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REVIEW ARTICLE

Cardiac complications and iron overload in beta thalassemia major patients—a systematic review and meta-analysis

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Abstract

Despite the major improvement in therapeutic management of thalassemia major, iron overload is considered a challenging conundrum in these patients and heart disease still remains a major cause of morbidity and mortality in these patients. Therefore, this study aimed to investigate the prevalence of cardiac iron overload and cardiovascular complications in transfusion-dependent thalassemia patients in the worldwide. The following databases were searched: ISI/Web of Science, Embase, PubMed, Scopus, up to February 30, 2018. The quality of the studies was evaluated using the Joanna Briggs Institute Prevalence Critical Appraisal Tool. The random model based on Metaprop was used. One hundred forty-two studies were included. The total number of patients included was 26,893. The mean age of patients was 22.6 (SD = 1.7) years. Based on Metaprop, the overall prevalence of cardiac iron overload/myocardial sidoresis (T2* < 20 ms) and cardiac complications in thalassemia major patients in the worldwide was 25% (95% CI 22–28%) and 42% (95% CI 37–46%), respectively. The results of this study show that the prevalence of cardiac iron overload and cardiovascular complications in patients with thalassemia major is almost high. Therefore, iron chelation and careful monitoring of serum ferritin level will prevent the cardiac iron overload, and interval monitoring of patients with transfusion-dependent thalassemia (TDT) by echocardiography and electrocardiography will help with early detection of cardiovascular complications.

Keywords Cardiac iron overload · Myocardial sidoresis · Cardiac complications · Major thalassemia

Introduction

Thalassemia is the most common of all inherited disorders which are resulted by reduced or absent synthesis of the hemoglobin chains [1]. It is estimated that there are 270 million carriers of different hemoglobinopathies of which 30% are carriers of β-thalassemia in the world's population [2]. About 300,000–400,000 new cases are born with a serious hemoglobin disorder each year [3]. Ineffective erythropoiesis is one of the major pathogenic mechanisms of disease manifestations, since years ago to now, blood transfusion has been used as regular therapy [4]. This makes them particularly vulnerable to iron accumulation in several organs that led to organ dysfunction and serious complications such as cardiac complications [5, 6]. β-Thalassemia major (β-TM) had a higher prevalence of cardiac iron overload (CIO) than other subtypes of thalassemia [5].

Despite the major improvement in therapeutic management of thalassemia major and the resulting substantial improvement of patients' survival, iron overload is considered a challenging conundrum in these patients and heart disease still remains a major cause of morbidity and the primary cause of mortality in these patients [6–9]. Myocardial iron deposition seems to be the trigger for the development of heart disease in thalassemia major [8, 10]. Cardiac complications are reported to be the cause of the deaths in 71% of the patients with β-TM [11, 12]. Heart failure and arrhythmias are the most important life-limiting complications of iron overload in these patients [12]. Due to the limited number of patients in reported centers,

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various cardiac complications have been reported in patients with iron deposition. Informing about the most common complication of iron deposition in the heart of patients in these comprehensive studies can be very helpful in introducing more effective approaches to preventing and treating patients. By providing these clinical-based approaches, quality of life can be improved, lifespan, and reduce the cost of patients care.

To our knowledge, no study has conducted on the meta-analysis of prevalence of cardiac iron overload and cardiac complications in patients with β-TM. Therefore, this study aimed to investigate the prevalence of cardiac iron overload and cardiovascular complications in transfusion-dependent patients with β-TM in the worldwide. It hoped the findings could help to contribute to the existing literature and provide evidence for future planning.

Methods

Data sources and searches

The current systematic review and meta-analysis are reported based on "Preferred Reporting Items of Systematic Reviews and Meta-Analyses" PRISMA guidelines [13]. To find the relevant articles, two researchers independently searched the Medline, Scopus, Web of Science, and Embase databases up to February 30, 2018. We used the keywords including; thalassemia major, β-thalassemia, beta-thalassemia, multitransfusen β-Thalassemia, cardiac siderosis, myocardial siderosis, cardiac complications, cardiovascular disease, heart disease, rheumatic heart disease, pulmonary heart disease, myocardial ischemia, cardiac failure, pulmonary hypertension, left ventricular hypertrophy, tricuspid regurgitation, tricuspid valve insufficiency, mitral valve prolapse, mitral regurgitation, aortic regurgitation, aortic valve insufficiency, arrhythmias, hypertrophy, angina, and etc. In order to find the additional relevant articles, websites of thalassemia and reference lists from identified studies also examined. No restrictions imposed on language and study period. This study has been approved by the ethics committee in the research of Birjand University of Medical Sciences (IR. BUMS. REC. 1397.273).

Inclusion and exclusion criteria

We imported all articles obtained into EndNote X7 software, then removed duplicate articles, and then screened titles and abstracts to remove those that did not appear to be relevant. Two authors independently reviewed the relevant full-text articles. The disagreements on study selections resolved by consensus with another author. The inclusion criteria was investigating the frequency of cardiac iron overload and cardiac complications, using cardiovascular magnetic resonance T2*, echocardiographic, and electrocardiographic, in a population of patients with β-TM. Exclusion criteria included studies non-relevant to the topic, thalassemia patients without blood transfusion, not investigating cardiac complications, review articles, letters to the editor, and case reports.

Study quality assessment

Two authors separately assessed quality of each included study, using Joanna Briggs Institute Prevalence Critical Appraisal Tool that recently validated and included 10 items that provide methodological quality assessment of prevalence studies [14]. Each item was rated as "yes," "no," or "unclear" according to information given by study, allowing a positive maximum score of 10 points.

Data extraction

Two authors independently extracted the data from the included studies for the meta-analysis. We extracted the following information from each study: the first author's last name, publication year, country of the study, study design, mean age of the population, sample size, prevalence of cardiac iron overload, and different types of cardiac complications in multitransfusion β-TM patients and standard deviation. If the full text of articles were not available, we contacted authors via email to ask for them.

Statistical analysis

The standard deviation of each study calculated according to the binomial distribution. In this study, Metaprop was used to perform meta-analyses of proportions close to or at the margins 0% or 100%. Metaprop pools proportions and presents a weighted subgroup and overall pooled estimates with inverse-variance weights obtained from a random-effect model [15]. Heterogeneity of the included studies was examined by using of chi squared (χ^2) tests at the 5% significance level ($P < 0.05$). We also calculated the I-squared (I^2) statistic, to reflect the percentage of total variation across studies [16]. According to the Cochrane handbook, $I^2 > 50\%$ reflects a substantial heterogeneity [17]. Therefore, random effect model is used to combine data in the meta-analysis [18, 19]. Subgroup analysis was carried out in terms of world region of studies for dealing with heterogeneity. The possibility of publication bias in the present study was examined by using Begg's test and Egger's test [20]. All data analyses were performed using the Stata 14 at 95% sig value, except for the quality assessment of studies, wherein we used Review Manager 5.3.

Results

The study characteristics and risk of bias within studies

The search of databases yielded 1188 articles. Of these, 484 duplicates were excluded. After reviewing the titles and abstracts, 167 articles were identified as potentially eligible for inclusion. After full review, 142 studies published from 1979 to 2018 were deemed eligible and were included in the current systematic review and meta-analysis (Fig. 1).

The sample size of included studies ranged between 15 and 3095 patients. The total number of patients included was 26,893. The mean age of patients was 21.3 (SD = 7.8) years.

Mean methodological quality was 7.6 out of 10 (ranging from 3 to 10). Eleven studies (7.7%) scored < 5. Methodological quality issues are reported in Fig. 2. The main issues were 14 studies (9.8%) did not fulfill item 6 (standard criteria used for measurement of cardiac complications), 30 studies did not fulfill item 7 (reliability in the identification of cardiac complications), 4 studies (21.2%) did not fulfill item 8 (statistical analysis and reporting of results appropriated for prevalence studies) and 35 studies (24.6%) did not fulfill item 9, and 12 studies (8.5%) did not fulfill 10 (identification and approach of potential factors that could affect the prevalence of cardiac complications).

Begg's test and Egger's test concerning of the cardiac siderosis rates revealed no evidence of publication bias in these analyses (0.086 and 0.533, respectively), but both tests revealed evidence of publication bias concerning of the cardiac complication rates (0.006 and < 0.0001, respectively).

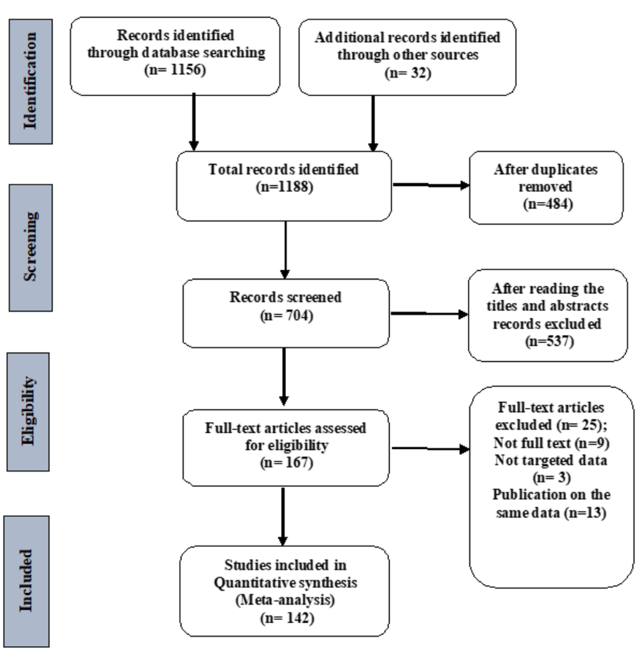

Fig. 1 Prisma flowchart of study selection

Prevalence of cardiac (myocardial) iron overload/siderosis

In all, 64 studies reported prevalence of CIO, defined as a cardiovascular magnetic resonance T2* < 20 ms, in patients with β-TM in the world. In all studies, assessment of myocardial iron with cardiovascular magnetic resonance (CMR) relaxation time T2* has been used. Patients with T2* of > 20 ms are regarded as having no cardiac iron load; those with T2* between 10 and 20 ms have mild to moderate cardiac iron load, and those with T2* of < 10 ms are considered to have heavy cardiac iron load.

The total number of patients included was 10,968 with a mean age 22.8 (SD = 7.5) years. Overall, pooled prevalence of myocardial iron loading with a T2* less than 20 ms was 25% (95% CI = 22–28%). Subgroup analysis by severity of iron overload showed that pooled prevalence of the severe cardiac siderosis (T2* < 10 ms) was 17% (95% CI = 14–21%), and pooled prevalence of the mild to moderate cardiac siderosis (T2* = 20–10 ms) was 26% (95% CI = 22–31%) (Fig. 3). In addition, subgroup analysis based on world region shows that pooled overall prevalence of cardiac iron overload (T2* < 20 ms) varied significantly between regions with the lowest level being found in patients from African countries (16%) and the highest in Europe (28%; $P < 0.001$) (Fig. 4). Also, pooled prevalence of severe CIO was lowest in Africa (12%) and highest in Asia (22%), and pooled prevalence of mild-to-moderate CIO was highest in Europe (31%) and lowest in America (15%).

Total prevalence of cardiac complications

Forty-three studies reported the prevalence of various types of cardiac complications in patients with β-TM. The total number of patients included to meta-analysis was 12,175 with a mean age 20 (SD = 8.2) years. Based on meta-analysis by Metaprop, the overall pooled prevalence was 42% (95% CI 37–46). Based on subgroup analysis by world region, the pooled prevalence of cardiac complications varied significantly between regions ($P < 0.001$). Regardless of the America subgroup which there is one study, the lowest pooled prevalence was found in patients from European countries (19%) and the highest in Africa (45%) (Fig. 5).

Prevalence of various types of cardiac complications

The pooled prevalence of various types of cardiac complications according to echocardiographic and electrocardiographic findings in patients with β-TM is shown in Table 1.

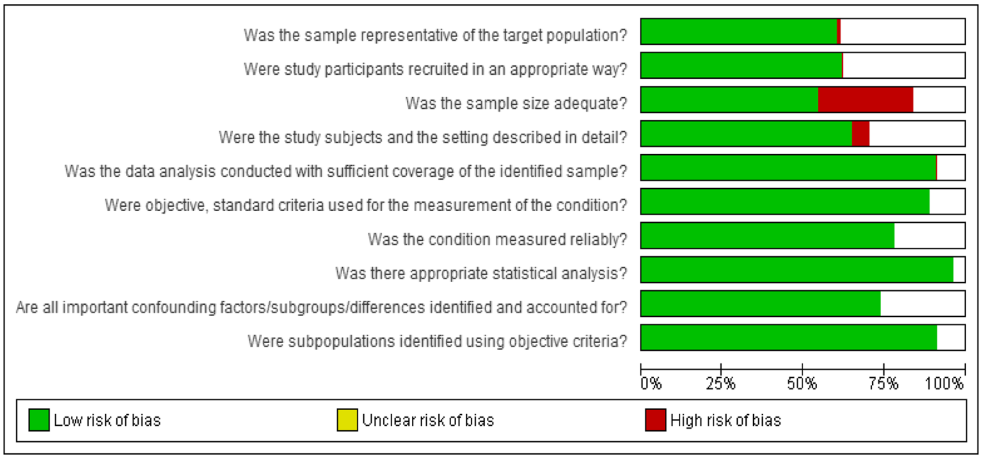

Fig. 2 Risk of bias graph; review authors' judgments about each risk of bias item presented as percentages across all included studies

Discussion

CIO and cardiac complications are the main cause of death in β-TM patients. CIO seems to be the trigger for the development of cardiac complications in β-TM [21]. The findings of this meta-analysis demonstrate that there is an overall prevalence of CIO with 25% having a myocardial T2* less than 20 ms, pooled prevalence of severe CIO (T2* < 10 ms) was 17%, and pooled prevalence of mild-to-moderate CIO (T2* = 20–10 ms) was 26%. In addition, there is considerable geographical variation in cardiac iron overload. In this study, the pooled prevalence of CIO estimated 28% in Europe, 26% in Asia, 16% in Africa, and 22% in America. In addition, the findings of this meta-analysis show that overall pooled prevalence of cardiac complications is 24% with highest prevalence in Africa (45%). The studies in various countries including China, North America, Greece, Italy, Australia, and Iran reported the prevalence of cardiac complications in patients with thalassemia major 5%, 10%, 12.9%, 13.3%, 48.6%, and 76.4%, respectively [22–27].

Several factors affecting geographical distribution in CIO are difference in access to transfusion and regular chelation therapy, volume of transfused blood and efficacy of iron chelation therapy, differences in age, genetic differences, total body iron burden, the treatment adopted for thalassemia, transfusion rates, and condition of blood transfusion [5, 7, 28, 29].

Carpenter et al. reported a prevalence of CIO among 3095 thalassemia patients in 27 centers from an international survey during 2001–2008 worldwide including 47% in Europe, 30% in North America, 32% in South America, 43.5% in Middle East, 25% in North Africa, 53% in Southeast Asia, and 44% in West Asia [10]. Authors of CORDELIA study reported a prevalence of CIO of 40.9% and 45.9% among 203 Far East and 259 Western population with the data collection from 2008 to 2012 [30]. In Carpenter's study, over 96% of patients were receiving regular iron chelation, but they did not have data on the type and dose of iron chelator, the number of transfusions per year, and the pre-transfusion hemoglobin threshold.

Patients in other studies received various chelation therapies with either a single chelating agent (deferasirox or deferiprone) or a combination therapy (deferasirox and deferiprone or desferrioxamine), and we did not have data on subgroups of type of iron chelation, so no inferences can be drawn on this problem.

Heart failure and arrhythmias are the most important life-limiting complications due to myocardial iron overload in β-TM [12]. In this study, the pooled prevalence of heart failure and arrhythmias estimated 9% and 10%, respectively.

In the current study, the most common echocardiography disorder was the diastolic dysfunction (34%), while the estimation of overall prevalence of systolic dysfunction was about 9%. Davis et al. found that diastolic left ventricular dysfunction develops early, but the systolic dysfunction determines the outcome in this patients and most patients die of systolic dysfunction [31].

Despite that the pulmonary hypertension is almost rare in β-TM patients, depending on lifelong regular blood transfusions and iron chelation therapy [32], in the current study, the prevalence of pulmonary hypertension estimated 13% in β-TM. In addition, an abnormally elevated tricuspid regurgitation > 2.5 m/s is measured by Doppler echocardiography, suggesting that a risk of a rising pulmonary hypertension is a common finding in TDT patients [33]. We estimated a 24% prevalence of an elevated TR.

Primarily, repetitive blood transfusions, as well as by hemolysis and increased intestinal absorption, results in iron overload [12]. Iron overload and increased cardiac output mainly affected on cardiac structure and function in thalassemia [34]. There is evidence that support a relationship between the severity of myocardial siderosis (T2* < 20 ms) and the risk of heart failure or arrhythmias,

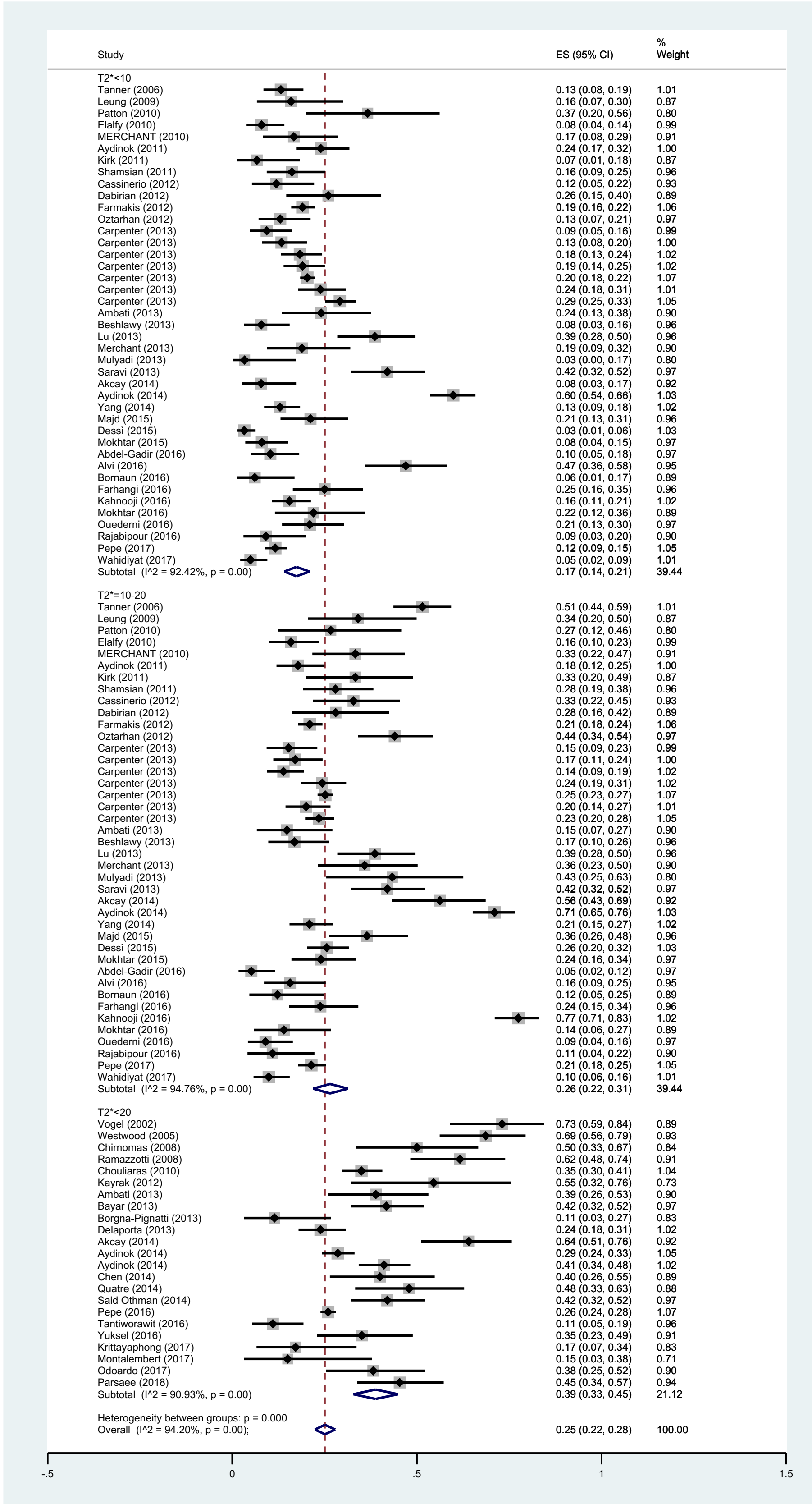

Fig. 3 Forest plot of the pooled prevalence of cardiac iron overload in thalassemia major patients, by severity of loading as analyzed by Metaprop

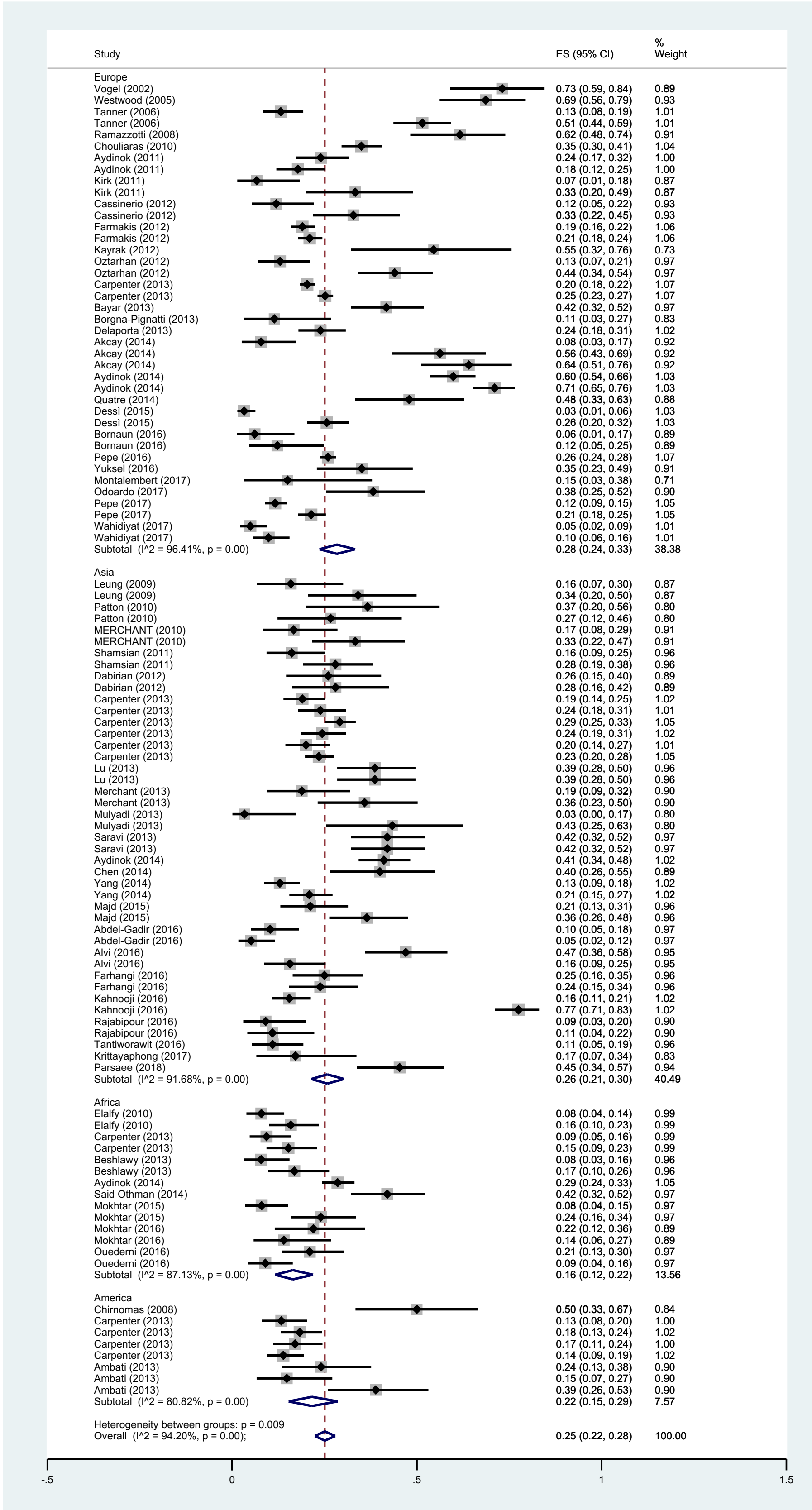

Fig. 4 Forest plot of the pooled prevalence of cardiac iron overload in thalassemia major patients, by world region as analyzed by Metaprop

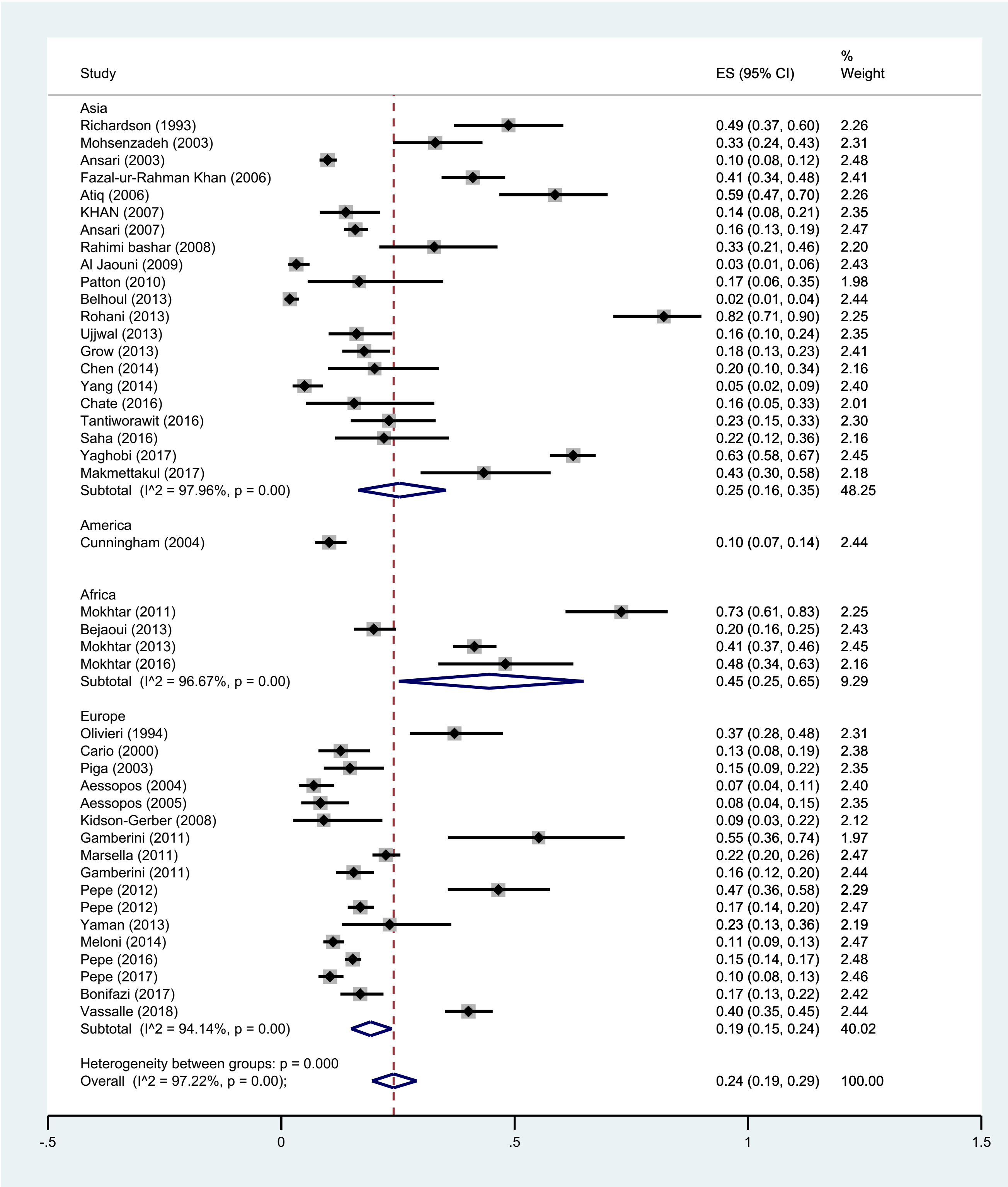

Fig. 5 Forest plot of the pooled prevalence of cardiac complications in thalassemia major patients, by world region as analyzed by Metaprop

thus supporting the validity of myocardial T2* as an early predictor of heart complications [35]. Cardiovascular magnetic resonance using T2* is widely used in many countries for assessment of myocardial iron deposition for clinical management and guiding chelation therapy tailored to the heart [10]. Although new iron-chelating agents have been developed, resulting in substantial improvement of patients' survival, heart disease still remains

Table 1 The pooled prevalence of various types of cardiac complications in patients with thalassemia major using Metaprop

Variable	Studies (*N*)	Sample size (*N*)	Mean age (± SD)	Prevalence (%)	95% CI	I^2 (%)
Heart failure	39	12,402	22. 4 (8.3)	9	7–11	93.07
Systolic dysfunction	21	2549	15.4 (6.4)	17	12–23	95.2
Left ventricular dilatation	23	5245	21.3 (8.9)	18	13–24	95.4
Cardiomyopathy	13	3039	20.6 (9.6)	11	4–20	97.8
Diastolic dysfunction	18	1379	15.6 (5.5)	39	25–53	96.2
Pulmonary hypertension	32	5647	21.9 (8.4)	13	9–19	96.0
Tricuspid regurgitation	19	2169	18.6 (7.2)	24	12–39	97.6
Myocardial fibrosis	14	4663	26.3 (7.2)	17	12–24	96.1
Left ventricular hypertrophy	9	1020	18.6 (5.6)	15	6–27	94.6
Pericardial effusion	6	369	13.5 (2.3)	3	0–8	70.3
Arrhythmia	30	9505	22.8 (8.8)	10	8–13	94.23
Electrocardiographic (ECG) abnormalities	6	244	16.8 (6.4)	28	17–41	85.9

N number, *CI* confidence interval

a major cause of morbidity and mortality in these patients as a result of iron overload [6]. However, a systematic review study showed that iron chelation therapy reduces iron overload significantly [36].

Limitations

Some limitations of the present study should be noted. Heterogeneity was high and statistically significant: the difference in the location of the studies, as well as the implementation of studies, could at least partially explain this observation. In some countries, we did not find any studies on the prevalence of CIO or cardiac complications in patients with β-TM. Furthermore, the data were inadequate for analyzing the impact of variables such as gender.

Conclusion

The results of this study show that in spite of regular blood transfusions and chelation therapy, CIO as well as cardiovascular complications is unavoidable in patients with β-TM. Therefore, appropriate chelating therapy combined with its early detection by a sensitive method such as MRI-T2* can significantly lower the morbidity and mortality rate in these patients.

Authors' contribution F. Koohi was the main investigator and drafted the manuscript. E. Miri-Moghaddam and T. Kazemi were the study supervisors and contributed to all aspects of the study.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Abbreviations *β-TM*, β-Thalassemia major; *TDT*, Transfusion-dependent thalassemia; *CIO*, Cardiac iron overload; *PH*, Pulmonary hypertension; *TR*, Tricuspid regurgitation; *MRI*, Magnetic resonance

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