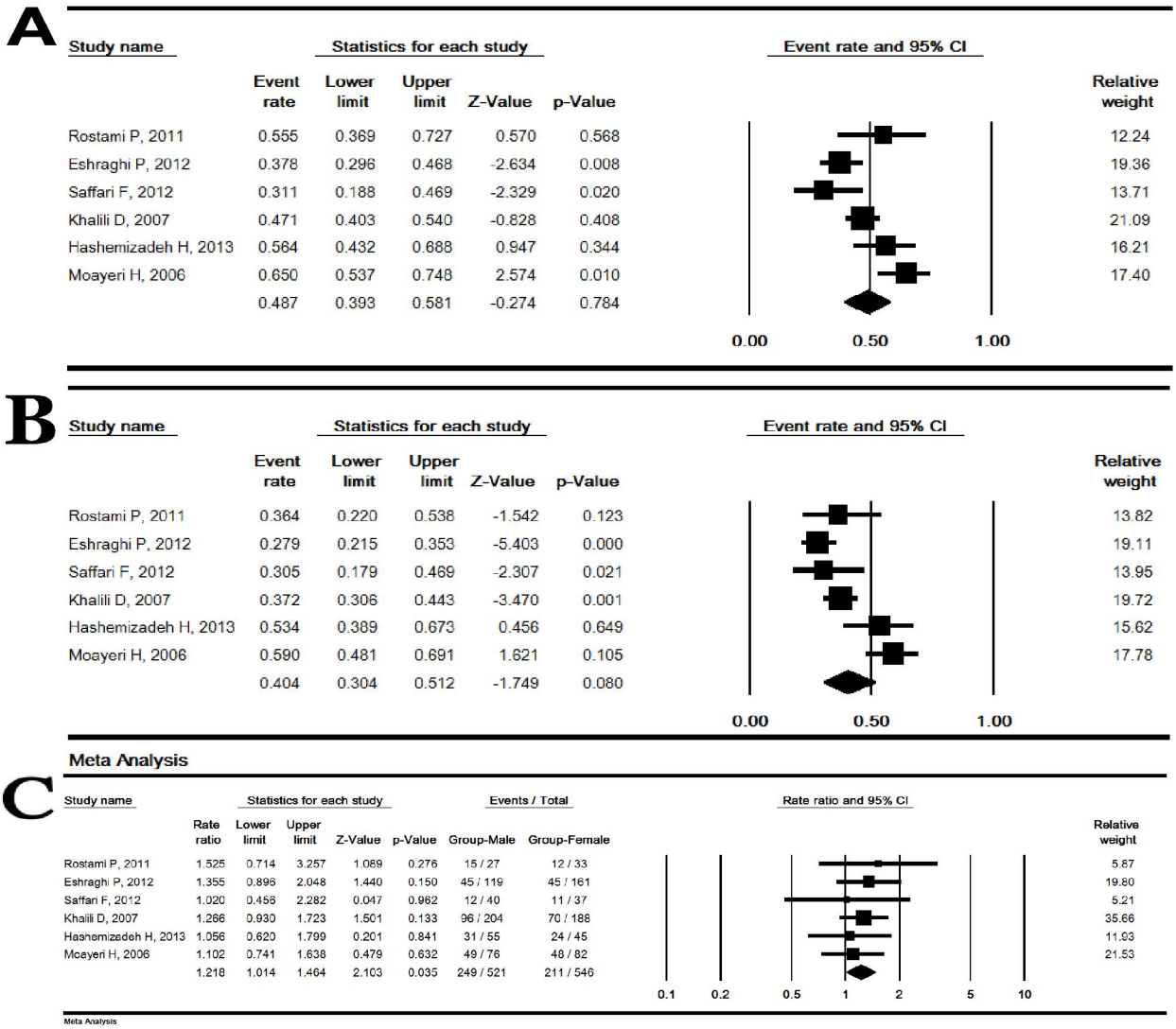

Figure 5: The prevalence of short stature in men (A) and women (B) patients with thalassemia major and odds ratio for male to female (C). Random effects model

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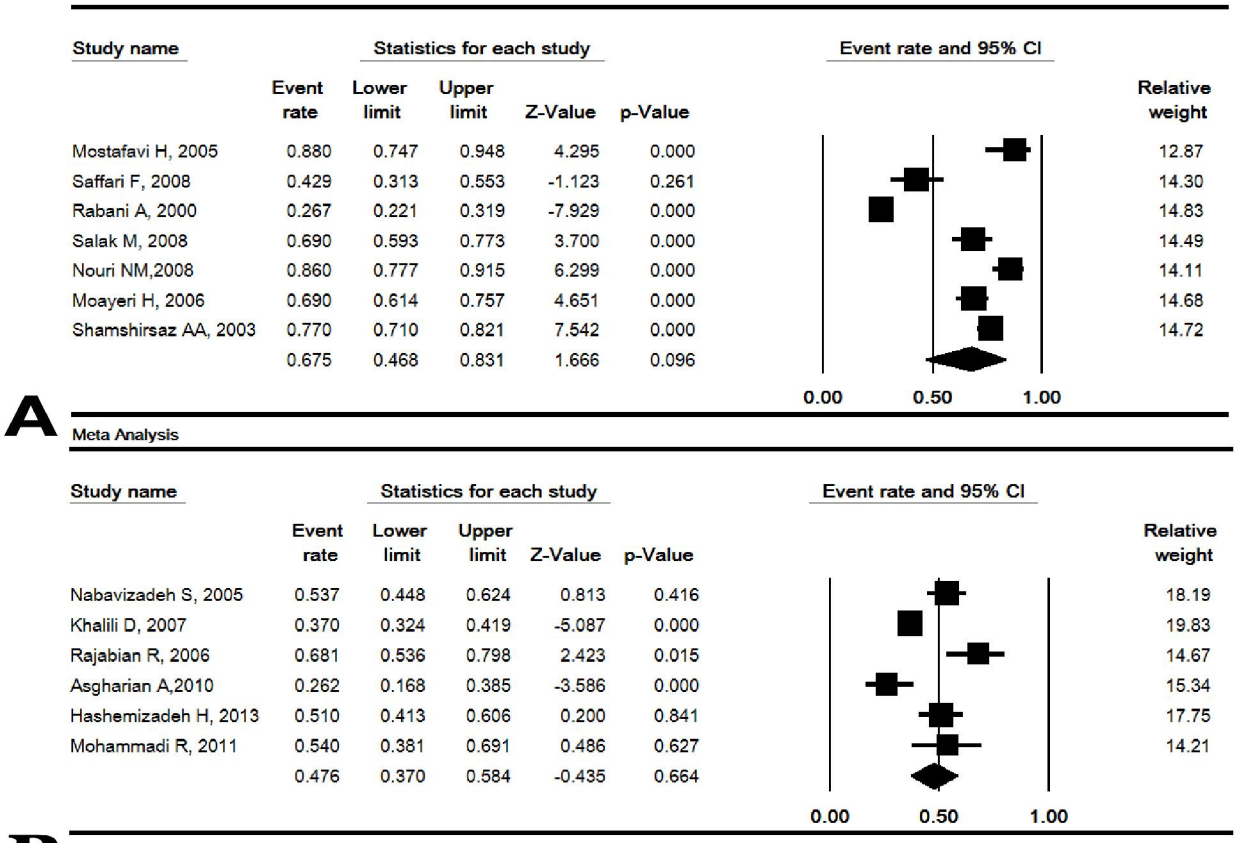

Figure 6: The prevalence of delayed puberty (A) and underweight (B) in patients with thalassemia major in Iran. Random effects model

Discussion

The present study is the first systematic review and meta-analysis on growth disorders in patients with thalassemia major in Iran. The prevalence of short stature, delayed puberty, and underweight was 52.3%, 67.5%, and 47.6%, respectively. Due to the heterogeneity of studies, subgroup analyzes were used and significant relationship was found between short stature and geographic regions and provinces of Iran. Due to limited number of studies on delayed puberty and underweight, subgroup analysis could not be used.

In other systematic reviews conducted on patients with thalassemia major in Iran, the prevalence of hypothyroidism, impaired glucose tolerance, diabetes, pre-diabetes, hypoparathyroidism, and hypogonadism were reported to be 5.7%, 9.6%, 10.1%, 12.9%, 9%, and 42.3%, respectively (6-11). It could be said that the most common endocrine disorder in these patients is delayed puberty, short stature and underweight, respectively. The pathogenesis of endocrine disorders in thalassemia major patients was iron overload due to frequent blood transfusion (55-56).

In a systematic review conducted on Iranian patients with thalassemia major, the frequency of regular chelation therapy was reported to be 54%, as this type of treatment was performed non-principally in most Iranian patients with thalassemia major. Poor acceptance of chelation therapy may cause high prevalence of Iron overload-related disorders (12). Growth disorder is a multifactorial disorder, and other studies have found different causes for this disorder, including gonadotropin secretory abnormalities, chronic anemia, hypoxia, diabetes, liver disease, zinc and folic acid deficiency, emotional factors, GH-IGF1 (Growth Hormone-Insulin-Like

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Growth Factor-1) axis disorders, and deferoxamine-induced bone dysplasia (57-58).

In other countries, the prevalence of short stature was reported to be 30-60% (59-62). Difference in prevalence of short stature in patients living in various countries could be due to genetic susceptibility to the toxic effects of iron overload in endocrine gland and serum ferritin. It may also indicate differences in quality of care, follow-up and treatment for these patients, quality of blood transfusion, chelation therapy type (regular or irregular) and beginning of desferrioxamine therapy.

In this study, no significant difference was observed between the prevalence of short stature in thalassemia major patients, below and above 10 years old. Despite the slow growth of thalassemia since the beginning of the patient's life, the growth rate declines clearly when they are 9-10 years old and a significant percentage of patients eventually become shorter. In a study conducted by Gomber et al. in India, 75% of the patients 10 years old or above were short (62). In addition, in a study conducted by Hamidah et al., short stature in patients older than 10 years had higher prevalence compared to patients under 10 years old (16.7%) (59).

One limitation of the study was lack of a unified definition in studies for the diagnosis of short stature, delayed puberty and underweight.

Conclusion

The results of this study demonstrated that the prevalence of short stature, delayed puberty, and underweight in Iranian patients with thalassemia major is very high and they are suffering from growth disorder since the beginning of their life. Therefore, new planning and policies seem to be necessary to minimize the complications in patients with thalassemia major. Some of the recommended plans include improvement of blood transfusion protocols, chelation therapy, informing the parents and patients about the complications of iron overload caused by endocrine glands. In addition, we suggest that these patients be examined at an early age in terms of growth every six months.

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Conflict of interest

In this study, the authors have no conflicts of interest.

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