



PREVALENCE OF CARDIAC COMPLICATIONS IN PATIENTS WITH MAJOR THALASSEMIA IN IRANIAN PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Zohreh Mahmoodi

Department of Cardiology, Zabol University of Medical Sciences, Zabol, Iran

Conflicts of Interest: Nil

Corresponding author: Zohreh Mahmoodi

ABSTRACT

Introduction: Thalassemia major is one of the most common blood diseases in Iran. Cardiac complications are one of the leading causes of death in these patients. The aim of this study was evaluated the Prevalence of Cardiac complications in patients with major thalassemia in Iranian patients.

Methods: The methods used in this systematic review were based on the Checklist (PRISMA) Guidelines. The searches were conducted by two independent researchers and the aim was to find the relevant studies published from 1/1/2000 to 30/5/2019.

Results: A total of 2516 patients and a total of 7 studies from 7 provinces that met the inclusion criteria were evaluated. Of the studies were retrospective. According to the random effect model, the total Prevalence of Cardiac complications in 2516 patients was 11% (10%-12% at a 95% confidence interval, $I^2 = 93.7\%$).

Conclusion: Early diagnosis of cardiac dysfunction is essential. Since the most important cause of death for patients with thalassemia major is cardiac involvement, regular control of the heart conditions of patients is essential. Also, clinical examinations, electrocardiography, and chest x-ray in the early stages of cardiac involvement of these patients are normal and the most common abnormal finding of patients is left ventricular diastolic failure that can be evaluated via thoracic transthoracic echocardiography. In recent studies, however, ECG and its variations have been of great importance. Therefore, it is recommended that the ECG be monitored regularly for ST-T changes or arrhythmias.

Key words: Major thalassemia , complication, Diastolic dysfunction , Echocardiography

INTRODUCTION

Thalassemia major is one of the most common blood diseases in Iran (1). Its symptoms begin with anemia and are associated with apparent skeletal deformity and disorders, weakness, and delayed growth (2). Thalassemia major has been reported in more than 60 countries worldwide, mostly in countries located in the Thalassemia Belt (3). About 15 million people worldwide carry the beta-thalassemia gene. There are over 18,000 thalassemia patients in Iran, mostly in areas in the vicinity of the Persian Gulf, the Caspian Sea and the Oman Sea, and the number of these patients is increasing every year in our country (4). To grow normally and lead a healthy life, patients are treated with repeated blood transfusions as the most common method of treatment worldwide, including Iran (5). Repeated blood transfusions increase the levels of iron in the body and precipitate iron in vital organs such as the liver, glands, and heart, and may lead to serious complications such as cirrhosis, cardiovascular

disorders, diabetes, hypothyroidism, hyperparathyroidism, and hypogonadism (6). If a blood transfusion is initiated regularly and the hemoglobin is maintained at a concentration of at least 9.5 to 10.5 g/dl, the growth of these patients will be normal up to the age of 10 to 12 years (7). These patients may experience complications related to iron overload due to repeated injections. Cardiac disease due to iron deposition in the myocardium is one of the major complications of iron accumulation in beta-thalassemia (8). In fact, the cause of death in 5% of patients with beta-thalassemia major is cardiac involvement. Cardiac complications are one of the leading causes of death in these patients. Each unit of red blood cells contains 200 to 250 mg of iron, with an injection of 50 to 100 units leading to severe iron overload and progressive left ventricular dysfunction (9). Free radicals play an important role in the pathophysiology of tissue damage in patients with thalassemia major. Cardiac complications of thalassemia include heart failure, pericarditis, and arrhythmia (10). The most common cardiac

complication of thalassemia is heart failure that is manifested first as diastolic and then systolic dysfunction.

Methods:**Inclusion criteria (eligibility criteria):**

The methods used in this systematic review were based on the Checklist (PRISMA) Guidelines. In this research, cross-sectional, case-control, and cohort studies were included and case studies, letters to editors, case reports, clinical trials, study protocols, systematic reviews were excluded.

Participants:

All studies of the Prevalence of Cardiac complications in patients with major thalassemia in Iranian patients.

Findings:

The main purpose of this study was to determine the Prevalence of Cardiac complications in patients with major thalassemia in Iranian patients and the findings were reported.

Sampling Methods and Sample Size:

All observational studies were included in the systematic review regardless of their design. The minimum sample size was 25 patients or more.

Search Strategy

The searches were conducted by two independent researchers and the aim was to find the relevant studies published from 1/1/2000 to 30/5/2019. The researchers searched for published studies in the English language in MEDLINE via PubMed, EMBASE via Ovid, the Cochrane Library and Trip database. For studies published in other languages, National Database (Magiran and SID, KoreaMed and LILACS), and for unpublished studies, OpenGrey (www.opengrey.eu/), World Health Organization Clinical Trials Registry (who.int/ictrp), and ongoing studies were searched. To ensure that the studies are adequate, the reference lists of the retrieved studies were also searched and studied. Systematic review articles were searched using MeSH and open terms in accordance with publication standards. After the MEDLINE strategy was finalized, the results were compared to search for other databases, as well as PROSPERO was searched for recent or ongoing systematic reviews. The keywords used in the search strategy are: Beta-Thalassemia, Electrocardiography, Radiography, Echocardiography

Study Selection and Data Extraction:

The two researchers independently analyzed the titles and abstracts of the articles according to eligibility criteria. After excluding additional studies, the full text of each study was evaluated on the basis of eligibility criteria and the information about the authors was collected as needed. The general information (the first author, province in which the study was conducted and year of publication), study information (the sampling technique, diagnostic criteria, data collection method, research conditions, the sample size, and risk of bias) and output scale (Prevalence of Cardiac complications in patients with major thalassemia) were collected.

Quality Assessment:

The extended scale of Hoy et al. was used to evaluate the quality of method and the risk of bias in each observational study. This 10-item scale assesses the quality of studies according to their external validity (items 1 to 4 evaluate the target population, sampling frame, and minimum selection bias) and internal validity (items 5 to 9 evaluate the data collection, problem statement, research scale and data collection tool, while item 10 evaluates the data analysis bias). The risk of bias was measured by two researchers independently and disagreements were resolved by consensus.

Data Collection:

All eligible studies were included in the data collection after a systematic review and the data were integrated using the cumulative chart. The random effect model was evaluated based on the overall prevalence of the disease among the participants. The heterogeneity of the initial studies was assessed using the I^2 test. In addition, subgroups were analyzed to determine the heterogeneity by participants' male to female, year of publication, and Province. Finally, a meta-analysis was performed using STATA14 statistical software.

Study Selection:

A total of 594 articles were extracted through preliminary searches in various databases. Of the 421 essential studies identified by the analysis of titles and abstracts, 563 ones were eliminated because of irrelevant titles. Of the 31 existing studies, 24 ones were excluded. Of the remaining studies, 7 met the study inclusion criteria. (Fig. 1)

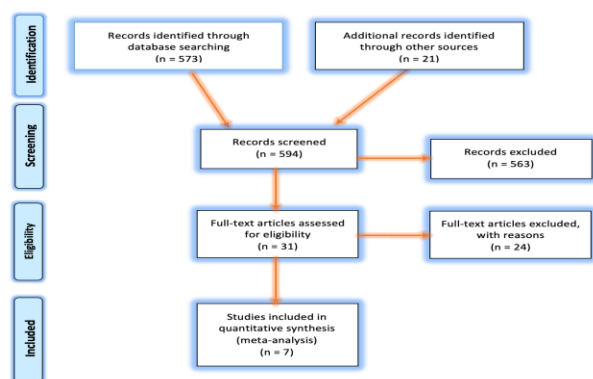


Figure 1: PRISMA flow diagram

Research Properties

A total of 2516 patients and a total of 7 studies from 7 provinces that met the inclusion criteria were evaluated. Of the studies were retrospective. Studies, were from Tehran, Zahedan, Kerman, Birjand, Ahvaz, Kordestan and khorramabad. In most studies the risk of bias was low. Data were originally collected from medical records. The hospital was the main study site. (Table 1)

Table 1: characteristics of the included studies

Author	Publication year	Province	Number of patients	Prevalence	Male to female	Mean of age
Vahidi 14	2011	Kerman	340	9.1%	155/185	14.72±7.6
Chahkandi 15	2012	Birjand	35	37%	18/17	9.06±4.33
Ansari 16	2007	Zahedan	806	15.9%	406/400	15.34±6.82
Kourosh 17	2002	Khorramabad	100	33%	---	-----
Farhangi 18	2009	Ahvaz	120	36%	57/63	16.6±6
Ansari 19	2003	Tehran	1069	8%	582/487	12.57±6.08
Kompani 20	2008	Kordestan	46	9%	-----	----

The meta-analysis of the Prevalence of Cardiac complications in patients with major thalassemia in Iranian patients:

According to the random effect model, the total Prevalence of Cardiac complications in 2516 patients was 11% (10%-12% at a 95% confidence interval, $I^2 = 93.7\%$). (Fig. 2)

Subgroup Analysis

Meta Regression Results

The results of meta-regression between participants' male to female and the Prevalence of Cardiac complications in patients with major thalassemia in Iranian patients:

The regression of the study was evaluated by the relationship between the Prevalence of Cardiac complications and participants' male to female and the total rate of Cardiac complications. There was no significant linear trend in the univariate meta-regression to explain the effect size of participants' male to female. (Fig. 4)

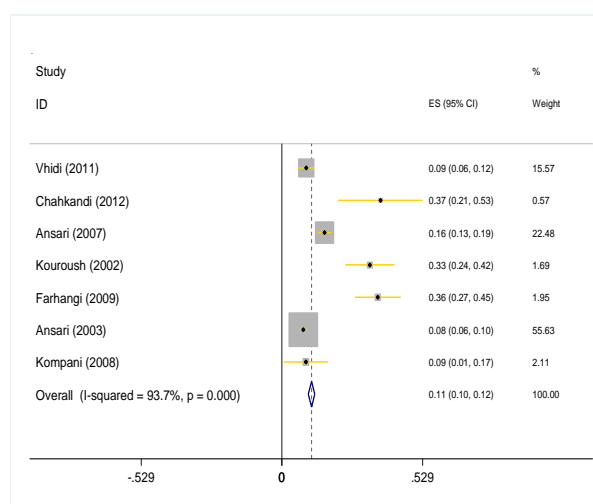


Figure 2: Prevalence of Cardiac complications in patients with major thalassemia in Iranian patients and its 95% interval for the studied cases according to the year the study was conducted based on the model of the random effects model.

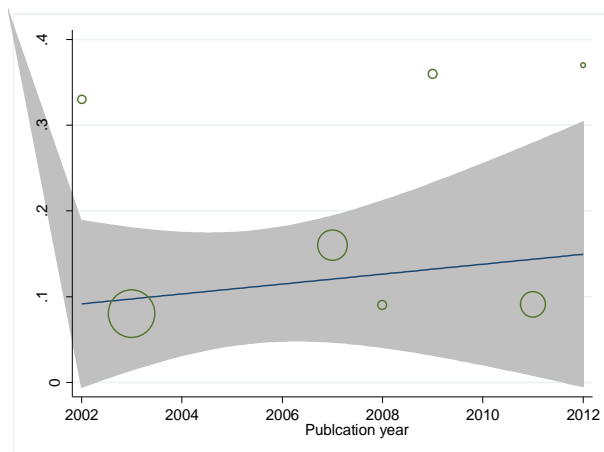


Figure 3: Meta-regression between publication year of study and Prevalence of Cardiac complications in patients with major thalassemia in Iranian patients

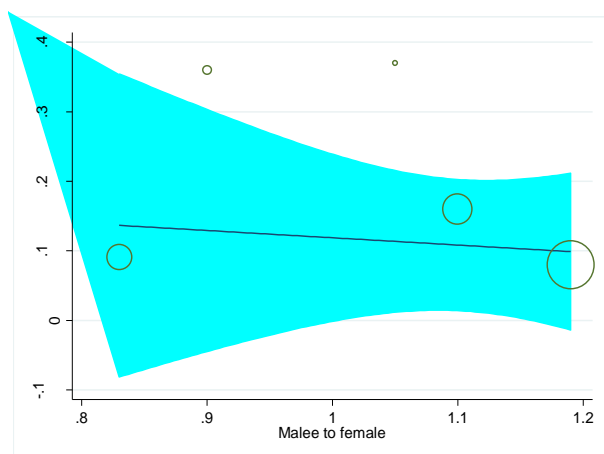


Figure 4: Meta-regression between male to female ratio of study and Prevalence of Cardiac complications in patients with major thalassemia in Iranian patients

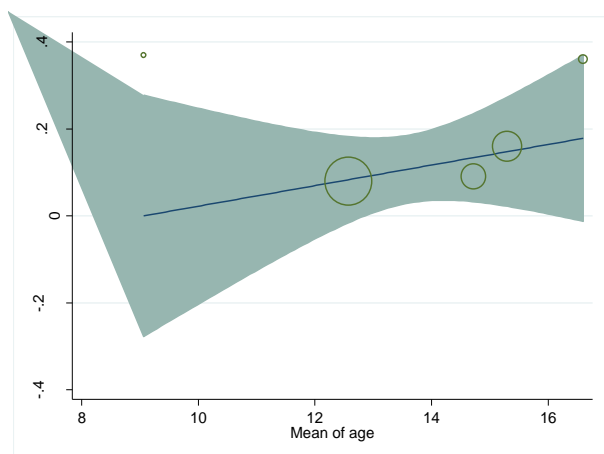


Figure 5: Meta-regression between mean of age ratio of study and Prevalence of Cardiac complications in patients with major thalassemia in Iranian patients

Discussion

According to the random effect model, the total Prevalence of Cardiac complications in 2516 patients was 11% (10%-12% at a 95% confidence interval, $I^2 = 93.7\%$). Nowadays, with the advances in treatment and especially after the beginning of iron deficiency treatment, there has been a great development in the treatment of patients with thalassemia major. With proper treatment, a relatively long life can be expected for these patients (11). Living with the complications for a long time may be impossible for the patient and may result in a cost to the patient and the healthcare system (12). Besides, patients and their families may face psychological and social problems and this reduces patient efficacy to a great extent by reducing the treatment value despite the heavy costs imposed on the community (13). Considering the points mentioned, it is of great importance to identify the effective factors in the early onset of these complications. Cardiac function is a major determinant of survival in patients with thalassemia major (14). Most major thalassaemic patients are likely to have a long life but when symptoms of heart failure appear, longevity decreases rapidly (15). Cardiac iron overload is the leading cause of cardiac dysfunction and death in these patients. Major cardiac problems reported in patients with thalassemia major include left ventricular systolic dysfunction, diastolic dysfunction, pulmonary hypertension, valvular disease, arrhythmias, and pericarditis (16). Heart failure is still considered one of the major causes of death in thalassemia. Therefore, early diagnosis of cardiac dysfunction is essential (17). Since the most important cause of death for patients with thalassemia major is cardiac involvement, regular control of the heart conditions of patients is essential. Also, clinical examinations, electrocardiography, and chest x-ray in the early stages of cardiac involvement of these patients are normal and the most common abnormal finding of patients is left ventricular diastolic failure that can be evaluated via thoracic transthoracic echocardiography. In recent studies, however, ECG and its variations have been of great importance. Therefore, it is recommended that the ECG be monitored regularly for ST-T changes or arrhythmias.

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